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ORIGINAL ARTICLE

The CredibleMeds® list: Usage of QT interval prolonging drugs in Germany and discordances with prescribing information

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Aims: A substantial number of Summaries of Product Characteristics (SmPCs)/Prescribing Information (PI) have warnings or contraindications on QT interval prolongation. The goal of this work was to quantify usage of QT interval prolonging drugs according to the CredibleMeds® database of the German outpatient drug prescription market and to evaluate discrepancies between German SmPCs/US PI and CredibleMeds®.

Methods: Drugs listed on CredibleMeds® with known, possible or conditional risk for torsade de pointes were evaluated from 2000 to 2020. The German drug prescription report was used as source for defined daily dose- (DDD-) based prescriptions of the German outpatient drug prescription market of the public health insurance system. German SmPCs and US PI of 253 CredibleMeds®-listed drugs were evaluated for contents regarding QT interval prolongation.

Results: Of the drugs currently listed on CredibleMeds®, 59.7% (95% confidence interval [CI] 53.5–65.5%) were listed after 2012. Due to newly listed drugs, the proportion of DDDs of CredibleMeds® drugs among all prescriptions increased from 4.6% in 2013 to 21.1% in 2019. DDD-based usage of the CredibleMeds® drugs already listed in 2013 was similar in 2019. Among the drugs with known QT risk according to CredibleMeds®, 7.5% (95% CI 2.6–19.9%) of German SmPCs and 21.1% (95% CI 11.1–36.3%) of US PI had no mention of QT issues whatsoever.

Conclusion: A significant proportion of all drugs prescribed in the outpatient sector is associated with QT risks according to CredibleMeds®. SmPCs and PI should systematically be evaluated for concordance with the widely used CredibleMeds® database to increase medication safety.

KEYWORDS
medication safety, prescribing information, QT interval, QT prolongation, Summaries of Product Characteristics, torsades de pointes

1 | INTRODUCTION

A plethora of structurally diverse drugs can cause QT interval prolongation,[1–3] which is associated with potentially lethal torsade de pointes arrhythmias (TdP). Pharmacoepidemiologic studies have shown that drug-induced QT interval prolongation is a risk factor for sudden cardiac death.[4–6] Moreover, sudden death is more frequent in certain QT interval prolonging drugs.[3]

New molecular entities are routinely screened for the potential to prolong the QT interval according to the requirements of the regulatory

authorities.[7–12] As a consequence, physicians have to pay attention to a continuously growing list of drugs with warnings and contraindications regarding QT interval prolongation in the Summaries of Product Characteristics (SmPCs)/Prescribing Information (PI). Dear Doctor Letters (or Direct Healthcare Professional Communications, DHPCs) with simple, QT-related warnings can have a significant impact on prescribing as has been shown for citalopram and escitalopram.[13]

The most widely used database for QT prolonging drugs is CredibleMeds®.[14,15] It was established in 1999, is regularly updated and lists drugs into the three categories: (1) drugs with known risk of TdP, (2) drugs with possible risk of TdP and (3) drugs with conditional risk of TdP.[14,15] The website of CredibleMeds® currently has approximately 20 000 unique visitors each month and has already received more than three million visitors, mainly from the US (87%), followed by Europe (7%) and Asia (3%).[16,17] In a study with 130 434 geriatric patients, we could show that 58.7% of the patients received at least one CredibleMeds®-listed drug and 22.1% received simultaneously at least two CredibleMeds®-listed drugs.[18] Of the patients prescribed at least one drug with known TdP risk, 55.9% received at least one further CredibleMeds®-listed drug.[18]

SmPCs/PI frequently state that the coadministration of other QT interval prolonging drugs should be avoided or is contraindicated. Unfortunately, neither the FDA (US Food and Drug Administration) nor the EMA (European Medicines Agency) or the German BfArM (Federal Institute for Drugs and Medical Devices) have their own official lists of QT interval prolonging drugs. Thus, physicians have to use other sources such as CredibleMeds® in order to clarify the correct use of the respective drugs. This is a potential risk because, to the best of our knowledge, concordances and discordances between SmPCs/PI and CredibleMeds® have not been systematically evaluated.

We therefore studied the extent of usage of CredibleMeds®-listed QT drugs since 2013 in the German outpatient drug prescription market of the public health insurance system and evaluated concordances/discordances of all 253 CredibleMeds®-listed drugs with German SmPCs and US PI.

What is already known about this subject

- Use of QT interval prolonging drugs is associated with patient risks.
- SmPCs/Prescribing Information have warnings or contraindications regarding coadministration of QT interval prolonging drugs.
- CredibleMeds® is a frequently used database for QT drugs.

What this study adds

- The proportion of defined daily doses of CredibleMeds® drugs among the top 3000 prescribed medicines increased 4.6-fold from 2013 (4.6%) to 2019 (20.9%) in Germany, largely due to newly listed drugs in CredibleMeds®.
- Major discrepancies between German SmPCs/US Prescribing Information and CredibleMeds® exist and pose a risk for medication safety.

2 | METHODS

2.1 | QT drugs

QT drugs (i.e., pharmaceutical ingredients) were those listed in CredibleMeds® (crediblemeds.com) in one of the three categories: (1) drugs with known risk of TdP, (2) drugs with possible risk of TdP and (3) drugs with conditional risk of TdP.[14]

2.2 | German drug prescription report (Arzneiverordnungsreport)[19–26]

The 3000 most frequently prescribed medicines based on prescription numbers for the years 2013 to 2019 were extracted from the German drug prescription report, which covers the German outpatient market of the public health insurance system.[19–26] The data for the reporting years 2013 to 2015 were extracted from the yearly published drug prescription report.[19–21] The data for the reporting years 2016 to 2019 were extracted from the "PharmMaAnalyst" database provided by the WIdO (Wissenschaftliches Institut der AOK, AOK Research Institute).[26] The dataset included medicines, active pharmaceutical ingredient, number of prescriptions and defined daily doses (DDDs). DDD has been defined by the World Health Organization (WHO) as "the assumed average maintenance dose per day for a drug used for its main indication in adults".[27]

2.3 | Top 500 drugs

The top 3000 medicines from the German drug prescription report were aggregated based on their active pharmaceutical ingredients according to their notation in the current version of the German ATC (Anatomical Therapeutic Chemical Classification System) index.[28] From the resulting approximately 900 pharmaceutical ingredients each year (2013: 880; 2014: 888; 2015: 912; 2016: 955; 2017: 962; 2018: 976; 2019: 968), the top 500 pharmaceutical ingredients based on number of DDDs were used for the analysis (corresponding to over 96% of all prescriptions). The CredibleMeds® status from 1 January of the reporting year was assigned to each drug in the respective year. Medicines with a combination of at least two drugs were assigned to the CredibleMeds® category of the individual drug with the highest QT risk.

2.4 | Analysis of ATC codes

The 3000 most prescribed medicines in 2019 based on prescription numbers from the German drug prescription report were extracted from the "PharmMaAnalyst" database provided by the WIdO.[26] The extracted dataset included medicines, number of prescriptions, DDDs, ATC drug name and ATC code. The data were aggregated based on the official heading of the first four digits in the German ATC index.[28] The CredibleMeds® status from 1 January 2019 was assigned to each drug. Medicines with a combination of at least two drugs were assigned to the CredibleMeds® category of the individual drug, which was ranked in a category with higher QT risks.

2.5 | QT drugs and prescribing information

For the analysis of the current prescribing information, the QT drugs from the CredibleMeds® list updated last on 17 December 2020 were used. The prescribing information was screened for warnings and precautionary measures in connection with the terms "QT", "torsade de pointes", "TdP" and "Q-T" using a full-text search. It was considered as "QT contraindication" if a combination with other QT drugs was specified analogously to the wording "must not be combined with other QT drugs". If the combination with other QT drugs has been formulated as "should not" or "is not recommended", it was considered as "QT warning". The wording was furthermore considered as "QT warning" if the risk of QT interval prolongation or TdP was mentioned or precautionary measures were recommended without consequences to a comedication.

2.6 | German prescribing information

The German marketing status of each QT drug was checked according to the AMIS database (Arzneimittel-Informationssystem, Drug Information System) provided by the German regulatory authorities, which was last updated on 19 March 2020.[29] For each approved QT drug, one exemplary SmPC, preferably by an original manufacturer, was evaluated. In the absence of an SmPC from an original manufacturer, the SmPC by the generic drug's manufacturer with the most recent date was chosen.

The SmPCs from the top 504 drugs from the 2019 drug prescription report were analysed in an analogous manner. The drug names from the German ATC index "imidazoles/triazoles in combination with corticosteroids", "combinations", "bandages with vaseline" and "various" are either not clear or lack a corresponding SmPC. Hence, the SmPC for drugs from the top 501 to 504 were analysed instead.

2.7 | US prescribing information

The US marketing status of each QT drug was checked in October 2020 according to the Drugs.com database, which provided the FDA approval status.[30,31] The US PI was taken from the FDA Professional Drug Information available via the Drugs.com database.[32]

A list of the SmPCs and Prescribing Information used for this work is shown in Supplemental Tables S1 and S2.

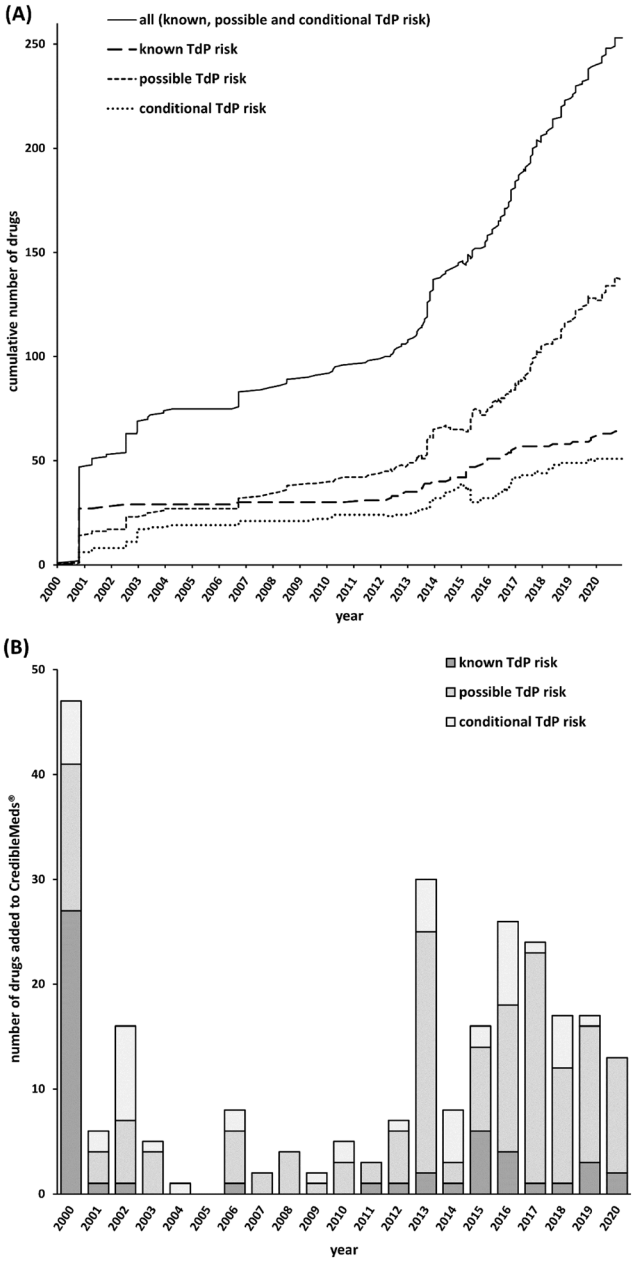

FIGURE 1 (A) Cumulative number of drugs listed in CredibleMeds® with known, possible or conditional torsade de pointes (TdP) risk. (B) Number of drugs added per year to CredibleMeds® with known, possible or conditional torsade de pointes (TdP) risk

2.8 | Statistical analysis

Descriptive data are shown as mean values. Key prevalence measures are presented with 95% confidence intervals (CI) calculated for a

sample proportion using Epitools epidemiological calculators with "Wilson" score interval.[33]

3 | RESULTS

3.1 | CredibleMeds® list of QT drugs

As of 17 December 2020, there were 253 QT drugs listed in CredibleMeds®, 65 (25.7%) with known TdP risk, 137 (54.2%) with possible TdP risk and 51 (20.2%) with conditional TdP risk (Figure 1A). Since its launch in 1999, the CredibleMeds® list has been modified 296 times to 17 December 2020, with 259 new entries (Figure 1B), 31 recategorizations (17 up- and 14 downgrades) and six removals. A downgrade never affected the highest category "known risk". Of all QT drugs, 59.7% (95% CI 53.5–65.5%, 151 of 253) were listed after 2012. The timespan between US market approval and the inclusion on the CredibleMeds® list was shorter for more recently approved drugs in comparison to long-term marketed drugs (listing in CredibleMeds®: 2006–2016: median 17.0 years after approval; 2017–2020: 14.3 years) (Supplemental Figure S1).

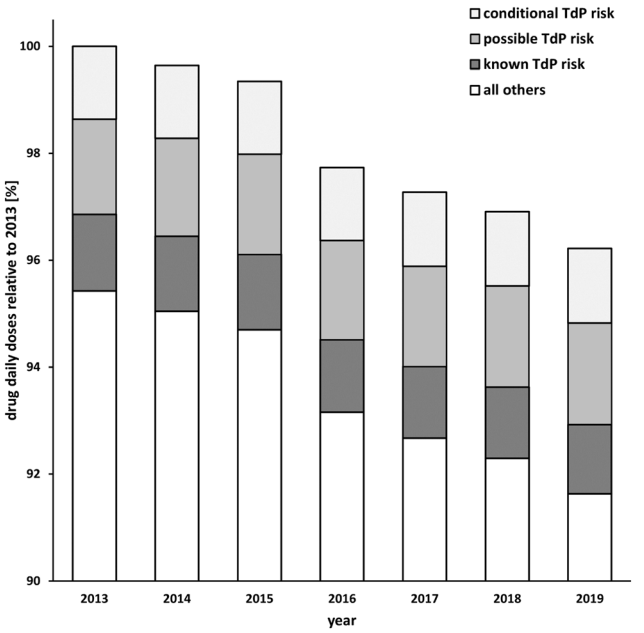

FIGURE 2 Development of drug daily doses relative to the top 500 drugs of the German outpatient drug prescription market of the public health insurance system in 2013 and share of QT drugs according to CredibleMeds® list of drugs with risk for torsade de pointes (TdP)

3.2 | QT drugs in the German drug prescription market

3.2.1 | Prescription development of QT drugs listed in 2013

Among the top 500 drugs from the German drug prescription report in 2013, 4.6% of the DDDs were associated with QT interval prolongation according to CredibleMeds®.[19] The absolute number of DDDs prescribed for 2013 QT drugs according to CredibleMeds® remained relatively constant until 2019 (2013: 4.57%; 2019: 4.59%) (Figure 2). Since the 2013 top 500 drugs were less frequently prescribed in the following years (2019: −3.8%), the fraction of QT interval prolonging drugs among these top 500 drugs increased only moderately from 4.6% to 4.8% in 2019 (based on DDDs).

3.2.2 | Prescription development of listed QT drugs from 2013 to 2019

Considering QT drugs newly listed by CredibleMeds® since 2013, the proportion of DDDs of QT drugs among the top 500 prescription drugs increased 4.6-fold from 4.6% in 2013 to 21.1% in 2019 (Figure 3A). In detail, the proportion of QT drugs with known TdP risk increased from 1.4% to 1.5% (Figure 3B), the proportion of QT drugs with possible TdP risk increased from 1.8% to 2.4% (Figure 3C) and the proportion of QT drugs with conditional TdP risk increased over 12.3-fold from 1.4% to 17.2%.

Of the 17 drugs with known TdP risk among the top 500 prescription drugs in 2019, four drugs accounted for 78.6% of the DDDs with known TdP risk (citalopram: 40.9%; escitalopram: 24.5%; amiodarone: 7.2%; donepezil: 6.1%) (Figure 3B).

In 2019, there were 30 drugs with possible TdP risk among the top 500 drugs. The four most prescribed drugs—venlafaxine, mirtazapine, tramadol and ofloxacin—represented more than 50% of all DDDs with possible TdP risk, with venlafaxine (20.7%) and mirtazapine (19.3%) having by far the highest share.

The DDD increase of QT drugs with conditional TdP risk is caused mainly by the inclusion of the following five drugs to this CredibleMeds® category between 2013 and 2016: hydrochlorothiazide (2013), furosemide (2013), pantoprazole (2014), torasemide (2015) and omeprazole (2016).

3.2.3 | QT drugs on ATC level

In order to obtain further insights into the relative importance of QT drugs within certain drug classes, an ATC-based evaluation was performed. The 1080 seven-digit ATC codes can be aggregated into 193 groups on a four-digit ATC level, of which 138 groups did not include any QT drugs (71.5%). The remaining 55 groups had a relative quantity of QT drugs between 0.1% and 100.0% with an average of 53.4% (SD = 38.9%). Thirty-eight of these 55 groups contained an above average (>21.1%) relative quantity of QT drugs (Figure 4).

Drugs with known TdP risk comprise from 50 to 100% of the total DDDs of the QT drugs in the respective ATC class for anti-

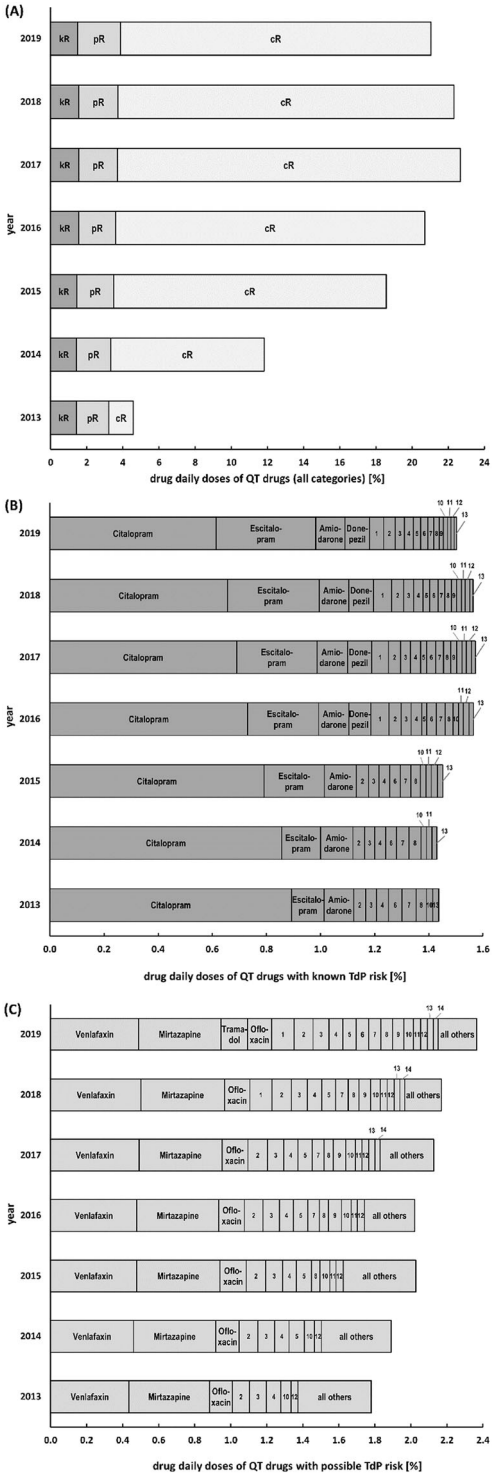

FIGURE 3 (A) Drug daily doses of CredibleMeds®-listed QT drugs with known, possible and conditional torsade de pointes risk in the top 500 drugs of the German outpatient drug prescription market of the public health insurance system from 2013 to 2019. kR: known TdP risk; pR: possible TdP risk; cR: conditional TdP risk; TdP: torsade de pointes. (B) Drug daily doses of CredibleMeds®-listed QT drugs with known torsade de pointes risk in the top 500 drugs of the German outpatient drug prescription market of the public health insurance system from 2013 to 2019. Individual drugs are shown in descending order based on quantity of drug daily doses in 2019: citalopram, escitalopram, amiodarone, donepezil, 1: ciprofloxacin, 2: flecainide, 3: azithromycin, 4: haloperidol, 5: methadone, 6: clarithromycin, 7: sotalol, 8: domperidone, 9: roxithromycin, 10: moxifloxacin, 11: dronedarone, 12: levofloxacin, 13: erythromycin. TdP: torsade de pointes. (C) Drug daily doses of CredibleMeds®-listed QT drugs with possible torsade de pointes risk in the top 500 drugs of the German outpatient drug prescription market of the public health insurance system from 2013 to 2019. Individual drugs are shown in descending order based on quantity of drug daily doses in 2019: venlafaxine, mirtazapine, tramadol, ofloxacin, 1: fluorouracil, 2: tamoxifen, 3: risperidone, 4: alfuzosin, 5: promethazine, 6: memantine, 7: leuprorelin, 8: aripiprazole, 9: trimipramine, 10: lithium, 11: pipamperone, 12: clozapine, 13: buprenorphine, 14: melperone. TdP: torsade de pointes

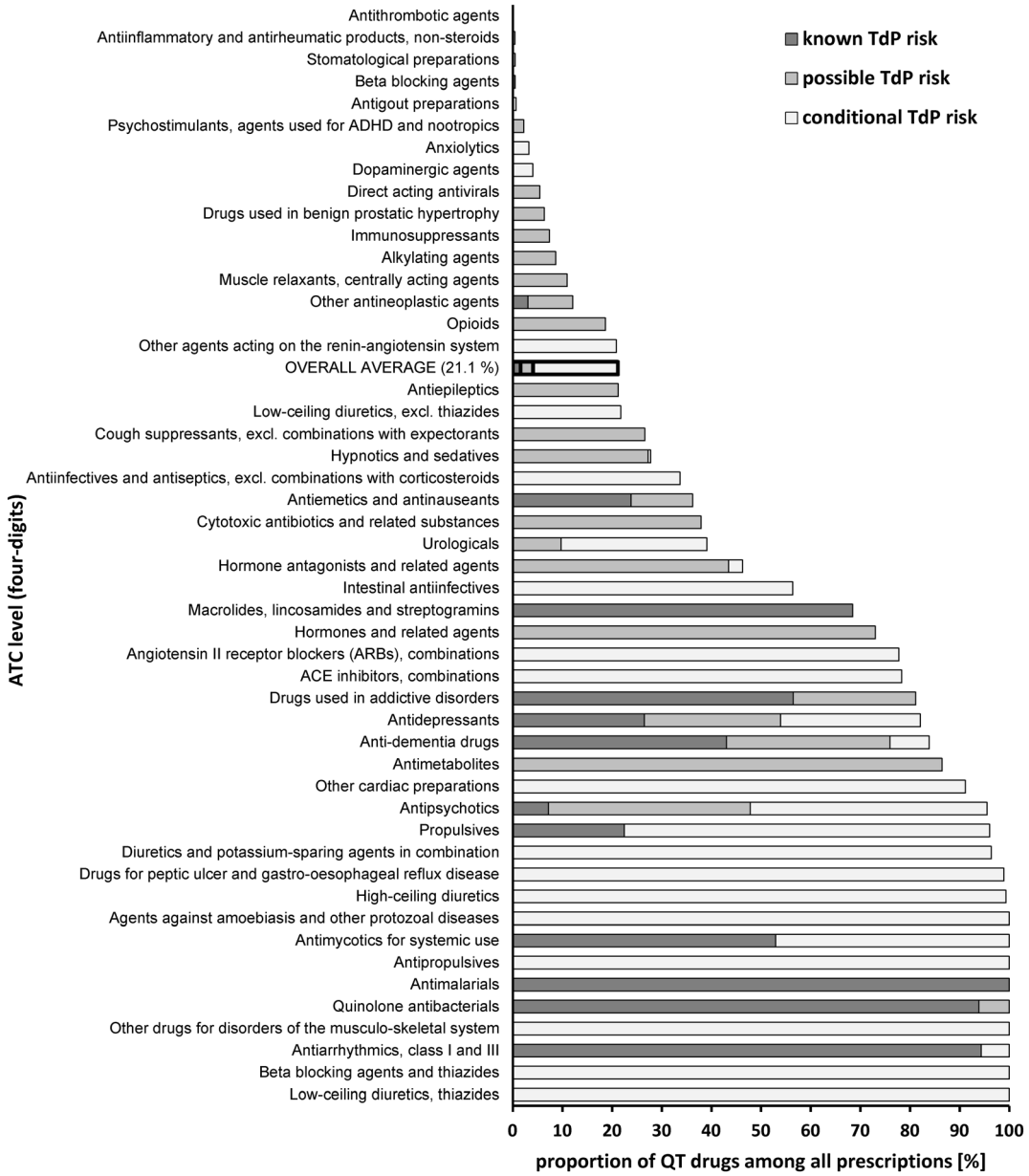

FIGURE 4 Proportion of prescribed drug daily doses of QT drugs within four-digit ATC code level drug classes. Data are based on prescriptions in the top 3000 drugs of the German outpatient drug prescription market of the public health insurance system in 2019. Shown are all groups at four-digit ATC code level with drugs in categories known, possible or conditional torsade de pointes risk according to the CredibleMeds® list except dermatics, ophtalmics and otologics. ATC: Anatomical Therapeutic Chemical Classification System, TdP: torsade de pointes

dementia drugs (51.3%), systemic antimycotics (52.9%), antiemetics and antinauseants (65.8%), drugs used in addictive disorders (69.6%), quinolone antibacterials (93.8%), antiarrhythmics classes I and III (94.4%), antithrombotic agents (100.0%), beta blocking agents (100.0%), macrolides, lincosamides and streptogramins (100.0%) and antimalarials (100.0%). Furthermore, within the groups of anti-protozoal drugs, antipropulsives, other drugs for disorders of the musculo-skeletal system, beta blocking agents with thiazides and low-ceiling diuretics/thiazides, all prescribed drugs were associated with a conditional TdP risk, which was caused mainly by hydrochlorothiazide alone or as a combination in the latter two groups.

3.3 | Prescribing information

As of 17 December 2020, CredibleMeds® listed 253 QT drugs, of which 185 were approved in Germany and 197 were approved in the US (Figure 5). There were 40 drugs with a known TdP risk approved in Germany. In the SmPCs of 14 of those (35.0%), the combination with other QT drugs was contraindicated. For further 23 drugs (57.5%), there was a warning regarding QT drugs in the SmPC. For the three drugs, donepezil, papaverine and propofol (7.5%, 95% CI 2.6–19.9%) (Supplemental Figure S2) with known TdP risk, there was neither a contraindication nor a warning regarding QT prolongation in

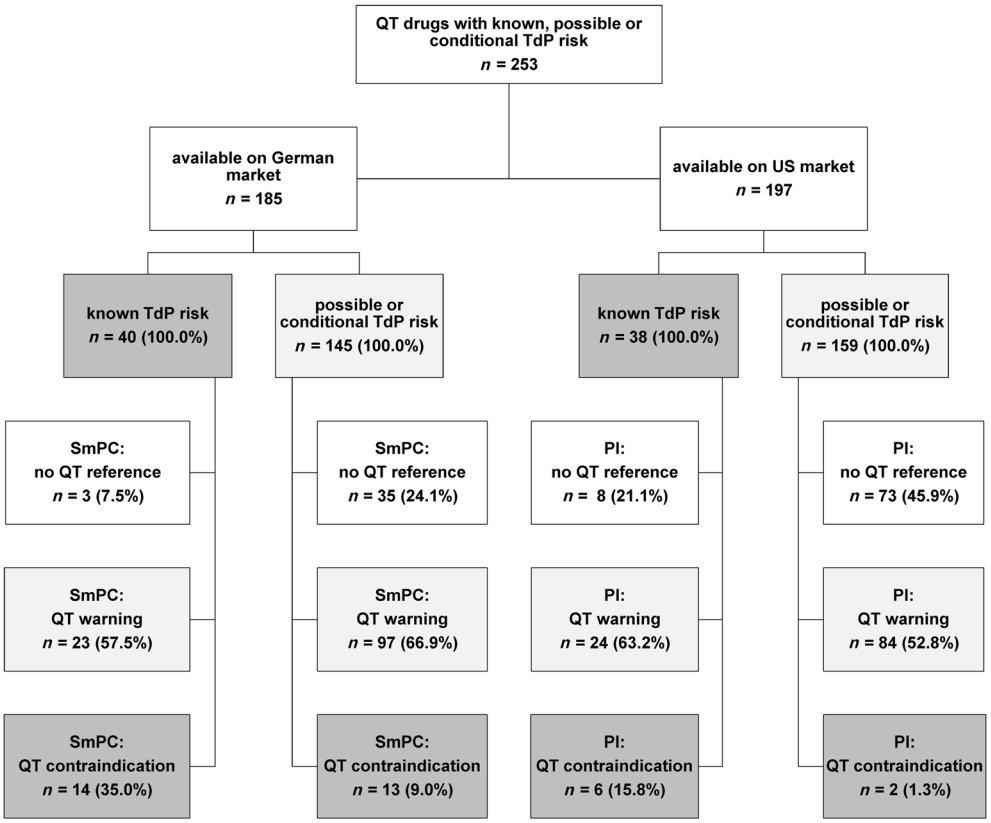

FIGURE 5 Concordances and discordances of US Prescribing Information and German Summaries of Product Characteristics with CredibleMeds®. The prescribing information was analysed for all products marketed in the respective country. QT warning: The risk of QT interval prolongation is mentioned and/or the combination with other QT interval prolonging drugs is not advised; QT contraindication: combination with other QT interval prolonging drugs is contraindicated; SmPC: German prescribing information/Summary of Product Characteristics; PI: US Prescribing Information; TdP: torsade de pointes

the SmPCs. A total of 145 drugs in the CredibleMeds® categories possible or conditional TdP risk were approved in Germany. The SmPCs for 110 (75.9%) of these had a warning regarding QT risk or a contraindication regarding a combination with QT drugs. The remaining 35 (24.1%) SmPCs did not have a reference to QT interval prolongation at all. In total, 61 of 185 (33.0%, 95% CI 26.6–40.0%) SmPCs lacked respective information regarding QT risk (Supplemental Figure S2).

In addition, the comparison of the SmPCs of the top 500 prescription drugs from 2019 with the CredibleMeds® QT drugs list revealed 18 drugs which had a stricter evaluation of the QT risk in the SmPC than CredibleMeds® (Supplemental Table S3). For amantadine (PK-Merz®), amisulpride (Solian®) and quinine (Limptar® N) a combination with QT drugs was contraindicated in the SmPC, whilst in CredibleMeds® they had a conditional TdP risk. Amitriptylinoxide (Amioxid-neuraxpharm®) contained a contraindication in the SmPC, but was not listed in CredibleMeds®. Furthermore, formoterol and combinations (Formatris® Novolizer®, Duaklir® Genuair®, Foster®, DuoResp® Spiromax®, flutiform® and Trimbow®), bicalutamide (Casodex®) chlortalidone (Hygroton®), cinacalcet (Mimpara®), dimenhydrinate/cinnarizine (Vertigo-Vomex® plus Cinnarizin), desfesoterodine (Tovedeso®), fluphenazine (Fluphenazin-neuraxpharm®), opipramol (Opipram®), perazine (Perazin-neuraxpharm®), piretanide (Arelix®), rivastigmine (Exelon®), triamcinolone (depot) (Lederlon®), triptorelin (Pamorelin®) and xipamide (Xipagamma®) had a warning regarding a QT risk in the SmPC, but were not listed in the CredibleMeds® categories known, possible or conditional TdP risk.

From the 38 drugs with a known TdP risk approved on the US market, the PI of 6 (15.8%) stated that the combination with other QT drugs was contraindicated. Furthermore, 24 PI (63.2%) had a warning regarding the combination with other QT drugs and eight (21.1%, 95% CI 11.1–36.3%) had no reference to QT prolongation at all. A total of 159 drugs on the US market had a possible or conditional TdP risk. For 86 of these drugs, the US PI (54.1%) had a warning regarding QT risk or a contraindication regarding QT drugs. The remaining 73 (45.9%) did not have a reference to QT interval prolongation at all. In total, 105 of 197 PI (53.3%, 95% CI 46.3–60.1%) lacked respective information regarding QT risk (Supplemental Figure S3).

4 | DISCUSSION

One major finding of our analysis was that there is a high frequency of use of drugs with known, possible or conditional risk according to CredibleMeds® in the German outpatient market. In 2019 more than one fifth of the prescribed doses (DDD) were related to CredibleMeds®-listed drugs. Major increases in the number of CredibleMeds®-listed QT drugs can be attributed to two main causes: Beginning in 2012, the CredibleMeds® list was expanded to drugs marketed outside the US, focusing on Europe, Japan and Canada.[15] Furthermore, guidelines have been implemented by the ICH

(International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use), FDA and EMA to ensure thorough QT studies from pharmaceutical companies resulting in more drugs being added to the category "possible TdP risk".[7–12,15] More than half of today's listed 253 QT drugs were added after 2012.

The analysis of the prescribed doses (DDDs) of CredibleMeds®-listed QT drugs in 2013 over the following years, without including drugs that were newly classified as QT drugs afterwards, showed that the increasing use of QT drugs in Germany was influenced not only by the increase in the number of CredibleMeds®-listed QT drugs. The results revealed that, whilst drugs not listed in CredibleMeds® were less frequently prescribed in the following years, the number of prescriptions of CredibleMeds®-listed QT drugs remained quite stable. The reasons why CredibleMeds®-listed QT drugs tend to be less often replaced with other or newly introduced drugs that are not QT drugs could not be determined in detail in this paper. One factor to consider is the increased regulatory requirements regarding QT studies, which might lead to older drugs whose QT prolonging potential is unknown being replaced by newer drugs with thorough QT studies. On the other hand, older drugs that have been revealed as QT prolonging are often removed completely from the market due to their suddenly disclosed cardiotoxic potential.[34,35] Moreover, by now, a majority of the drugs with a very long marketing history may simply have been studied, leading to a relative decline in the new inclusion of very old drugs into the CredibleMeds® list.

We have included drugs from the category "conditional TdP risk" in the analysis, which do not prolong the QT interval directly, but create conditions, that favour TdP or result in TdP under certain conditions. Hence, these drugs contribute to the overall QT risk of the patients.[36,37] The high number of prescriptions of drugs with known or possible QT risk in combination with a high number of prescriptions of drugs with conditional QT risk (e.g., potassium lowering diuretics) puts a considerable proportion of the patients at QT risk and is therefore an issue of medication safety, which deserves in our opinion more attention. In line with the present study, an analysis of a large geriatric study population of more than 130 000 patients by Schächtele et al. revealed that co-prescriptions of two or more QT drugs listed either in CredibleMeds® or with any warning or precaution in the German SmPCs occurred in 22.1% of the patients.[18]

The 20 most common drug–drug combinations were responsible for more than 90% of the co-prescriptions with involvement of at least one drug with known TdP risk according to CredibleMeds®.[18] Both the present analysis of prescriptions of QT drugs in the German outpatient market and the work of Schächtele et al. in patients treated in geriatric units revealed that the major burden of drugs with known QT risk is caused by a few, frequently prescribed drugs.[18] These were in the present analysis citalopram, escitalopram, amiodarone and donepezil, which contributed 78.6% to all DDDs of this risk category. According to the Pareto principle, measures to minimize QT risks should focus primarily on these frequently prescribed drugs.[38] Given the number of patients, the clinical consequences should be evaluated more systematically for the most common combinations of QT prolonging drugs due to their possible, but in many cases not yet proven, additive effects with respect to arrhythmias and sudden death.[39–41] The prescribing information for a QT drug in the CredibleMeds® category "known risk" was rated as adequate in this analysis if the combination with other QT drugs was mentioned as contraindicated. We would like to indicate that in our opinion more data about clinical risks due to simultaneous use of two or more QT prolonging drugs is needed.

The second major finding of this work is that a significant proportion of QT-related prescribing information in Germany and the US did not reflect or agree with the QT/TdP risk categories assigned by CredibleMeds®. The problem of outdated or contradictory prescribing information was shown in the past in several studies for different therapeutic areas.[42–45] A systematic investigation into inconsistencies in prescribing information in the UK, US and German drug markets revealed that reciprocal warnings regarding drug–drug interactions were missing in more than 40% of the cases.[46] A study from the UK observed major differences between the prescribing information and scientific guidelines for Attention Deficit Hyperactivity Disorder (ADHD) medicines.[42] Another study on anticancer drugs found that clinically relevant information was outdated, in particular for older drugs, and significant discrepancies between evidence-based guidelines and the FDA recommendations with regard to their use were observed.[43] A recently published commentary emphasized several considerations for the FDA on how to update outdated prescribing information and labelling of oncology drugs to ensure their relevance for clinical practice.[44]

A study from 2014 screened European drug labels for the term "QT" and concluded that for 43% of the SmPCs that mentioned QT prolongation, a clear statement was missing on whether the drug induced QT prolongation.[45] In our present study using CredibleMeds® as QT reference database, we detected inadequate information in 33.0% of German SmPCs and 53.3% of US PI.

Furthermore, prescribing information for the same drug approved by different regulatory authorities such as the FDA or EMA show discrepancies. For example, in a recently published study, the comparison between the FDA's and EMA's prescribing information showed little harmonization regarding the labelling of new vaccines.[47] In addition, it was shown that drug labels are updated more frequently in the period after their introduction to the market than later in its product life cycle, which leads to lack of updated information especially for long-established drugs as well as generic drugs.[43,48]

To the best of our knowledge, the FDA and EMA do not have their own official lists published for QT interval prolonging or torsadogenic drugs. Along with the implementation of ICH and GMP (Good Manufacturing Practice) guidelines, the harmonization is well advanced in areas such as drug manufacturing and clinical studies, whilst for drug information and medication safety there are still persistent discrepancies. With regard to QT/TdP risk, it would be important that the pharmaceutical industry, regulatory authorities, CredibleMeds® and other interested stakeholders find a standardized and harmonized approach to avoid outdated as well as contradictory prescribing information and recommend the prescribing physicians updated easy-to-use reference databases. The period for mandatory

updates of the prescribing information (e.g., as part of periodic safety updates) varies regionally. Both the FDA and EMA generally require a frequent update of the prescribing information every few months for newly marketed drugs up to every few years for long-term marketed drugs.[49,50] Nevertheless, despite these mandatory deadlines, both agencies do recommend an update of the prescribing information as soon as new information emerges throughout the product life cycle.[51–53]

The content of the prescribing information should constantly be checked for up-to-dateness as part of the product life cycle after approval to cover the importance of new evidence sources for medication safety such as spontaneous reports.[54] It should be noted that the present analysis did not differentiate between systematic and non-systematic drug use, but drugs with topical, ophthalmic or otologic administration represented less than 5% of all DDDs.

5 | CONCLUSION

A significant proportion of all drugs prescribed in the outpatient sector is associated with QT risks according to CredibleMeds®. Medication safety and awareness of QT drugs could be increased considerably if physicians have in mind at least their own frequently prescribed "top-QT drugs" as well as the respective ATC groups frequently associated with QT risk. SmPCs and PI should systematically be evaluated for concordance with the widely used CredibleMeds® database to increase medication safety and to provide easy to use information for prescribers.

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COMPETING INTERESTS

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CONTRIBUTORS

M.I.T., R.M. and M.F.F. designed the study. M.I.T. performed the data extraction from the databases. M.I.T., W.A., R.M. and M.F.F. analysed the data. M.I.T. and M.F.F. wrote the first version of the manuscript. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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