

SHORT COMMUNICATION

Who prescribes quetiapine in Denmark?

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Funding information

Mental Health Services in the Region of Southern Denmark, Grant/Award Number: A2957

The second-generation antipsychotic quetiapine is commonly used off-label for its anxiolytic and hypnotic properties. However, quetiapine is associated with problematic side-effects. We used Danish Medicinal Product Statistics and a 20% random sample of the Danish population's prescription fills (2001–2020) to describe the utilization of quetiapine and proportion of various prescriber types (general practitioner [GP], specialist in private practice, hospital physician and other prescribers) both in connection to first-time and subsequent prescriptions. In 2020, 92% of all quetiapine was dispensed outside hospitals and the average daily dispensed quantity of quetiapine per user corresponded to 100 mg/user/d. A GP issued 53% of first-time prescriptions and 75% of subsequent prescriptions for quetiapine in 2020. The proportion of quetiapine prescriptions issued by GPs varied by age group—from 14% among 0–17-year-olds to 93% among the ≥80-year-olds. Future initiatives on the rational use of quetiapine and related drugs, especially among adults, should target GPs.

KEYWORDS

antipsychotics, off-label, prescriber, quetiapine

1 | INTRODUCTION

Quetiapine is a second-generation antipsychotic licensed for treatment of schizophrenia, bipolar disorder and major depression.¹ However, due to its anxiolytic and hypnotic properties, quetiapine is commonly used off-label in conditions such as anxiety, insomnia, or behavioural and psychological symptoms of dementia.^{2,3} Worldwide, the number of quetiapine users has steadily increased since its introduction, with quetiapine now being the most frequently prescribed antipsychotic in several countries such as Australia, Denmark, Finland, Germany, Iceland, Norway, Spain, Sweden and the USA.^{4,5}

Increased awareness to reduce the use of benzodiazepines due to their potential for dependency and adverse events, might have offset

a corresponding increase in the off-label use of quetiapine (and other antipsychotics).⁶ However, the use of quetiapine is problematic as it has been associated with adverse events, including QT-prolongation, somnolence, weight gain and metabolic dysregulation.⁷

A prior study on off-label use of antipsychotics in Denmark indicated that a substantial proportion of the off-label use might be driven by prescription in general practice.⁸ To form the basis for future initiatives to ensure rational use of quetiapine, we aimed to characterize: (i) the use of quetiapine in Denmark; and (ii) the prescriber profile for quetiapine, including the development from 2001 towards 2020 in these 2 areas.

2 | METHODS

We conducted a nation-wide drug utilization study using both Danish national medicinal product statistics and individual-level drug

The authors confirm that the Principal Investigator for this paper is Mikkel Højlund

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dispensing data. Based on these data sources, we analysed: (i) the overall development in the use of quetiapine between 2001 and 2020; (ii) the distribution of various prescriber types, overall and in various subgroups; and (iii) compared the development for quetiapine with that of other medications commonly used off-label for anxiolytic, sedative or hypnotic purposes. The study was registered at the University of Southern Denmark's inventory (rec.10.825). According to Danish legislation, no ethical approval was required for a purely register-based study such as the present.

2.1 | Data sources, sample and study drugs

For analyses of overall drug consumption, data were obtained from the Danish Register of Medicinal Product Statistics.⁹ This registry holds information from 1995 and onwards on sales in both the primary sector (i.e., prescriptions filled at community pharmacies) and at hospitals, although the latter is not referable at the individual level. Aggregate data on total number of users and total amount sold is available by both World Health Organization Anatomical Therapeutic and Chemical classification (ATC)-codes and age groups.

For analyses of prescriber type, we obtained a 20% random sample of the Danish population alive at any point between 1 January 2001 and 31 December 2020 from the Danish Civil Registration System.¹⁰ For this sample, relevant prescriptions were obtained from the Danish National Prescription Registry,¹¹ including information on individual prescriptions, ATC-code and the prescriber identifier. The latter was used to categorise the issuer of each prescription as either general practitioner (including out-of-hours services), practicing specialist, hospital physician or *other* prescribers (e.g., dentists).

Prescriptions for quetiapine were identified by the ATC-code N05AH04. For comparison with other commonly used antipsychotics and other medications commonly used off-label for anxiolytic, sedative or hypnotic purposes (and subject to increasing attention¹²), we additionally identified prescriptions for **flupentixol** (ATC:N05AF01), chlorprothixene (ATC:N05AF03), **olanzapine** (ATC:N05AH03), **risperidone** (ATC:N05AX08), **aripiprazole** (ATC:N05AX12), **hydroxyzine** (ATC:N05BB01), **melatonin** (ATC:N05CH01), **pregabalin** (ATC:N03AX16) and **promethazine** (ATC:R06AD02).

Prescriptions were subsequently classified as *first-time prescriptions* (i.e. initiation) if there were no prescriptions for the same drug within 5 years prior to the reimbursement date. Otherwise, the prescription was classified as *subsequent prescription* (i.e. renewal).

2.2 | Analyses

Based on sales data from the Danish Register of Medicinal Product Statistics (including all users in Denmark), we described the use of quetiapine from 2001–2020 using 5 measures: (i) total number of users per calendar year (defined as filling at least 1 prescription within that year); (ii) 1-year prevalence as the number of unique users per 1000 inhabitants during that year; (iii) total consumption expressed in

What is already known about this subject

- Off-label use of antipsychotics is increasingly common.
- Off-label use of quetiapine is potentially problematic due to the risk of side-effects, especially weight gain and metabolic disturbances.
- Prior studies have indicated that quetiapine is increasingly prescribed by non-psychiatrists.

What this study adds

- General practitioners are responsible for the majority of prescriptions for quetiapine in Denmark, especially among the elderly.
- Future interventions to facilitate rational use of quetiapine, especially among adults, should be directed towards general practitioners.

World Health Organization defined daily doses (DDD) per 1000 inhabitants per day; (iv) average daily dose per user expressed as DDD per user per day; and (v) total amount sold expressed in DDDs. The total number of users, the derived 1-year prevalence proportions and the average daily dose per user were broken down by predefined age categories (0–17, 18–24, 25–44, 45–64, 65–79, ≥80 y) and sex. The total amount of quetiapine sold was broken down by sales in the primary sector (i.e., prescriptions filled at community pharmacies) and sales in the secondary sector (i.e., use in hospitals or out-patient clinics).

Based on data from the Danish National Prescription Registry (the 20% random sample of inhabitants in Denmark alive 2001–2020), we described the distribution of prescribers, using 4 categories: general practitioners, practicing specialists, hospital physicians and other. The distribution of prescribers was assessed both for first-time prescriptions, and for subsequent prescriptions, and broken down by age categories (as described above) and sex.

Lastly, we redid the analyses for the other medications selected for comparison.

Analyses were performed using Stata, version 17 (StataCorp, College Station, TX, USA).

3 | RESULTS

During 2020, 73 230 Danish inhabitants filled at least 1 prescription for quetiapine, corresponding to a 1-year prevalence for quetiapine-use of 12.6 users per 1000 inhabitants. From the introduction of quetiapine in Denmark in 2001 and onwards, the prevalence increased continuously, whereas the total consumption somewhat stabilized after 2013 (Figure 1a). The average daily dose was

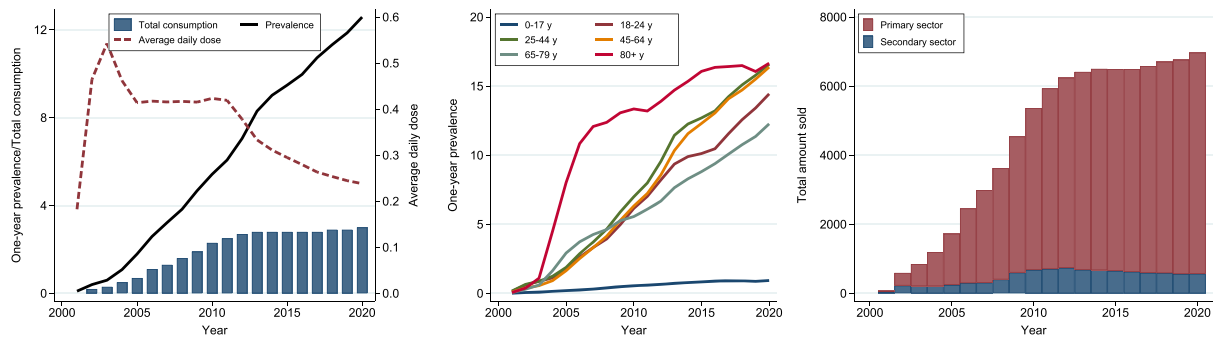


FIGURE 1 Overall development in the use of quetiapine in Denmark (2001–2020). Left panel: 1-year prevalence (users/1000 inhabitants), average daily dose per user (DDD/user/d) and total consumption (DDD/1000 inhabitants/d). Centre panel: 1-year prevalence (users/1000 inhabitants) by age groups. Right panel: Total amounts of quetiapine sold by sector (1000 DDDs). Source: The Danish Register of Medicinal Product Statistics. Available at: www.medstat.dk/en

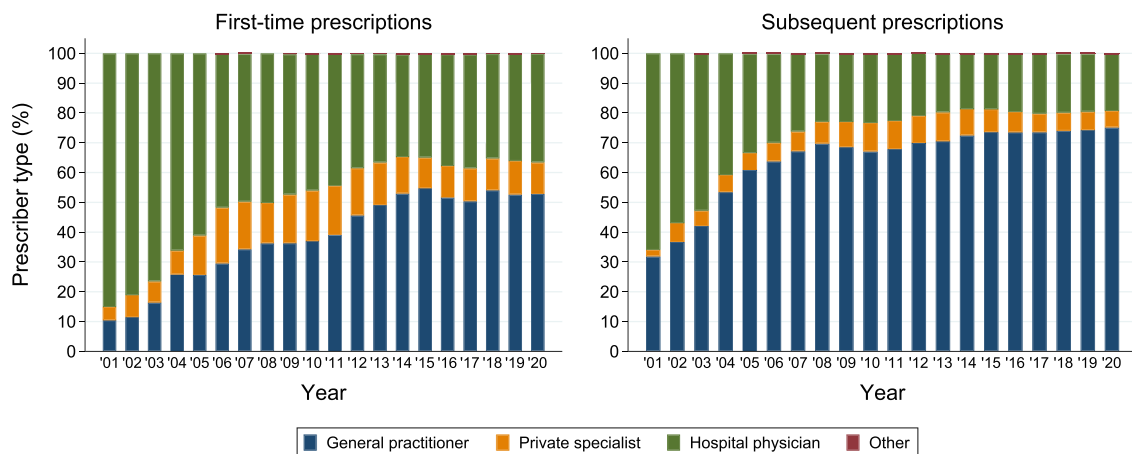


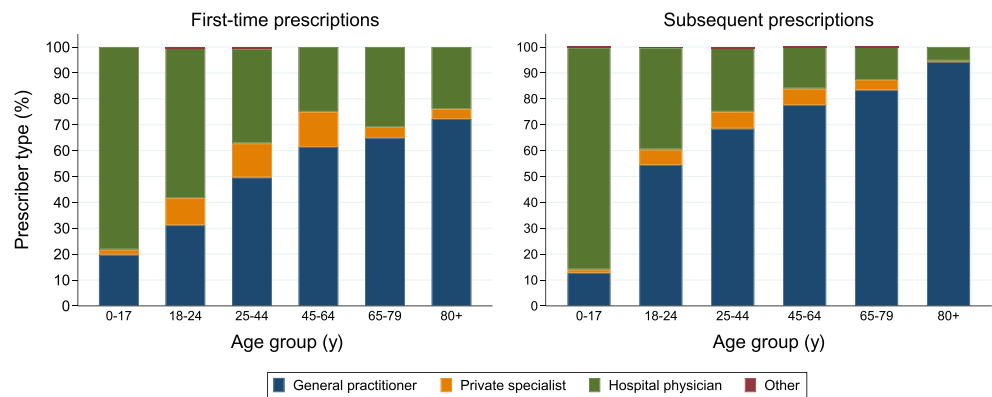
FIGURE 2 Proportion of prescriptions for quetiapine issued by general practitioners, private specialists and hospital physicians in Denmark (2001–2020)

approximately 0.25 DDD (100 mg) per user per day in 2020 (Figure 1a) with some variation between age groups from 43 mg/d in those aged ≥ 80 years to 117 mg/d in those aged 45–64 years (Table S1). The prevalence of quetiapine use rose similarly over the study period among age groups between 18 and 64 years (Figure 1b). However, an earlier and much steeper increase in use was seen around 2004 in those ≥ 80 years, and a less pronounced increase throughout the study period among those 0–17 years (Figure 1b). In 2020, 1075 users (1.5%) were ≤ 17 years, 8615 (12%) were ≤ 24 years, 15 380 (21%) were ≥ 65 years and 4535 (6%) were ≥ 80 years. Accordingly, in 2020, the 1-year prevalence reached 0.93 per 1000 among 0–17-year-olds, 14.4 per 1000 among 18–24-year-olds, 16.6 per 1000 among 25–44 year-olds, 16.4 per 1000 among 45–64 year-olds, 12.3 per 1000 among 65–79 year-olds and 16.7 per 1000 among ≥ 80 year-olds (Figure 1b). One-year prevalence were higher for females than males in all age categories (females/males 0–17 years: 1.2 vs. 0.7 users/1000 inhabitants, 18–24 years: 16.8 vs. 12.1, 25–44 years: 17.1 vs. 16.1, 45–64 years: 18.1 vs. 14.6, 65–79 years: 13.8 vs. 10.7 and ≥ 80 years: 17.4 vs. 15.5). In 2020, 92% of the total volume was sold by prescription (i.e., use outside hospitals, Figure 1c).

The proportion of various prescriber types for first-time and subsequent prescriptions for quetiapine from 2001 to 2020 is depicted in Figure 2. The proportion of first-time prescriptions issued by general practitioners rose during the study period mainly at the expense of prescriptions issued by hospital physicians (Figure 2a). The pattern was similar for subsequent prescriptions, although general practitioners issued a greater proportion of these (Figure 2b). In 2020, first-time prescriptions for quetiapine were issued by a general practitioner in 53% of users, a hospital physician in 36% of users and a practicing specialist in 11% of users (Figure 2a). Subsequent prescriptions were most often issued by a general practitioner (75%), while hospital physicians and practicing specialists accounted for 19 and 6% of subsequent prescriptions, respectively (Figure 2b, year 2020). There were no clear differences between males and females in the proportion of quetiapine prescriptions issued by general practitioners (males: 75% vs. females: 74%; Table S2).

The proportion of various prescriber types for quetiapine by age groups (2020) is depicted in Figure 3. Among those aged ≤ 17 years, 80% had their first prescription issued by a hospital physician or practicing specialist, while 20% was initiated by general practitioner.

FIGURE 3 Proportion of prescriptions for quetiapine issued by general practitioners, private specialists and hospital physicians in Denmark (2020) by age group



Among those aged 18–24 years, 69% had their first prescription issued by hospital physicians or a practicing specialist, while 31% were initiated by general practitioners. The proportion of first-time prescriptions issued by general practitioners increased with age of the patient, reaching 72% among those aged ≥ 80 years.

In 2020, the total number of quetiapine-users were considerably higher than for any other frequently used antipsychotic (Table S3). In comparison with other medications, commonly used off-label, the number of quetiapine-users was only exceeded by melatonin, although pregabalin and promethazine also had a considerable number of users (Table S2).

Similarly to quetiapine, a considerable proportion of first-time prescriptions for chlorprothixene (53%), flupentixol (59%) and risperidone (47%) were issued by a general practitioner (Figure S1). However, first-time prescriptions for aripiprazole and olanzapine were rarely issued by a general practitioner (6 and 17%, respectively), while subsequent prescriptions for all 5 antipsychotics were commonly issued by a general practitioner (57–91%; Figure S1). Both first-time and subsequent prescriptions for hydroxyzine, melatonin, pregabalin and promethazine were frequently issued by a general practitioner (Figure S2).

4 | DISCUSSION

We found that the number of quetiapine-users has increased considerably over the last 20 years; however, the average daily dose has decreased during the same period. Further, a large and increasing proportion of quetiapine prescriptions are issued in general practice, with general practitioners now responsible for most quetiapine prescriptions in adults.

Collectively, these findings suggest increasing use of quetiapine for off-label purposes especially in adults: both because the average quantity per user is much lower than those typically needed in treatment severe mental disorders, and because treatment is frequently initiated by general practitioners. The doses typically used for treatment of severe mental disorders (i.e. approved uses, such as schizophrenia, bipolar disorder) would be ≥ 400 mg/d, and such conditions are normally treated in a psychiatric setting.

Off-label use of quetiapine in general practice might occur for several reasons. The prescription of benzodiazepines has been subject to considerable attention for their association with dependency and adverse effects,¹³ and their use has substantially decreased over the last 20 years in Denmark.¹⁴ This might have left a *clinical vacuum* as general practitioners will meet patients, who may not need referral to a psychiatrist, but do need some intervention for symptoms such as anxiety or insomnia. As quetiapine has considerable anxiolytic and hypnotic properties, especially in low doses, it might be considered a viable treatment option for these patients. A Canadian study⁶ has explored physicians' reasons for use of quetiapine and found complex psycho-social needs, the positive attitude of colleagues towards quetiapine, and the apparent absence of adverse events with low doses, to be potential explanations for off-label use of quetiapine. Additionally, low-dose use of quetiapine has not been associated with increased risk of diabetes¹⁵ or increased risk of dependency, although reports accumulate on extramedical use of quetiapine.¹⁶ Additionally, the high prevalence (and low average doses) among those aged ≥ 80 years together with the substantial proportion of quetiapine being prescribed by general practitioners might suggest that quetiapine is used for treatment of off-label conditions as behavioural and psychological symptoms of dementia. Considerable off-label use has also been documented in other European countries, e.g. in Norway¹⁷ and among nursing home-residents in Switzerland.¹⁸ Off-label use of other psychotropic medications has also been observed (e.g., pregabalin¹⁹), and the attention to off-label use of psychotropic drugs could be considered as more general trend.

The main strength of the present study is the direct evidence of the prescriber type through a specific variable, which has been found to have high validity in prior studies.²⁰ Additionally, the nation-wide coverage of our data sources allowed us to investigate quetiapine utilization in an entire population, without the potential selection bias that could occur with studies based on e.g. specific insurance systems. Our study has a few limitations. We did not have information on the exact indication for initiating treatment with antipsychotics, and could thus not separate actual off-label use from on-label use. However, the prescriber identifier can be used as a proxy for off-label use as treatment with antipsychotics should generally only be installed after specialist evaluation—especially in children and adolescents. In addition,

the low average daily dose of quetiapine supports the interpretation that quetiapine is commonly used off-label. Furthermore, the prescriber identifier did not allow us to conduct a more detailed investigation of the medical specialty among the categories hospital physicians or practicing specialists, whether these were psychiatrists or nonpsychiatrists. This would also be of interest for future studies as e.g. frequent quetiapine use after discharge from internal medicine departments has been found to be quite common in the USA.²¹

In conclusion, we document a considerable and increasing potential off-label use of quetiapine in Denmark among adults, and that this development was mainly driven by general practitioners. The issue of off-label use is not restricted to quetiapine, but also concerns other psychotropic drugs. The reasons underlying this development should be investigated in detail, and any initiatives to reduce off-label use of quetiapine, especially among adults, should include general practitioners.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in.

<http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.²²

ACKNOWLEDGEMENTS

None.

M.H. was supported by a grant from Mental Health Services in the Region of Southern Denmark (grant A2957).

COMPETING INTERESTS

Mikkel Højlund reports personal honoraria for consultancy/lecturing from the Lundbeck Foundation and Otsuka Pharmaceutical Co., Ltd. unrelated to this work. Lotte Rasmussen reports participation in research projects funded by Novo Nordisk with no relation to the work reported in this paper. Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all regulator-mandated phase IV-studies, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. The remaining authors reports no conflict of interest.

AUTHOR CONTRIBUTIONS

M.H., L.R., T.M.O. and A.P. designed the study. M.H. and M.O. analysed the data. M.H. and L.R. drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the final version before submission.

DATA AVAILABILITY STATEMENT

Data on overall drug use statistics are publicly available from the Danish Health Data Authority at www.medstat.dk. Data on individual prescriptions used for assessment of prescriber profile is not publicly

available due to confidentiality issues but can be obtained through application to the Danish Health Data Authority.

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SUPPORTING INFORMATION

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How to cite this article: Højlund M, Rasmussen L, Olesen M, Munk-Olsen T, Pottegård A. Who prescribes quetiapine in Denmark? *Br J Clin Pharmacol*. 2022;88(9):4224-4229. doi:[10.1111/bcp.15388](https://doi.org/10.1111/bcp.15388)