

Free-of-charge dispensing of antipsychotics for schizophrenia in Denmark: Impact on the nationwide prescription registry and redemption of somatic medications

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Abstract

Objective: Free-of-charge dispensing of antipsychotics for schizophrenia was introduced in Denmark around 2008. However, free-of-charge dispensing is not recorded in the Danish National Prescription Register (DNPR), potentially introducing bias and misclassification.

Methods: We identified all 30 275 individuals with a first-episode schizophrenia diagnosis in Denmark between 1 January 1999 and 1 March 2017 including all redeemed prescriptions registered in the DNPR during the 2 years after the schizophrenia diagnosis. For each calendar year, we calculated the proportion of individuals who had filled ≥ 1 prescription for psychotropic and/or somatic medications within the first 2 years after the schizophrenia diagnosis.

Results: From 2007 to 2017, the proportion of individuals with prescription-records for any psychotropic medication during the 2 years after the schizophrenia diagnosis decreased from 88% to 74%, particularly antipsychotics (from 83% to 61%) and antidepressants (from 49% to 35%). This was particularly observed among those aged 18–30 years at the schizophrenia diagnosis. A similar decrease was not observed for prescription-records of somatic medications.

Conclusion: The introduction of free-of-charge antipsychotics has affected the redemption of specific psychotropic drugs in the DNPR in first-episode schizophrenia. This limitation needs to be considered in register-based studies and emphasizes the need to identify solutions.

KEYWORDS

antipsychotics, Danish National Prescription Register, free-of-charge medication, schizophrenia

Christopher Rohde and Mikkel Højlund contributed equally to this work.

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1 | INTRODUCTION

Schizophrenia is a severe mental disorder with high psychiatric and somatic comorbidity.¹⁻³ In addition to specific antipsychotic treatment, patients often require other psychotropic drugs, such as antidepressants, and somatic medications. One major clinical challenge in the treatment of schizophrenia is that many patients have low adherence to pharmacological treatment,⁴ which can be caused by side effects, difficulties paying for treatments or lack of insight into their disorder.⁴ To improve adherence in first-episode schizophrenia in Denmark, antipsychotic drugs for relapse prevention were offered free-of-charge from 2008 and onwards, meaning that newly diagnosed patients with schizophrenia would receive antipsychotic medications from their treating hospital at no cost during the first 2 years after the diagnosis.⁵⁻⁸

Free-of-charge medications are dispensed for several patient groups with chronic conditions but dispensed by hospital pharmacies and not community pharmacies. Outpatient prescriptions in Denmark are usually collected at community pharmacies and thus registered in the Danish National Prescription Register (DNPR).^{8,9} The DNPR contains individual-level data of all prescriptions redeemed at all Danish community pharmacies since 1995, which can be used in combination with other nationwide registers,⁹⁻¹³ making the DNPR a powerful and frequently used tool in epidemiological research.⁹ Hence, as free-of-charge medications are not recorded in the DNPR,⁷ the introduction of free-of-charge antipsychotics may have affected the completeness of DNPR data for patients with first-episode schizophrenia and led to fewer registered redeemed prescriptions. This may result in two major challenges. First, the concept of free-of-charge medication may have affected the data quality of registering of antipsychotics for schizophrenia. Second, free-of-charge medications may also have affected prescription patterns for other medications in this population. Although drugs that are not specific for the treatment of the disorder (i.e., other psychotropic drugs, such as antidepressants, or somatic drugs) are not covered, it can be hypothesized that for a vulnerable group like patients with schizophrenia, having fewer visits to a community pharmacy could lead to a decrease in redeemed prescriptions for other medications, for example, somatic drugs or other psychotropic drugs.

1.1 | Aims of the study

Hence, the introduction of free-of-charge medication for patients with schizophrenia, although representing a valuable tool for the treatment of the individual patient,

may have affected the registration patterns in the DNPR, both regarding antipsychotic drugs and other prescription-based drugs. In this nationwide study among all patients with a first-episode schizophrenia in Denmark between 1999 and 2017, we aimed to answer the following questions:

1. Has the introduction of free-of-charge antipsychotics resulted in a decrease of redeemed antipsychotics in the DNPR?
2. Has the introduction of free-of-charge antipsychotics resulted in a simultaneous decrease of redeemed prescriptions for other psychotropic drugs and somatic medications?

2 | MATERIALS AND METHODS

We addressed these study questions via the following approaches. In order to obtain an overview of the actual implementation patterns of free-of-charge antipsychotics in the five different Danish administrative regions, we collected information from each of the regions to describe the implementation of free-of-charge antipsychotics for individuals with first-episode schizophrenia. To study the development in DNPR coverage for antipsychotics and patterns of usage of other psychotropic medications and somatic medications, we conducted a nationwide descriptive study based on Danish health-care registers.

2.1 | Introduction of free-of-charge antipsychotics in the Danish regions

Since 1 January 2007, Denmark has been divided into five administrative regions. The main responsibility of the regions is to administrate the health-care system within each region, primarily consisting of all public hospitals and general practitioners.¹⁴ The five regions with the respective number of inhabitants are Northern Denmark Region (approximately 600 000), Central Denmark Region (approximately 1 300 000), Region of Southern Denmark (approximately 1 200 000), Region Zealand (approximately 825 000) and Capital Region of Denmark (approximately 1 800 000).

On 1 January 2008, all Danish regions officially introduced free-of-charge treatment with antipsychotic drugs during the first 2 years after a first-episode schizophrenia diagnosis. In order to investigate potential discrepancies in the individual introduction and implementation timing between the five regions, we contacted several different departments within each region, including psychiatric and administrative departments, hospital

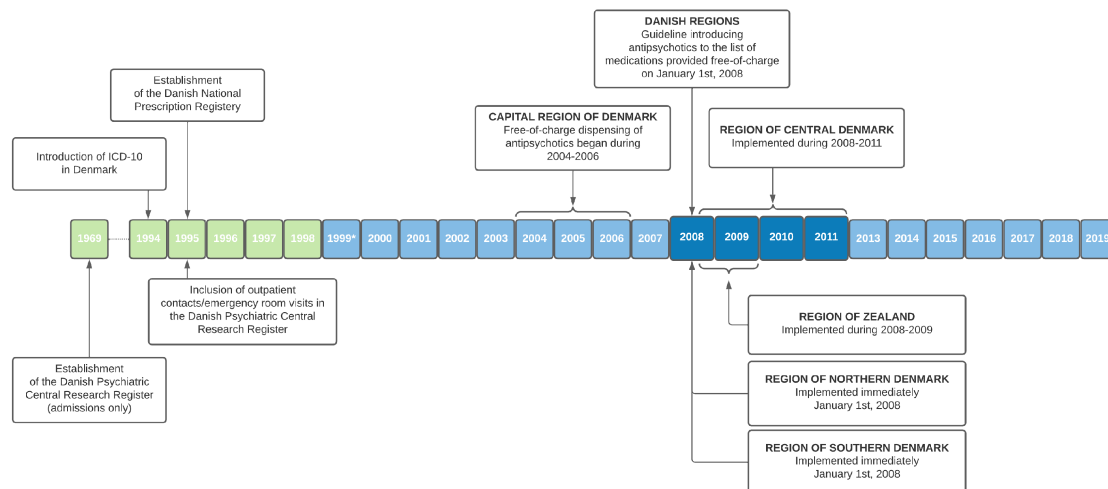


FIGURE 1 Implementation of free-of-charge antipsychotic medication in the respective Danish regions. *Note:* *The study cohort included all individuals diagnosed with schizophrenia (ICD-10 F20) between 1 January 1999 and 1 March 2017. The individual observation period was the 2 years after the first schizophrenia diagnosis, and the study period covered from 1 January 1999 to 1 March 2019.

pharmacies and early-intervention services for first-episode psychosis (OPUS-teams).¹⁵

2.2 | Register-based study

2.2.1 | Design and data sources

We performed a descriptive study based on the Danish nationwide registers. At the time of birth or immigration, all residents are assigned a unique personal registration number enabling registration in the Danish Civil Registration System¹⁰ and linkage of individual-level data from various registers.⁹⁻¹³ The Danish Data Protection Agency and Statistics Denmark have approved the use of the data for this study.

We obtained information from two nationwide registers (Figure 1): the Danish Psychiatric Central Research Register (DPCRR), which contains information on diagnoses from all inpatient (since 1969) and outpatient and psychiatric emergency room (since 1995) contacts at Danish psychiatric hospitals.¹¹ The DNPR contains data on all prescriptions filled at Danish community pharmacies since 1995.⁹ The DPCRR does not contain information on medication use during inpatient hospitalizations.

2.2.2 | Study population

We identified all individuals registered with a diagnosis of schizophrenia according to International Classification of Diseases, 10th revision (ICD-10 code: F20)¹⁶ during an inpatient, outpatient or emergency room contact registered in the DPCRR between 1 January 1999 and 1 March

2017. From this population, we excluded individuals with records of a schizophrenia diagnosis (1) before 1 January 1999, to have a “wash-out” period of 5 years because of the change from ICD-8 to ICD-10 in 1994,¹¹ which has been used in previous studies,¹⁷ or (2) before the age of 10 years, as a diagnosis at such a young age is rare and difficult.^{1,2} We defined the index date as the date of the first contact to a psychiatric hospital (i.e., either an inpatient, outpatient or emergency room contact) leading to a diagnosis of schizophrenia. However, we excluded patients who only had a schizophrenia diagnosis from an emergency room visit alone, without a subsequent inpatient or outpatient contact, because of the diagnostic uncertainty of these brief treatment contacts.

2.2.3 | Pharmacotherapy

For each individual, we identified all redeemed prescriptions within 2 years after the index date and categorized them into the following drug classes based on ATC codes:

1. Antipsychotics (N05A, excluding N05AN01);
2. Other psychotropic drugs, including antidepressants (N06A), mood stabilizers (lithium [N05AN01] and anticonvulsants [N03AB02, N03AF01, N03AF02, N03AG01, N03AX09, N03AX11 and N03AX12]), benzodiazepines (N03AE01 and N05BA) and hypnotics (N05C);
3. Somatic medications (all other ATC codes excluding N03-N07).

Table S1 provides a detailed list of all ATC codes.

2.2.4 | Statistical analyses

To investigate time trends in the prevalence of psychopharmacological and somatic drug use from 1999 to 2019, we calculated the proportion of individuals with schizophrenia with an index date in the respective calendar year who had redeemed at least one prescription for the drugs of interest within 2 years after the index date. The 2-year prevalence estimates are presented according to the year of the index schizophrenia diagnosis. This was also performed for psychotropic and somatic drugs, with both being divided into (i) any prescription and (ii) prescriptions for the specific groups of medications (Table S1).

Furthermore, we conducted the analysis stratified by administrative regions to investigate if the proportion of individuals redeeming prescriptions for antipsychotics had changed in each region and if a change could be related to the introduction of free-of-charge antipsychotics in the respective regions.

As treatment differs depending on the age of the individuals, we investigated differences in treatment patterns depending on age at the time of diagnosis and show treatment patterns within the following three age groups: 10–17 (i.e., adolescents), 18–29 (i.e., young adults) and ≥ 30 years (late schizophrenia diagnosis).

Since our study includes all patients with a schizophrenia diagnosis within the study period, and since we claim no inference to other study populations, our data cannot be considered a sample and are thus presented without statistical tests and confidence intervals. We used STATA version 17 for all statistical work.

3 | RESULTS

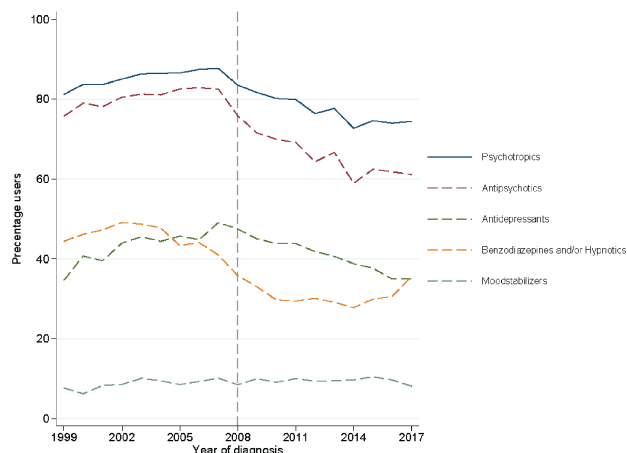
3.1 | Differences in timing of implementation of free-of-charge antipsychotics

The official introduction of free-of-charge antipsychotics for patients with a first-episode schizophrenia diagnosis became effective on 1 January 2008; however, implementation schedules of the five regions differed by some years (Figure 1).

3.2 | Changes between 1999 and 2019 in medication use patterns within the 2 years after the schizophrenia diagnosis

We identified 30 275 individuals with a first-episode schizophrenia diagnosis (58% males, mean age at

Panel A: Psychotropic drugs by ATC-class



Panel B: Somatic drugs by ATC-class

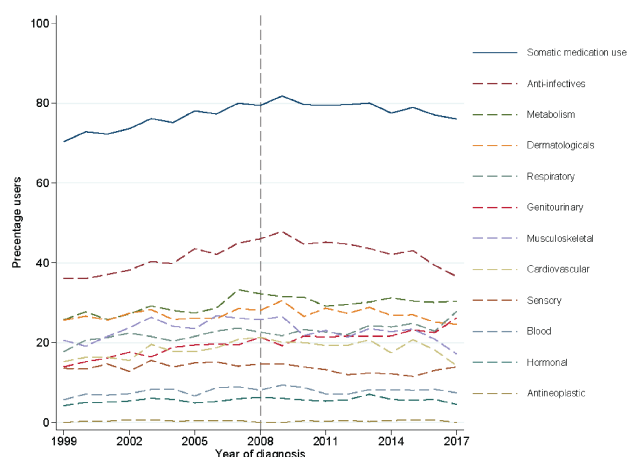


FIGURE 2 Proportion of individuals with first-episode schizophrenia filling prescriptions for (A) psychotropic medications and (B) somatic medications within the 2 years following the first-episode schizophrenia diagnosis. *Note:* Analyses covers 30 275 individuals diagnosed with schizophrenia from 1 January 1999 to 1 March 2017. The graphs show, for each calendar year, the proportion of patients with a first-episode schizophrenia diagnosis who were prescribed psychotropic (Panel A) and somatic (Panel B) medications in the 2 years following the date of the schizophrenia diagnosis. The dotted vertical line indicates the year when the Danish regions introduced free-of-charge antipsychotic drugs for patients with first-episode schizophrenia. This occurred on 1 January 2008, and the figure shows a clear decrease in redeemed prescriptions from 2007 to 2008. Abbreviations: ATC: WHO Anatomical Therapeutic and Chemical-classification system

diagnosis 34 years) in the period between 1 January 1999 and 1 March 2017.

The percentage of individuals filling prescriptions for any psychotropic drug during the 2 years after the schizophrenia diagnosis was relatively stable during the period between 1999 and 2007 (Figure 2A), showing a slight increase for both antipsychotics and antidepressants,

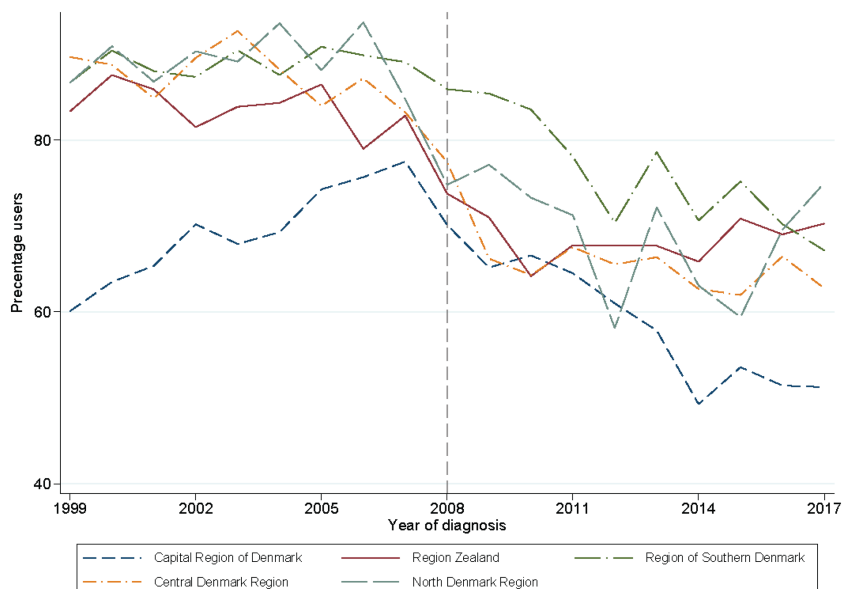


FIGURE 3 Proportion of users of antipsychotic drugs during the 2 years after the schizophrenia diagnosis among 30 275 individuals diagnosed during 1999 to 2017, stratified by administrative region. *Note:* Analyses covers 30 275 individuals diagnosed with schizophrenia from 1 January 1999 to 1 March 2017. The graphs show, for each calendar year and separately for the five Danish regions, the proportion of patients with a first-episode schizophrenia diagnosis who were prescribed antipsychotic medications in the 2 years following the date of the schizophrenia diagnosis. The dotted vertical line indicates the year when the Danish regions introduced free-of-charge antipsychotic drugs for patients with first-episode schizophrenia. This occurred on 1 January 2008, and the figure shows a clear decrease in redeemed prescriptions from 2007 to 2008.

while the use of benzodiazepines and hypnotics decreased from 2002. We observed a considerable decrease in all types of psychotropic prescriptions from 2007 and onwards, except for mood stabilizers (Figure 2A). During the period from 2007 to 2017, the percentage of individuals with redeemed prescriptions during the 2 years after the schizophrenia diagnosis decreased for any psychotropic drug (from 88% to 74%), antipsychotics (from 83% to 61%) and antidepressants (from 49% to 35%). The most frequently used antipsychotic drugs after the introduction of free-of-charge antipsychotics were quetiapine and aripiprazole and risperidone and olanzapine (Figure S1). The proportion of users who filled prescriptions for somatic medications was not subject to the decrease observed for psychotropic drugs around 2007 (Figure 2B).

Analyses by regions showed differences between the regions, with the decrease in antipsychotic drug redemptions matching the timing of the implementation of free-of-charge antipsychotics in each region (Figure 3). Particularly the Capital Region of Denmark showed differential patterns, showing an increase from 60% in 1999 to 77% in 2007 followed by a decrease to 51% in 2017.

When studying differences depending on age, the decrease in the proportion of individuals with psychotropic prescription fills was particularly evident among

those aged 18–29 years at the time of the schizophrenia diagnosis (Figure S2). In this group, the proportion of users redeeming a prescription for an antipsychotic increased from 66% in 1999 to 80% in 2007 but decreased again to 50% in 2014 followed by a slight increase towards 2019.

The proportion with prescription fills for somatic prescriptions was rather stable across age groups (Figure S3). In all age groups, approximately 80% of patients had filled at least one prescription for a somatic drug during the 2 years after the schizophrenia diagnosis.

4 | DISCUSSION

The Danish regions introduced antipsychotics for newly diagnosed patients with schizophrenia to the list of free-of-charge medication on 1 January 2008, but it has not been studied whether this has affected the quality of DNPR data. The present study highlights two important aspects: First, the implementation of free-of-charge antipsychotics varied between regions by some years. Second, the proportion of individuals filling a prescription for an antipsychotic during the first 2 years after their schizophrenia diagnosis decreased by 22% from 2007 to 2019, in particular among those aged 18–29 years (showing a

decrease of 30% from 2007 to 2019). This decrease was also observed for antidepressant drugs but not for somatic medications.

Hence, among patients with first-episode schizophrenia, the decrease of registered prescriptions for antipsychotic medications during the first two post-diagnostic years correlates with the introduction of the free-of-charge concept. The most obvious explanation for this is that free-of-charge medication is not registered in the DNPR, supporting our hypothesis that the introduction of free-of-charge antipsychotic medication has affected DNPR data and consequently the possibilities of performing research on the safety and effectiveness of antipsychotic drugs during this critical period of the schizophrenia disorder. A potential explanation for the fact that redeemed antipsychotics did not drop to 0% may be our definition of antipsychotic use. One redeemed prescription for any type of antipsychotic drug was sufficient, and patients may have received prescriptions from other clinicians than their primary outpatient psychiatrist (e.g., general practitioner or in the emergency room).

To put our findings into context, during 2016, 1744 individuals were diagnosed with schizophrenia in Denmark,¹⁸ and 34% of these (585 individuals) did not have any records of prescription fills for antipsychotic drugs in the DNPR during the two post-diagnostic years. These individuals might have received antipsychotic medication free-of-charge from hospitals, but their antipsychotic medication use status is unknown when relying on the DNPR. For studies in first-episode schizophrenia, the 585 individuals constitute a considerable proportion of subjects (34%), whereas they constitute less than 0.5% in relation to the total number of users of antipsychotics in Denmark in 2016 (106 710 individuals).¹⁹

Importantly, we did not observe a similar trend for somatic medications, suggesting that free-of-charge antipsychotic medications did not affect prescription patterns of somatic medications for patients with schizophrenia.

To the best of our knowledge, this is the first study evaluating the effects of free-of-charge medication on DNPR coverage, despite the fact that free-of-charge medications for almost 15 years have been dispensed to several patient groups, such as cancer, tuberculosis or congenital immune deficiency.⁶ Our findings show a clear limitation in the otherwise high-quality Danish nationwide registers.^{9,20–24}

The question is how to solve this challenge and ensure correct and complete registration of real-world prescription patterns. Discontinuing the dispensing of free-of-charge medication is not relevant, as this concept has a commendable purpose. Potential solutions could be to ensure that data on medications dispensed by Danish

hospitals are registered in the DNPR or that a register covering medications dispensed by hospital pharmacies can be combined with DNPR data. This would be relevant for all types of free-of-charge medications. For example, biological drugs used for cancer patients are primarily dispensed by hospitals, clearly limiting possibilities to study important real-world outcomes of these high-risk drugs, such as treatment and safety, on a population level.

4.1 | Conclusion

From 2007 and onwards, there is a considerable decrease in the DNPR of redeemed antipsychotic drug prescriptions during the 2 years after the schizophrenia diagnosis, which is consistent with the introduction of free-of-charge antipsychotics. This illustrates a limitation in the DNPR during an important period of the schizophrenia disorder, which needs to be considered in future pharmacoepidemiological studies. These findings should lead to considerations how to incorporate data on medication dispensed by hospital pharmacies for outpatients in the DNPR in order to obtain more correct data on medication use patterns. Furthermore, the issue of inadequate registration should be investigated for other patient populations with free-of-charge dispensing of essential medications.

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CONFLICTS OF INTEREST

CR received the 2020 Lundbeck Foundation Talent Prize. MH has received personal honoraria for consultancy from the Lundbeck Foundation. OKF has received speaker fees from Lundbeck Pharma A/S and is a consultant for WCG Clinical, Inc., all unrelated to the present work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Danish Health Data Authority. Restrictions apply to the availability of these data, which were used under licence for this study.

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SUPPORTING INFORMATION

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

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