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Data Resource Profile

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Data Resource Profile: The Danish National Prescription Registry

Anton Pottegård,[1]* Sigrun Alba Johannesdottir Schmidt,[2] Helle Wallach-Kildemoes,[3] Henrik Toft Sørensen,[2] Jesper Hallas[1] and Morten Schmidt[2,4]

[1]Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense, Denmark, [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, [3]Social and Clinical Pharmacy, University of Copenhagen, Copenhagen, Denmark and [4]Department of Internal Medicine, Regional Hospital of Randers, Randers, Denmark

*Corresponding author. Clinical Pharmacology and Pharmacy, University of Southern Denmark, JB Winsløwsvej 19, 2 5000 Odense C, Denmark. E-mail: apottegaard@health.sdu.dk

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Data resource basics

Nationwide Danish data for research

Denmark has a long tradition of creating nationwide administrative and health registries.[1,2] Examples include its registries on causes of death,[3] hospitalizations[4] and cancer,[5] and on socioeconomic parameters such as income[6] and education.[7] A registry central to Danish pharmacoepidemiology is the Register of Medicinal Product Statistics, established in 1994. This registry includes data on all drugs sold in primary care or purchased for use in Danish hospitals. Whereas aggregate data on gross sales of drugs are freely available online [www.medstat.dk],[8] individual-level data on prescriptions filled by Danish residents at community pharmacies are available as an independent subregistry—the National Prescription Registry (NPR).[9] NPR data have been available to researchers through Statistics Denmark since 2003, and more recently also through the Danish Health Data Authority. Given these recent changes in data access and the need to evaluate the Registry's strengths and limitations, this data resource profile provides a review of the NPR, with emphasis on its role in research.

Prescription drugs in the Danish healthcare system

The Danish National Health Service[10] provides universal tax-supported healthcare, guaranteeing all Danish residents free access to general practitioners (GPs) and hospitals. GPs are the cornerstone of the Danish healthcare system, providing health care free at the point of delivery and acting as gatekeepers for specialist care. GPs often resume the responsibility for treatment after a diagnosis has been established by a specialist. Therefore, GPs issue \most prescriptions in Denmark.[11]

Patient co-payments are required for prescription drugs. A central authority (the Reimbursement Committee) decides whether a particular medicine is reimbursable, and all reimbursable medicines are covered by a tax-financed drug reimbursement scheme. According to this scheme, the percentage of reimbursed costs increases with an individual's total expenditures for reimbursable medicines during the most recent 365 days.[12] At present, the first 130€ is paid in full by the patient (except for children, who immediately receive a 60% reimbursement). Then, reimbursements cover increasing percentages of costs, in steps of

Table 1. Key variables included in the Danish National Prescription Registry

Variable description	Variable name	Explanation
Patient details		
Personal identifier	CPR	Civil Personal Register (CPR) number, which encodes date of birth and gender and enables unambiguous linkage to other Danish registries
Dispensing details		
Date	EKSD	Date of completed sale/debit/dispensing
Packages	APK	Number of packets/units of the product dispensed
Product code	VNR	Product code of the product dispensed
Name*	PNAME	Product name
ATC*	ATC	WHO-defined Anatomical Therapeutical Chemical code
DDD*	VOLUME	Number of defined daily doses per package
Amount*	PACKSIZE	Number of tablets/units per package
Strength*	STRNUM	Numerical strength per tablet/unit
Form*	DOSFORM	Formulation of the drug
Other		
Prescriber	RECU	Identifier for the prescriber, e.g. a hospital or a general practice unit
Pharmacy	IBNR	Identifier for the dispensing pharmacy

*Within Statistics Denmark, these variables are included directly in the registry, whereas at the Danish Health Data Authorities they are obtained via linkage with the product code.

50%, 75% and 85%, until out-of-pocket expenditures are capped at about 500€.[13] All residents are automatically covered by the reimbursement scheme.

The Danish community pharmacy sector consists of 314 large pharmacies, on average covering about 17 000 residents and serving about 600 customers per day. Pharmacies are privately operated, but subject to state regulation. The Danish Ministry of Health and the Danish Medicines Agency control the sector through a licensing system, which determines the number of pharmacies and their location. Although patients are not obliged to use a single pharmacy, they generally are loyal to their preferred pharmacy.[11]

Prescription drugs are mainly dispensed in their original packs. No upper limit exists for the amount of drug that can be dispensed at any one time. However, when medical treatment is stable, patients typically receive a 3-month supply (corresponding to packages of 100 tablets for drugs used once daily).[14] About 62 000 Danish residents, mostly elderly, receive their drugs as dose-dispensed medications with a 14-day supply period.[15]

Data collected

Coverage

Since 1995, the NPR has recorded detailed information on prescriptions redeemed in Denmark. Drugs prescribed to nursing-home residents are also included. Prescriptions for children were issued under the name of the mother until 1996, and then under the child's name. There are three notable instances when drugs are not filled at community pharmacies and thus are not captured by the registry: (i) drugs used during hospital admissions; (ii) drugs used by certain institutionalized individuals (typically due to psychiatric illnesses); and (iii) drugs supplied directly by hospitals or treatment centres (e.g. chemotherapeutic agents, immunosuppressant drugs and methadone for substance abusers).

Contents

The NPR receives data recorded in the electronic dispensing systems of community pharmacies. The Registry contains 46 variables that characterize each redeemed prescription, including those describing the patient, the drug dispensed, the health provider issuing the prescription and the dispensing pharmacy. An overview of the main variables is provided in Table 1. Complete documentation is provided in Danish by Statistics Denmark[16] and by the Danish Health Data Authority.[17]

The core variables are the Civil Personal Register (CPR) number (a unique personal identifier used in all Danish registries), the dispensing date (i.e. date the prescription was redeemed) and the Nordic article number (a unique six-digit code designating each drug package). This number encodes several other variables, including package size, strength, form and Anatomical Therapeutic Chemical (ATC) code. The ATC system, a hierarchical classification system developed by the World Health Organization (WHO), is described in full elsewhere[18] and is searchable at [http://www.whocc.no/atc_ddd_index/]. The total amount of drug purchased can be calculated by combining data on package size, strength and number of dispensed

packages. As an alternative, the number of defined daily doses (DDDs) is also recorded in the NPR.[18]

Data quality

Data in the NPR are considered both complete and valid as from 1995. Although data were also collected in 1994, they are not considered of sufficient quality to be used for research purposes and are therefore not made available to researchers. Use of bar codes throughout the dispensing process at Danish pharmacies minimizes the risk of data entry errors. As well, pharmacies receive a financial incentive for complete registration of all purchases through the reimbursement scheme.

Only two studies, performed in the mid-1990s, have directly validated the content of the NPR.[19,20] Each examined a specific therapeutic group (oral anticoagulants[19] and strong analgesics[20]) and reported a high degree of completeness of registration. These studies were based on the regional Aarhus University Prescription Database (AUPD)[21] (see below), whose data are identical to those also included in the NPR. An indirect validation has also been performed, comparing data in the NPR with women's self-reported drug use during pregnancy,[22] and a high degree of concordance was found.

The validity of recorded prescriber information has previously been questioned, because pharmacy staff manually enter prescriber information from non-electronic prescriptions. However, a recent study found that the validity of classification into prescriber type (GPs, hospital physicians and physicians in private practice) was generally high for non-electronic prescriptions.[23] Since the proportion of non-electronic prescriptions is declining and the variable is considered valid for electronic prescriptions, prescriber information in the NPR may be considered valid overall (at least in recent years). Still, the sensitivity towards prescriptions issued by private-practising specialists remains a concern.[23]

Data resource use

NPR data have been used extensively in pharmacoepidemiological research.[24] Thus, the registry has been used as a stand-alone resource for basic drug utilization studies,[25] and also in studies of treatment quality.[26] The full potential of the NPR is enabled through linkage to other registries, e.g. the Danish National Patient Registry,[4] allowing population-based drug outcome studies. Flawless linkage is achieved using the CPR number assigned to all Danish residents since 1968.[2] This has been employed in studies of acute drug effects, with outcomes such as risk of haemorrhage.[27] Also, collection of data in the NPR for more than 20 years allows for studies of long-term exposure or diseases with a long latent period, such as associations between prescription drug use and cancer.[28] Prescriptions recorded in the NPR also have been used as disease proxies, particularly when diseases cannot be identified with sufficient sensitivity based solely on hospital-based diagnoses. Examples include using drugs to treat alcohol abuse to identify alcoholics,[29] using antibiotics to identify acute infections[30] and using antidiabetic drugs to identify patients with diabetes.[31]

Strengths and weaknesses

Weaknesses

The NPR's major limitation is lack of data on indication for use, intended duration and dosage. This problem is further complicated by 'original pack dispensing', i.e. drugs are supplied for a period of time that is in principle unknown. Thus, researchers need to make transparent and educated assumptions regarding treatment duration, based on treatment guidelines, pill strength, package size and number of packages. This is particularly important in studies mapping person-time of exposure to a given drug. Examples are studies of NSAID-associated risks of myocardial infarction[32] and studies of drug use during pregnancy.[33] Necessary assumptions can be made using the waiting time distribution[34] or specific clinical input, e.g. assuming an intake of one tablet a day for statin[35] or antiplatelet treatment.[27] Regardless of the basis for such assumptions, it is necessary to consider deviations caused by irregular prescription refills (e.g. stockpiling) or non-adherence. This issue is of particular concern in studies of drugs used on an 'as needed' or irregular basis (e.g. non-aspirin NSAIDs[34]) and in studies using designs that rely heavily on the exact timing of drug intake (e.g. use of self-controlled designs in studying acute drug effects[36]).

Another limitation of the NPR is its lack of data on over-the-counter (OTC) drugs. However, this limitation does not preclude analyses of drugs that can be obtained both with and without prescriptions. First, it is possible to estimate the extent of OTC use through the online datasource [Medstat.dk].[8] Second, OTC use is often unequally distributed in the population, as persons with frequent use of reimburseable medications (e.g. elderly individuals) have a financial incentive to obtain them by prescription. A study that quantified the potential of the NPR to capture individual-level aspirin and non-aspirin NSAID use[37] found that its ability to identify NSAID use was high. It also found that unless the relative risk measure was very high, misclassification due to OTC use (even at a magnitude similar to that of NSAIDs) had little impact on the

relative risk estimate, rate difference or aetiological fraction associated with the drug.[37].

Left truncation or censoring due to lack of data before 1995 is also a concern in some studies. While the time frame of the NPR is superior to many other similar registries,[24] it still may be too short to correctly identify the time of treatment initiation or cumulative dose of a drug. In some situations, the resulting potential misclassification can be assessed by comparison with the regional prescription registries, i.e. the Odense Pharmacoepidemiological Database (OPED)[38] or AUPD,[21] which date back to 1989–90 (see below).[39]

Strengths

The NPR provides more than 20 years of nationwide coverage, which in the Nordic setting is paralleled only by the Finnish prescription registry established in 1994.[24] Another important strength is its national coverage. Other data sources, such as those based on American health maintenance organizations, may have coverage beyond 20 years, but most have large annual turnover in beneficiaries.[40] In studies using the NPR, loss to follow-up is caused only by emigration, which can be traced through the Danish Civil Registration System.[2]

In contrast to other large databases, such as the UK Clinical Practice Research Datalink (CPRD)[41] and the Health Improvement Network (THIN),[42] the NPR is based on redemption of prescriptions rather than on issued prescriptions. This provides an important advantage, as a filled prescription is a better surrogate for actual drug intake than a written prescription. Thus, about one-tenth of prescriptions issued in Danish general practices are not subsequently filled (primary non-adherence).[43] For prescriptions that were filled, the date of dispensing was a valid proxy for the date of issue, as most patients filled their prescription within 2 days.[43]

Another important feature of the NPR is its inclusion of drugs used by nursing-home residents, unlike the otherwise similar Finnish and Norwegian prescription registries.[44,45] This feature limits differential misclassification of exposure status due to frailty among elderly individuals and permits investigation of drug consumption among the very elderly.

Comparison with other sources of prescription data

The NPR is compared with other Danish and Nordic prescription registries[24] in Table 2. Denmark has three other prescription registries: two regional registries (OPED[38] and AUPD[21]) and one nationwide registry (Danish

Table 2. Comparison of the Nordic prescription registries

	Denmark				Sweden	Norway	Iceland	Finland
	Danish National Prescription Registry (NPR)	Danish National Health Service Prescription Database (DNHSPD)*	Odense Pharmacoepidemiological Database (OPED)	Aarhus University Prescription Database (AUPD)	Swedish Prescribed Drug Register (SPDR)	Norwegian Prescription Database (NorPD)	The Icelandic Medicines Registry (IMR)	Finnish Prescription Register (Reseptitiedosto)
Geographical coverage	Entire Denmark	Entire Denmark	Southern Denmark	Northern Denmark	Entire Sweden	Entire Norway	Entire Iceland	Entire Finland
Population coverage	5.6 mill	5.6 mill	1.2 mill	1.8 mill	9.5 mill	5.0 mill	0.32 mill	5.4 mill
Starting year	1995	2004	1990	1989	2005	2004	2003	1994
Drug coverage	All prescription drugs	Reimbursed prescription drugs	Reimbursed prescription drugs	Reimbursed prescription drugs	All prescription drugs	All prescription drugs	All prescription drugs	Reimbursed prescription drugs
Requires anonymization	Yes	No	No	No	No	Yes	Yes	Yes
Data transfers outside country?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Mill, million.
*Previously referred to as Danish National Database of Reimbursed Prescriptions (DNDRP).

National Health Service Database, DNHSD).[46] The OPED has covered the Region of Funen (600 000 inhabitants) since 1990 and the Region of Southern Denmark (1 200 000 inhabitants) since 2007. The AUPD has covered the former North Jutland county since 1989 and most of the Central and Northern Denmark Regions (1 800 000 inhabitants) since 1998. The DNHSD has nationwide coverage since 2004, and has to a large extent replaced the use of AUPD.[46] Importantly, these three additional prescription registries cover only reimbursed prescription drugs, precluding analysis of such agents as benzodiazepines, oral contraceptives and certain antibiotics. However, in contrast to the NPR, they can provide data in a non-anonymized form to researchers when necessary approvals are obtained. This is particularly useful in intervention studies involving certain drugs, in validation studies and in other studies where additional information, for instance from medical charts, is essential.

Data resource access

Data access

Since 2003, the NPR has been available to researchers through an anonymized duplicate copy stored on servers within Statistics Denmark. As well, it has been possible to access the NPR on servers within the Danish Health Data Authority since 2014. The servers hosted by the Research Service at Statistics Denmark have been described previously,[47] and the set-up at the Danish Health Data Authority is very similar. The two institutions offer a server environment where researchers can gain access to data for well-defined research projects. Data are accessed through a double log-on procedure and all data are provided in anonymized form. The servers contain conventional analytical packages, such as STATA, SAS, R and SPSS. Importantly, the NPR data are only available in anonymized form and cannot be accessed outside the Statistics Denmark and Danish Health Authority platforms. Thus, data from the NPR cannot be transferred to an outside researcher or any other institution. Within Statistics Denmark and the Danish Health Data Authority, data can be linked to other registries or other types of individual-level information (e.g. surveys) using the 10-digit personal identifier previously described.[2]

The most important differences between the platforms at Statistics Denmark and the Danish Health Data Authority pertains to data recency and linkage to socioeconomic registries (Table 3). As socioeconomic data, such as income[6] and education,[7] are kept within Statistics Denmark, they cannot be utilized in studies using the servers at the Danish Health Data Authority. Regarding data recency, the Danish Health Data Authority server is considered superior. Most health registry data stored on this server, including NPR data, are made available to researchers with as little as a 1-2 month delay. This facilitates studies of early uptake of recently marketed drugs[48] and allows researchers to address ongoing public health concerns in a timely manner.[49] In contrast, the duplicate copy of the NPR within Statistics Denmark is usually updated only twice annually, resulting in a delay of up to 9 months. Access to the two platforms, and thus to the NPR, is granted by application to their respective boards. A formal affiliation or collaboration with a Danish research institution is required.[47]

Table 3. Comparison of the platforms used for data access to the Danish National Prescription Registry at Statistics Denmark and the Danish Health Data Authority

	Statistics Denmark	Danish Health Data Authority
Year prescription data became available	1995	1995
Linkable to other health registries	Yes	Yes
Linkable to socioeconomic registries	Yes	No
Permissible for researchers to add his/her own data	Yes	Yes
Non-anonymized data available	No	No
Recency of data	Up to 9 months old	Up to 2 months old

Approvals and legislation

In addition to legislation covering all Danish health registries, the NPR is governed by the Pharmacy Sector Act.[50] This law imposes special restrictions on use of the NPR, to ensure the anonymity of individuals beyond the anonymization of any direct personal identifiers. In practice, anonymization is often achieved by removing or granulating any data that could be used to indirectly identify single individuals, e.g. by replacing exact birthdate with birth month and municipality of residence with region of residence. The research services at Statistics Denmark and the Danish Health Data Authority guide and facilitate this process. Upcoming legislative changes, expected to take effect early 2017, will likely lift these restrictions.

A formal approval regarding data protection is not always needed, since the Danish Data Protection Agency has given overall approval to both Statistics Denmark and the Research Services at the Danish Health Data Authority

because of their high-security systems. As such, projects based solely on data from either agency and confined to their servers are indirectly approved by the Data Protection Agency once the projects receive agency approval from either Statistics Denmark or the Danish Health Data Authority. If researchers add external data to the project, a data protection approval becomes necessary. Approval by an ethics review board is not required in studies involving the NPR, as projects based solely on registry data are exempt from ethical approval according to Danish law.[47] Furthermore, the NPR cannot be accessed for studies requiring a non-anonymized version, where such approval is typically required.

Profile in a nutshell

- The NPR was established to monitor drug use in Denmark for administrative purposes.
- The NPR contains individual-level data on all prescriptions filled at Danish community pharmacies since 1995, and these data are linkable to all other Danish registries using the Civil Personal Register number.
- Data are registered using electronic dispensing systems at Danish pharmacies and therefore considered accurate and complete.
- The NPR includes 46 variables describing the patient, the drug dispensed (including prescription filling date, drug composition and amount of drug), the health provider issuing the prescription and the dispensing pharmacy. No valid data are obtained on indication for use, prescribed daily dose or intended duration of use.
- The NPR can be accessed in anonymized form via servers at Statistics Denmark and the Danish Health Data Authority. Data cannot be transferred outside these servers.

Author Contributions

AP and MS conceived the study idea. AP, SAJS and MS wrote the initial draft. All authors contributed to critical revision of the paper, and agreed to be accountable for all aspects of the work.

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