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MiniReview

Odense Pharmacoepidemiological Database: A Review of Use and Content

Jesper Hallas[1,2], Maja Hellfritzsch[1], Morten Rix[1,2], Morten Olesen[1], Mette Reilev[1,3] and Anton Pottegård[1]

[1]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense C, Denmark, [2]Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark and [3]The Research Unit of General Practice, Department of Public Health, University of Southern Denmark, Odense C, Denmark

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Abstract: The Odense University Pharmacoepidemiological Database (OPED) is a prescription database established in 1990 by the University of Southern Denmark, covering reimbursed prescriptions from the county of Funen in Denmark and the region of Southern Denmark (1.2 million inhabitants). It is still active and thereby has more than 25 years of continuous coverage. In this MiniReview, we review its history, content, quality, coverage, governance and some of its uses. OPED's data include the Danish Civil Registration Number (CPR), which enables unambiguous linkage with virtually all other health-related registers in Denmark. Among its research uses, we review record linkage studies of drug effects, advanced drug utilization studies, some examples of method development and use of OPED as sampling frame to recruit patients for field studies or clinical trials. With the advent of other, more comprehensive sources of prescription data in Denmark, OPED may still play a role as in certain data-intensive regional studies.

The Odense University Pharmacoepidemiological Database (OPED) is a prescription database established in 1990 by the University of Southern Denmark, covering reimbursed prescriptions from the county of Funen in Denmark, and since 2007 the entire region of Southern Denmark. OPED has been extensively used in drug utilization research, FDA- and EMA-initiated phase IV safety trials and cause–effect record linkage studies.

Despite OPED having operated for more than 25 years, the history, content and applicability of OPED have never been formally reviewed. With this paper, we therefore aim to provide a thorough description of OPED with emphasis on its application for research purposes.

History

Odense University Pharmacoepidemiological Database was established by an agreement between researchers at the University of Southern Denmark and the county of Funen. The source of inspiration was an American study by Avorn and an editorial by Bergman describing how data that were generated as a by-product of reimbursement accounting were effectively used to conduct high-quality pharmacoepidemiological research [1,2]. This was seen by the University of Southern Denmark as a potentially major breakthrough, and it was soon clarified that both legal and technical conditions for establishing a similar data source were met. The earliest prescription records in OPED are from August 1990.

As OPED was framed within a research department of clinical pharmacology with strong collaborations with general practice research groups, the first research endeavours of the OPED group were focused on quality of care [3–5], drug utilization in general [6–8] and to a lesser extent cause–effect studies. As is evident from the section on use of OPED below, the OPED group has broadened its portfolio considerably since then.

Danish Health Care

The healthcare system in Denmark is tax-funded, thereby entailing free access to general practitioners (GPs) and hospitals. Except for emergencies, GPs compose the initial contact to patients and serve as gatekeepers to provide referrals to hospitals and specialists if needed [9]. When medication initiated by a specialist is stable, the GPs often resume the responsibility for drug prescription. Accordingly, 92% of patients' prescriptions of medicine are issued by GPs (Morten Olesen, personal communication).

The Danish community pharmacy sector consists of 234 privately operated community pharmacies [10]. The sector is controlled and regulated by the Danish Ministry of Health and the Danish Medicines Agency. Patients are not obliged to use a specific pharmacy, but are nonetheless generally loyal to

Author for correspondence: Jesper Hallas, Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, J. B. Winsløws Vej 19, 2., 5000 Odense C, Denmark (e-mail jhallas@health.sdu.dk).

one pharmacy [11]. If a resident of the Region of Southern Denmark or Zealand redeems his prescription outside of the regions covered by OPED, the record will eventually be transferred to OPED through an administrative clearing between regions.

Most prescription drugs are covered by a general reimbursement scheme that applies to all Danish residents. In general, the size of reimbursement depends on the patient's age and annual drug expenses. As such, the percentage of patient co-payment decreases with increasing drug expenditures. Some drugs are ineligible to general reimbursement (described below). However, individual reimbursement may be granted in certain circumstances, that is, to chronic or terminally ill patients or to patients requiring treatment with a more expensive drug or a drug not covered by the general reimbursement scheme [12].

Database Content

Odense University Pharmacoepidemiological Database is based on data reported from community pharmacies to the Danish Health and Medicines Authority as a part of the calculation of patients' reimbursement of medicines. From the establishment of OPED in 1990 until December 2006, the register covered the former Funen County population (N = 480,000). After approval from the Danish Data Protection Board and negotiations with the regional governments, OPED was expanded to cover the region of Southern Denmark (population 1,200,000) from January 2007, and during the period of 2009–2012, also the Region of Zealand (fig. 1). With these extensions, the population in this database is approximately two million people. Due to the nature of the data collection, the coverage of these regions is complete; that is, all pharmacies in the included areas, with no exception, contributed data to OPED. Both the former Funen County and Region of Southern Denmark have been found to be representative samples of the entire Danish population, considering factors such as age composition, income, education and healthcare utilization [13]. Importantly, data also cover residents at nursing homes, as, unlike other Nordic countries, they have had their own individual GPs and their own prescription drug dispensings, as all other citizens.

Each record contains the variables listed in table 1. In essence, a record includes the Danish Civil Registration (CPR) number of patient, the prescriber, the dispensed package, the pharmacy, the quantity and the date of dispensing. The dosing instruction and the indication are not recorded, as they are not part of the basis for assigning reimbursement. Often, the daily dose can be inferred from patterns of prescription renewal.

Odense University Pharmacoepidemiological Database does not cover drugs that are not reimbursed. These drugs include among others benzodiazepines, other hypnotics, drugs to promote weight loss or tobacco abstinence, oral contraceptives, certain antibiotics (e.g. quinolones, tetracyclines) and drugs that are dispensed over the counter. It is possible for a physician to issue a prescription for some drugs available over the counter and thereby achieve reimbursement for the patient. The physician may also apply for individual reimbursement for a prescription drug that is generally exempt from reimbursement. In both of these instances, the dispensing will be recorded in OPED. Researchers who intend to make use of OPED for research purposes should be aware of the reimbursement status of the drugs of interest, including their history of reimbursement. Further, OPED does not cover drugs dispensed during hospital admissions and drugs provided free of charge in ambulatory care or at treatment centres, for example monoclonal antibodies, methadone for substance abuse or anticancer chemotherapeutics.

Finally, OPED also contains a demographic module, which includes information on births, migrations and death. The demographic module is used to account for censoring in drug utilization or analytical studies and to extract control individuals in cohort or case–control studies. The variables included in the demographic module are listed in table 2.

An analysis of the number of individuals, prescriptions and cumulative number of DDD for selected drugs and drug classes is shown in table 3. Several drugs and drug classes have very high numbers of users; for beta-lactam antibiotics, the number is 1,338,000, which exceeds the standing population of the Region of Southern Denmark. This is explained by the fact that OPED has been operated for 26 years, wherein a substantial number of persons have migrated, died or been born. A more detailed version of table 3 can be downloaded as a Data S1.

Linkage

Linkage of OPED with other data sources can be achieved using the CPR number [14]. The CPR number is a unique 10-digit identifier assigned to all individuals with permanent Danish residency. This identifier is used in all contacts with the healthcare system, thereby allowing flawless linkage between all Danish health registers [14]. Persons with short or indeterminate residency may be given a special temporary CPR number. Such persons are not covered by OPED.

National and regional data sources that can supplement OPED data include among others the laboratory database NetLAB, the cancer registry [15], the cause-of-death registry [16] and, most important, the Danish National Patient Registry [17] (table 4). The Patient Registry contains data on all non-psychiatric hospital admissions since 1977 and both psychiatric and non-psychiatric outpatient encounters since 1995. The registered data include inpatient and outpatient diagnoses and procedures. Further, it is possible to link OPED to data concerning socio-economic status and family members through data sources contained within Statistics Denmark [18].

Strengths and Limitations; Coverage and Validity

The records in OPED reflect what has been dispensed and reimbursed by the regional health authorities. As it is used to administer reimbursement, it is assumed to be highly accurate. There are no known examples of fraud. The validity of the data in OPED is ensured by the steps undertaken from prescribing until the patient has the drug dispensed. Today, the

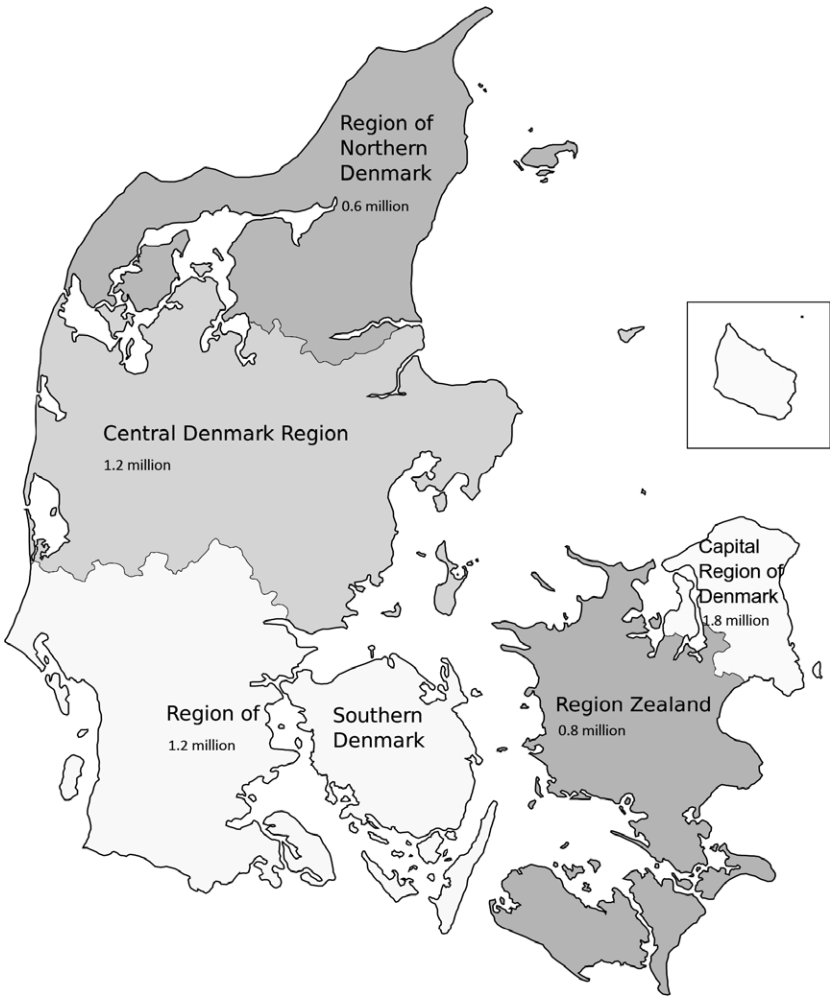

Fig. 1. Danish regions.

Table 1.
Variables included in the prescription module of Odense University Pharmacoepidemiological Database.

The patient's Danish Civil Registration (CPR) number[1]
The date of dispensing
The Nordic product code[2]
The number of packages
The dispensing pharmacy
The prescriber ID

[1]Personal identification number, a unique number assigned to all residents in Denmark and used ubiquitously in healthcare registers.
[2]Identifies the package that is being dispensed in terms of pharmaceutical substance, ATC code, number of dosing unit, unit strength, quantity in defined daily dose, etc.

Table 2.
Variables included in the demographic module of Odense University Pharmacoepidemiological Database.

The patient's Danish Civil Registration (CPR) number[1]
Municipality code
Date of moving in
Date of moving out (if any)
Date of death (if any)
Whether the municipality is located in Funen

[1]Personal identification number, a unique number assigned to all residents in Denmark and used ubiquitously in healthcare registers.

physician issues the prescription electronically on the FMK (Fælles Medicin Kort) server, which is accessible from all Danish pharmacies. Secondly, when the patient purchases the drug in the pharmacy, it is registered to his or her personal identifier by scanning the barcode on the drug package. The barcode holds the Nordic product code, which provides information about name, strength, form and number of dose units. During these procedures, further information regarding patient, pharmacy and prescriber is also stored [19].

The prescription records in OPED are more likely to reflect actual drug intake than records of what has been prescribed, for example in GPs' administrative systems, as 4–9% of issued prescriptions are never redeemed [20]. There are, however, a number of potential circumstances where the redeemed prescriptions do not reflect actual intake; patients may have had medication from other sources, for example family, friends, hospitals, illegitimate sources or from over-the-counter purchases, or they may have failed to take what has been

Table 3.
Overview of prescription records in the Region of Southern Denmark component of Odense University Pharmacoepidemiological Database for the period of 1990–2016. Drugs and drug classes with <100,000 registered users are not included. A more complete table is given as a Data S1.

Drug class (ATC-code)	Number of users (×1000)	Number of prescriptions (×1000)	Number of defined daily doses (×1,000,000)
Proton pump inhibitors (A02BC)	412	4837	48
Drugs for functional gastrointestinal disorders (A03)	119	391	4
Drugs used in diabetes (A10)	101	5470	55
Antithrombotic agents (B01)	252	6727	67
Diuretics (C03)	336	7398	74
Beta-blocking agents (C07)	232	4756	48
Calcium channel blockers (C08)	223	4508	45
Agents acting on the renin–angiotensin system (C09)	302	7983	80
Lipid-modifying agents (C10)	251	5508	55
Antifungals for dermatological use (D01)	316	872	9
Corticosteroids, dermatological preparations (D07)	635	2635	26
Antiacne preparations (D10)	104	424	4
Sex hormones and modulators of the genital system (G03)	195	3159	32
Corticosteroids for systemic use (H02)	292	1508	15
Antibacterials for systemic use (J01)	1443	10,383	104
Antimycotics for systemic use (J02)	223	702	7
Antivirals for systemic use (J05)	120	368	4
Anti-inflammatory and antirheumatic products (M01)	855	6574	66
Analgesics (N02)	647	14,340	143
Opioids (N02A)	445	6829	68
Antiepileptics (N03)	103	2980	30
Psycholeptics (N05)	177	4006	40
Antidepressants (N06A)	337	7616	76
Antiprotozoals (P01)	254	816	8
Nasal preparations (R01)	272	1741	17
Drugs for obstructive airway diseases (R03)	471	10,180	102
Cough and cold preparations (R05)	124	657	7
Antihistamines for systemic use (R06)	308	1768	18

dispensed. Due to the patient co-payment, it is considered unlikely that patients would repeatedly buy prescription drugs they do not use. There are a number of studies where OPED has been used as the sampling frame to identify certain users [21–25], who have then been presented with their own prescription records. Although it has only been formally analysed a few times [21,23,24], examples of prescriptions representing non-use of the drug have rarely been encountered.

Through the drug statistics homepage from the Danish National Health Board, it is published what proportion of a given medication is dispensed by person-identifiable prescriptions [26]. For example, low-dose aspirin, omeprazole and NSAIDs are available over the counter, but nonetheless, 91%, 99% and 69% are sold on prescription [27]. For drugs whose use in the population is generally low, it can be shown that even a substantial proportion of over-the-counter sale does not necessarily invalidate analytical studies of drug effects [28].

One of the specific variables in OPED is the prescriber ID. It has recently been shown that this has a high degree of validity, at least with respect to establishing the prescriber type [29].

Governance and Ethical Issues

Odense University Pharmacoepidemiological Database has a formal status of public research registry, and it is owned, governed and run by the University of Southern Denmark. As such, it may only be used for research purposes. Individual-level data from OPED can be obtained after an application to OPED's contact person and director, Jesper Hallas. To achieve data access, researchers are required to deliver a description of the requested prescription data (ATC number, calendar period, etc.), a brief description of the project and an approval from the Danish Data Protection Agency. For the majority of studies, approval from an ethics board is not necessary, as purely register-based studies are exempt from such requirements in Denmark [18]. It is possible to exchange data with non-EU countries, after removal of the person identifiers.

When providing data to other researchers, person identifiers can be included if required for the research purpose, for example linkage with other data sources. These researchers are obliged to follow regulations stipulated from the Danish Data Protection Agency; for example, that the person identifiers should only be used for updating data sources and should be removed from the data sourced and replaced by non-descript serial numbers ('pseudonymized') as soon as possible.

Odense University Pharmacoepidemiological Database's Use in Research

Odense University Pharmacoepidemiological Database is closely linked with the research environment of clinical pharmacology and pharmacy that has well-established contacts with

Table 4.
Examples of other data sources that can be linked with Odense University Pharmacoepidemiological Database (OPED) by using the person identifier, Danish Civil Registration Number (CPR).

Data resource	Type of data provided by the data source	Examples of what can be explored or obtained through linkage of OPED with this data source
The Danish National Patient Registry	Administrative information including registered diagnoses and operations performed at Danish hospitals	Medical history of drug users. Drug use in patients with a specific condition. Identification of outcome in studies on drug safety
The Danish Medical Birth Registry	CPR number and data on the newborn (e.g. length and weight at birth, gestational age) and the mother (e.g. parity and smoking status)	Association between drug use and pregnancy outcome. Utilization studies on drug use during pregnancy
The Danish Cancer Registry	Diagnosis, classification and additional information on all incident cancer cases in Denmark	Carcinogenic effects of drugs. Drug use among patients with cancer
NetLAB	Data on blood samples analysed at hospitals in the region of Southern Denmark	Assessment of the safety and/or effectiveness of drug use through changes in specific biochemical markers. Assessment of appropriate dosing with regard to, for example, renal function
The National Health Insurance Service Registry	Health services provided by general practitioners and other private practising specialists in primary health care	Healthcare utilization among specific drug user. Specialist involvement in drug therapies where this is highly recommended (e.g. prescribing of psychotropics for children)
Registers within Statistics Denmark	Data on annual and highest level of completed education	Socio-economic status of drug users. Adjustment for socio-economic confounding

general practice and medical subspecialities at the neighbouring hospital, Odense University Hospital. Traditionally, OPED has been used for three types of studies: (i) analytical linkage studies (outcome studies), (ii) descriptive drug utilization studies and (iii) method development studies. Finally, it has also been used as a sampling frame for other studies.

Analytical linkage studies.
Data from OPED have most commonly been used for outcome studies – frequently within the field of gastroenterology and typically designed as case–control studies. Seminal papers include case–control studies linking use of proton pump inhibitors to an increased risk of pneumonia [30], use of statins to neuropathy [31] and use of single and combined antithrombotic therapy to an increased risk of gastrointestinal bleeding [32]. All studies were based on validated cases obtained via chart reviews from Odense University Hospital.

Benefitting from the 5-year extended coverage of OPED compared to the national prescription database, OPED has also been used to supplement nationwide analyses. As such, it has been used to provide additional utilization measures in studies of both lithium and disulfiram and the risk of various cancers [33,34].

Drug utilization.
Odense University Pharmacoepidemiological Database has also demonstrated its usefulness in drug utilization studies. As one example, a nationwide study on the use of the antidiabetic drug class GLP-1 analogues contained a regional sub-analysis where additional data (HbA1c, eGFR, etc.) on incident users covered by OPED were collected from local data sources. The study thus allowed a direct comparison of real-life users to patients included in the trials [35]. Another example is a study on the potential misuse of the antimigraine drug sumatriptan, where basic utilization parameters based on the Lorenz curve [36] revealed a subgroup of very heavy users. Again, this study was supplemented with additional data in the form of an interview study [23]. A final example is a study where GPs' antiasthmatic prescribing pattern was compared to their participation in industry-sponsored clinical trials on asthma drugs. This study showed that the sponsor's share of the individual GP's prescription increased, without any discernible improvement in the overall quality of prescribing [37].

Method development.
Odense University Pharmacoepidemiological Database has provided data to illustrate methods developed by the pharmacoepidemiological research group hosting OPED. Such methods include the original presentation of the symmetry analysis design [38], and the individualized drug utilization statistics [8], including the concept of the waiting time distribution [7,39].

Odense University Pharmacoepidemiological Database as sampling frame.
The fact that OPED is legally allowed to provide person-identifiable data to third parties enables use of OPED as a sampling frame for clinical studies [21–25]. One such example is

the clinical descriptive study of heavy users of sumatriptan mentioned above, where identification of patients in OPED allowed supplement with additional data from other sources. Recently, OPED has been used to identify persons who are chronic users of NSAIDs or allopurinol, with the purpose of recruiting participants to large pragmatic trials of drug safety conducted by the Phase IV unit at the University of Southern Denmark [22,40].

Odense University Pharmacoepidemiological Database's Future

There is a plethora of prescription data sources in Denmark [41], and OPED is not the only one that allows transfer of data to third-party researchers [19]. Recently, legislation has been proposed, whereby the data stored in the Danish National Prescription Database can be transferred for research as well, which will enable all Danish prescription data since 1995 to be accessed outside the anonymized environments of Statistics Denmark and the Danish Health Data Authority. Obviously, these new opportunities could potentially obviate the need for maintaining OPED.

Historically, the principal strength of OPED has been its mere existence, allowing population-based studies that were not otherwise possible to conduct. When the national Prescription Registry was made available to researchers in 2003 [41], the use of OPED changed into OPED being predominantly a supporting registry in studies based on other data sources. Several strengths facilitate this role. It is legally possible to contact users of drugs identified in OPED, thereby using OPED as a sampling frame and for validation purposes. Among the other strengths, the follow-up of more than 26 years is important. This allows for identification of late drug effects. Finally, OPED has a role in certain data-intensive studies that take advantage of regional data that are not available on a national scale, for example data from discharge summaries [32], microbial specimens [30], inpatient drug use [42], X-rays [30] or laboratory results [35,43]. All these aspects considered, it is likely that OPED will continue to play an important role for a long time to come.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Data S1. Extended version of table 3.