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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Primary non-adherence in general practice: a Danish register study

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Abstract
Purpose The aim of this study was to describe primary non-adherence (PNA) in a Danish general practitioner (GP) setting, i.e. the extent to which patients fail to fill the first prescription for a new drug. We also assessed the length of time between the issuing of a prescription by the GP and the dispensing of the drug by the pharmacist. Lastly, we sought to identify associations between PNA and the characteristics of the patient, the drug and the GP.
Methods By linking data on issued prescriptions compiled in the Danish General Practice Database with data on redeemed prescriptions contained in the Danish National Prescription Registry, we calculated the rate of PNA among Danish patients from January 2011 through to August 2012. Characteristics associated with PNA were analysed using a mixed effects logistic regression model.
Results A total of 146,959 unique patients were started on 307,678 new treatments during the study period. The overall rate of PNA was 9.3 %, but it varied according to the major groups of the Anatomical Therapeutic Chemical (ATC) Classification System, ranging from 16.9 % for "Blood and bloodforming organs" (ATC group B) to 4.7 % for "Cardiovascular system" (ATC group C). Most of the patients redeemed their prescriptions within the first week. Older age, high income and a diagnosis of chronic obstructive pulmonary disease were found to be significantly associated with lower rates of PNA, while polypharmacy and a diagnosis of ischaemic heart disease were associated with higher rates of PNA.
Conclusions The overall rate of PNA among Danish residents in a GP setting was 9.3 %. Certain drug classes and patient characteristics were associated with PNA.

Keywords Patient adherence · Medication adherence · General practice · Registries · Pharmacology · Pharmacoepidemiology

Introduction

Non-adherence to medications is a well-known challenge in pharmacological treatment. Conceptually, non-adherence can be divided into primary and secondary non-adherence. Primary non-adherence (PNA) occurs when the patient fails to initiate treatment altogether, while secondary non-adherence is used to describe a complex range of situations, such as when the patient intentionally or unintentionally skips doses, uses lower doses than prescribed or uses medical devices incorrectly [1].

The term non-adherence is often used in the sense of secondary non-adherence, and most research conducted to date has focused on secondary non-adherence. However, when only secondary non-adherence is considered, i.e. PNA is not taken into account, the overall rate of non-adherence is an underestimation, as the number of patients who do not redeem their prescription at all is not included in the analysis [2]. Furthermore, from a clinical perspective, a patient failing to initiate treatment, i.e. showing PNA, constitutes a challenge that is different from that of a patient who at one point accepted treatment but who later fails to adhere to the

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agreed-upon regimen. As such, a knowledge of overall rates of and factors associated with PNA is an important aspect of prescribing.

When compared to the extensive research that has focused on secondary non-adherence [1, 3, 4], the amount of research done on PNA is relatively modest, albeit increasing in more recent years. In the pivotal study by Beardon et al. [5], 5.2 % of prescriptions issued in primary care were never filled at the pharmacy, while newer studies have reported rates ranging from 2.4 to 30.7 % [6–19]. Several papers have reported variance in PNA according to patient characteristics [5, 7–14, 16–19], prescriber characteristics [9, 10, 12, 16, 19], drug type [5, 7–10, 13, 14, 16] and level of patient co-payment [5, 13, 14]. However, comparisons between studies are complicated by differences in setting (primary care [5, 11, 14, 19], secondary care [8, 12, 15, 17] or both [7, 9, 10, 13, 16, 18]) and major differences in methodology. Follow-up times in studies reported to date range from 2 days [15] up to 6 months [9], and while some studies include all prescriptions [5, 7, 10, 11, 13, 14, 18, 19], others only consider the first prescription for a new drug [8–10, 15–17], with the latter group showing markedly higher rates of non-adherence.

The aim of our study is to describe PNA in a Danish general practitioner (GP) setting. Specifically:

1. To estimate the rate of PNA, overall as well as specified by subgroups of patients and drug types;
2. To describe the timing between prescriptions being prescribed by the physician and filled at the pharmacy;
3. To identify factors associated with PNA, including characteristics of the patient, of the drug and of the GP.

Method

The study was a register-based study conducted in Denmark. We calculated the rate of PNA in the primary care setting among Danish patients by linking data on issued prescriptions compiled in the Danish General Practice Database (DAMD) with data on redeemed prescriptions contained in the Danish National Prescription Registry.

Setting

All Danish residents (5.6 million) have free and direct access to GPs, ophthalmologists, and ear, nose and throat office-based specialists, as well as hospital emergency services. The GPs are the gatekeepers who control further patient access to the secondary health care system [20], and the majority of all prescriptions are issued by GPs. In Denmark, the Danish Health and Medicines Authority assigns reimbursement status to a medicine. Consequently, when a resident purchases a prescription medicine, reimbursement is automatically deducted from the price charged at the pharmacy. Reimbursement applies to all citizens, irrespective of income.

Data sources

The DAMD was implemented in 2006 and is a database that contains a patient's clinical data and prescription information related to individual consultations with a GP [21, 22]. DAMD uses a data capture module incorporated in the GP's IT-system. This module automatically sends information on prescribed medication, diagnoses and laboratory data to DAMD for each contact between a GP and a patient. Drugs are categorised according to the Anatomic Therapeutic Chemical (ATC) Classification System, which is a classification system developed and maintained by the World Health Organization (WHO) [23]. Diagnoses are coded according to the International Classification of Primary Care system (ICPC) [21]. A national agreement states, that as of April 2013, all 2,100 GP practices in Denmark are obliged to use the data capture module and consequently contribute data to DAMD [21].

The Danish National Prescription Registry [24] contains data on all prescription drugs dispensed in retail pharmacies to Danish citizens since 1994. The data include an exact account of the dispensed pharmaceutical product, including substance, brand name, dose unit and quantity, date of dispensing, age and gender of the drug user and identifiers for the prescribing physician and the dispensing pharmacy.

All data sources were linked by use of the personal identification number, a unique identifier assigned to all Danish residents since 1968 that encodes gender and date of birth [25]. All linkages were performed within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes [24, 26, 27].

Population

Our study population consisted of all GPs contributing data to the DAMD who were classified as "up-to-standard" in the database throughout the entire study period, as well as all patients aged ≥18 years assigned to these GPs. Being classified as "up-to-standard" implies ≥70 % of all consultations were encoded with an ICPC diagnosis.

Analysis

Data were obtained for the period of January 2010 through to December 2012. The primary study outcome was PNA, defined as not having redeemed a prescription within 4 months from the day the prescription was issued. Due to this 4-month window, only data on prescriptions issued between 1 January

2011 and 31 August 2012 were included in the analysis. Only new prescriptions were included, defined as the patient not having filled a prescription for the same drug substance within the last 2 years prior to the new prescription being issued, according to the Prescription Registry. Drugs were classified at the fifth level of the ATC system, i.e. at the level of single drug substances. We also described the timing of the pharmacy visit relative to the issuing of the prescription at the GP's office, by calculating the cumulative proportion of prescriptions having been filled each day for the first 30 days after the prescriptions were issued. Lastly, we compared PNA across patient characteristics, drug classes and GP characteristics:

Patient characteristics included gender, age at 1 January 2011 (categories: 18–29, 30–49, 50–69, and 70+ years), cohabitation (married vs. not-married), total family income in 2010 (<250,000 DKK[1], 250,000–499,999 DKK and ≥500,000 DKK), level of education by 1 January 2011 (≤10, 11–12 and 13+ years), polypharmacy (use of 0–2 drugs, 3–7 drugs and 8+ drugs during 2010) and the presence of selected diagnoses at any time during the study period: diabetes mellitus (T89–T90), chronic obstructive pulmonary disease (R95) and ischemic heart disease (K75).

Drug characteristics were analyzed according to all main ATC groups, i.e. the first level of the ATC system, one by one. Fifteen specific subgroups representing frequently used drugs were also selected and analysed.

The GP characteristics included were age (<50, 50–59, and 60+ years) and number of GPs in the given practice (solo practice, 2, and 3+ GPs). For practices with ≥2 GPs, age corresponded to the mean age of the GPs in the given practice.

These associations were firstly explored as subgroups, i.e. stratifying all issued prescription by the above-mentioned characteristics. Secondly, we estimated odds ratios (ORs) for PNA associated with the different characteristics using logistic regression. PNA is an individual trait, and we therefore employed a mixed effects logistic regression model with random effects for both the subject and the prescriber. Also, since the rate of PNA is assumed to be fairly low, the ORs reported are reasonable estimates of the corresponding risk-ratios.

All calculations were performed using STATA Release 12.0 (StataCorp, College Station, TX).

The study was approved by the scientific board of Statistics Denmark and by DAMD (project 52–13). According to Danish law, ethical approval is not required for registry-based studies.

[1] 1 Euro ≈ 7.50 DKK

Results

Eighty-three GPs were included in the study. During the study period 307,678 new treatments were initiated among 146,959 unique patients. The characteristics of the patients are presented in Table 1.

Table 2 shows the PNA within subgroups of patients. The overall rate of PNA was 9.3 %. PNA was more frequent among those aged 18–29 years (13.8 %) and decreased with age, with patients aged 70+ years having the lowest rate of PNA (7.5 %). Patients with incomes of <250,000 DKK per year had a higher rate of PNA (10.0 %) than those in the two higher income categories (9.3 and 8.9 %, respectively).

The numbers of unfilled prescriptions for each main ATC group are shown in Table 3. PNA varied by main ATC group, ranging from 4.7 to 73.9 %. The rate was highest for "Various" (ATC group V) (73.9 %) and "Antineoplastic and immunomodulating agents" (ATC group L) (70.1 %). However, these two groups were rarely prescribed (119 and 197 prescriptions, respectively). Among the remaining

Table 1 Demographics of patients

Characteristics	*N*=146,959 unique patients
Gender	
Male	64,673 (44.0 %)
Female	82,286 (56.0 %)
Married/cohabiting	
Yes	103,694 (70.6 %)
No	43,265 (29.4 %)
Age (years)	
18-29	15,941 (10.8 %)
30-49	52,072 (35.4 %)
50-69	55,773 (38.0 %)
70+	23,173 (15.8 %)
Number of prescribed drugs	
0–2	65,604 (44.6 %)
3–7	57,153 (38.9 %)
8+	24,202 (16.5 %)
Comorbidity	
Diabetes mellitus	10,753 (7.3 %)
Chronic obstructive pulmonary disease	4,998 (3.4 %)
Ischaemic heart diseases	2,709 (1.8 %)
Income (DKK per year)	
<250.000	28,838 (19.6 %)
250.000–499.999	46,105 (31.4 %)
500,000+	72,016 (49.0 %)
Education	
≤10 years	28,761 (19.6 %)
11–12 years	17,861 (12.2 %)
13+ years	100,337 (68.3 %)

Table 2 Primary non-adherence[a] in different patient subgroups

Characteristics	% Primary non-adherence (unfilled/issued prescriptions)
Overall	9.3 (28,526/307,678)
Gender	
Male	9.1 (10,758/117,646)
Female	9.4 (17,768/190,032)
Married/Cohabiting	
Yes	8.8 (18,329/207,681)
No	10.2 (10,197/99,997)
Age (years)	
18–29	13.8 (3,819/27,651)
30–49	10.9 (10,569/96,666)
50–69	7.8 (9,079/116,097)
70+	7.5 (5,059/67,264)
Polypharmacy	
0–2 drugs	9.5 (9,897/103,875)
3-7 drugs	9.2 (11,182/121,819)
8+ drugs	9.1 (7,447/81,984)
Comorbidity	
Diabetes mellitus	8.5 (2,772/32,570)
Chronic obstructive pulmonary disease	7.0 (1,343/19,270)
Ischaemic heart diseases	8.4 (664/7,877)
Income (DKK per year)	
<250.000	10.0 (7,107/71,318)
250,000-499,999	9.3 (9,587/102,877)
500,000+	8.9 (11,832/133,483)
Education	
≤10 years	8.6 (6,152/71,153)
11–12 years	10.2 (3,949/38,710)
13+ years	9.3 (18,425/197,815)

[a] Primary non-adherence (PNA) is calculated as the proportion of prescriptions that were not filled within 4 months of being issued by the general practitioner (GP)

Table 3 Primary non-adherence[a] according to different drug classes[b]

Drug classes	% PNA (unfilled issued prescriptions)
Main groups of ATC	
Gastrointestinal and metabolism (A)	9.9 (2,339/23,598)
Blood and blood-forming organs (B)	16.9 (974/5,760)
Cardiovascular system (C)	4.7 (1,661/35,421)
Dermatologicals (D)	10.2 (3,830/37,636)
Genitourinary system (G)	12.3 (1,759/14,354)
Systemic hormonal preparations (H)	5.2 (306/5,855)
Antiinfectives (J)	6.5 (4,168/64,372)
Antineoplastic and Immunomodulating drugs (L)	70.1 (138/197)
Musculoskeletal system (M)	9.4 (2,314/24,601)
Nervous system (N)	9.9 (3,967/40,092)
Antiparasitic products (P)	11.4 (553/4,852)
Respiratory system (R)	11.2 (3,531/ 31,402)
Sensory organs (S)	8.8 (1,593/18,114)
Various (V)	73.9 (88/119)
Specific drug subgroups[c]	
Proton pump inhibitors	6.9 (695/10,056)
Antidiabetics	4.0 (133/3,340)
Low-dose acetylsalicylic acid (ASA)	6.9 (145/2,106)
Bendroflumethiazide	3.3 (96/2,923)
Dihydropyridine derivatives	2.4 (96/3,966)
Angiotensin-converting enzyme (ACE) inhibitors	3.3 (44/1,322)
Angiotensin II receptor (AT-II) antagonists	2.5 (142/5,580)
Statins	6.2 (309/4,984)
β-Lactams	3.2 (295/9,091)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	9.1 (1,815/20,046)
Tramadol and Codeine	5.2 (588/11,297)
Benzodiazepines (anxiolytics)	5.9 (174/2,960)
Selective serotonin re-uptake inhibitors (SSRIs)	6.4 (283/4,445)
Bronchodilators	8.6 (470/5,449)
Inhaled corticosteroids	8.8 (167/1,889)

[a] PNA is calculated as the proportion of prescriptions that were not filled within 4 months of being issued

[b] Classes/groups of the Anatomic Therapeutic Chemical (ATC) Classification System

[c] For definition of these drug classes, see Appendix

groups, the highest rate of PNA was for "Blood and bloodforming organs" (ATC group B) (16.9 %) and the lowest for "Systemic hormonal preparations" (ATC group H) (5.2 %) and "Cardiovascular system" (ATC group C) (4.7 %). Among the pre-selected drug classes, we found that PNA ranged from 9.1 % for nonsteroidal anti-inflammatory drugs (NSAIDs) to 2.4 % for dihydropyridine derivates. Patients prescribed NSAIDs, inhaled corticosteroids and bronchodilators showed the highest rate of PNA.

Figure 1 shows the number of days between the prescribing of a prescription by the GP and the redemption of the prescription by the patient at a pharmacy. We found that 65.2 % of the patients redeemed their prescription on the same date that the prescription was issued and that 89.3 % patients had redeemed their prescription by day 30. The majority of the patients filled their prescriptions within the first week.

Table 4 shows the association of the different variables with the rate of PNA in a mixed-effect multivariable logistic regression model. Age had the strongest association with PNA, with age 70+ years associated with a lower PNA, with an OR of 0.48 [95 % confidence interval (CI) 0.45–0.51], compared to age 18–29 years. Similarly, having an income of > 500,000 DKK and having a diagnosis of chronic obstructive

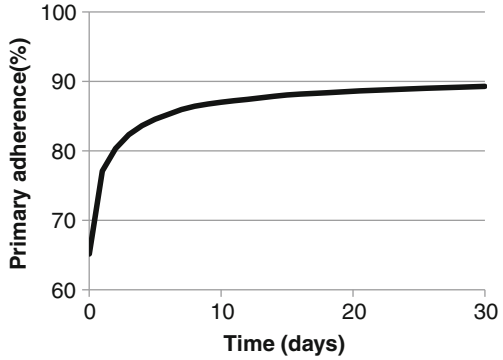

Fig. 1 Proportion of redeemed prescriptions during the first 30 days following issuing of the prescription by the general practitioner

pulmonary disease were also associated with lower PNA rates, with an OR of 0.77 and 0.80, respectively. Polypharmacy, i.e. taking more than eight drugs, showed an OR of 1.15 (95 % CI 1.10–1.21). While larger practice size were associated with lower rates of PNA, these estimates did not reach statistical significance. Lastly, having a diagnosis of ischaemic heart disease increased the risk of PNA, with an OR of 1.22. Gender, cohabitation and education had little or no association with the degree of PNA.

Discussion

The results of this study show that overall, 9.3 % of patients in Danish primary care failed to fill their prescriptions within 4 months of issue during the study period. The lowest rate of PNA was for drugs for the "Cardiovascular system" (ATC group C). Most of the patients redeemed their prescription within the first week. Age was found to be the most important factor associated with PNA.

The primary strength of the study is its high internal validity due to the high quality of the data sources used [21, 24] and the large sample size.

Our study also has a number of limitations. First, the requirement that all GPs included in this study had to be classified as "up-to-standard" might imply that the GPs included are not representative of all Danish GPs. However, we have no reason to believe, that "up-to-standard" GPs handle adherence problems better than other GPs in Denmark. A second potentially important limitation is a lack of knowledge on the level of agreement between the GP and patient regarding the treatment, i.e. we do not know if the GP and the patient agreed on initiating treatment the same day or 1 month after the prescription was issued. Furthermore, the data contain no means to uniquely identify a single prescription. Therefore, later prescriptions redeemed for the same drug, issued by different prescribers, would also result in the patient being classified as adherent for the GP prescription, even though the original prescription was never redeemed. This might decrease the observed rate of PNA, especially among patients followed by hospitals or other specialists. However, the rapid saturation seen in Fig. 1, which shows that the vast majority of patients did pick up their prescriptions within the first week of issuing indicates that this factor did not play a major role.

In some studies, the PNA proportion was calculated for all prescriptions [5, 7, 10, 11, 13, 14, 18, 19] while in other

Table 4 Mixed effects[a] logistic regression analysis of the dependence of primary non-adherence on various patient- and GP-related variables

Patient- and GP-related variables	Odds ratio [95 % confidence interval]
Gender	
Female	(Reference)
Male	1.03 [0.99–1.06]
Cohabitation	
No	(Reference)
Yes	1.01 [0.96–1.05]
Age (years)	
18–29	(Reference)
30–49	0.85 [0.80–0.89]
50–69	0.55 [0.52–0.58]
70+	0.48 [0.45–0.51]
Polypharmacy	
0–2 drugs	(Reference)
3–7 drugs	1.05 [1.01–1.09]
8+ drugs	1.15 [1.10–1.21]
Comorbidity	
Diabetes mellitus	0.98 [0.93–1.04]
Chronic obstructive pulmonary disease	0.80 [0.74–0.86]
Ischaemic heart diseases	1.22 [1.10–1.35]
Income (DKK)	
<250,000	(Reference)
250,000–499,999	0.91 [0.87–0.95]
500,000+	0.77 [0.72–0.81]
Education	
≤10 years	(Reference)
11–12 years	1.01 [0.95–1.06]
13+ years	0.96 [0.92–1.00]
Practice size	
Solo GP	(Reference)
2 GPs	0.74 [0.55–1.00]
>3 GPs	0.83 [0.65–1.04]
GP age	
<50 years	(Reference)
50–59 years	1.00 [0.79–1.25]
>60 years	0.90 [0.67–1.21]

[a] Random factors: Subject and prescriber

studies—such as our study—only the first prescription for a new drug treatment was taken into account [8–10, 15–17]. This different methodology explains some of the apparent discrepancy in reported PNA rates; if you include the second or later prescriptions for a given drug, the likelihood that a patient will stop treatment, i.e. not fill the prescription, conditional on several previous prescriptions, is probably lower. To our knowledge, only three studies have used an approach similar to ours, i.e. studying new treatments outside the hospital setting, namely, the two studies by Fischer et al. [9, 10] and the study by Shin et al. [16]. The overall rate found in our study is markedly lower than the 24–28 % reported by Fischer et al. [9, 10], but comparable to the rate of 9.8 % reported by Shin et al. [16]. However, some differences in study design, for example, the inclusion of specialist prescribers and children, make the comparison difficult. Furthermore, it is likely that the substantial differences in the structure of the health care in the USA and Denmark explain a significant proportion of the differences observed.

PNA varied by ATC drug class, ranging from 73.9 % for drugs in the "Various" category (ATC group V) to 4.7 % for drugs related to the "Cardiovascular system" category (ATC group C). Although drugs in the categories "Various" (ATC group V) and "Antineoplastic and immunomodulating agents" (ATC group L) had the highest rate of PNA, they did not affect the overall PNA, as both drug classes are prescribed infrequently in generally practice. In addition, the "Various" category includes drugs that are exempt from reimbursement, and patients might therefore buy them over-the-counter to save prescriptions charges. Outside these two special groups, drugs related to "Blood and bloodforming organs" (ATC group B) had the highest rate of PNA (16.9 %). The PNA for "Antiinfectives" (6.5 %) and for "β-Lactams" (3.2 %) was lower than the overall rate of PNA, possibly due to the former drug being used for the short-term treatment of infections and patients usually needing them urgently [14, 17].

According to Fig. 1, most of the patients included in this study redeemed their prescription within 1 week after issuing. This result is confirmed in other studies which also have reported that most prescriptions are redeemed within 1 week [12, 17]. About 90 % of the patients who redeemed their prescriptions within 4 months redeemed their prescriptions within the first week (data not shown). This was seen for all drug main groups except the genitourinary system and sex hormones, where only 80 % of those filling the prescription did so within the first week. This group also generally had a higher rate of PNA compared to the other groups (Table 3).

Our findings have both a clinical and a general research aspect. The clinical aspect is that GPs can largely expect their patients to redeem their prescriptions and to do so quite soon. We were also able to identify the patients who were most likely to do so: The embodiment of a compliant patient would be an elderly, rich woman who is prescribed a cardiovascular drug by an experienced doctor in a large practice. The research perspective is that GP's data are very useful for pharmacoepidemiological research, as aptly illustrated by the tremendous success of the General Practitioners Research Database in the UK. The ultimate measure of interest in pharmacoepidemiological research is what the patients have actually ingested. One may argue that data sources based on drug dispensing, such as the pharmacy-based system, is one step closer to the actual ingestion rate than data sources based on drug prescribing. However, this would usually be a matter of non-differential misclassification of drug exposure, and the approximately 10 % discrepancy found in our study would rarely be critical. In contrast, there are epidemiological designs that are particularly vulnerable to exposure misclassification and where accurate data on the timing of drug intake is crucial, such as the case-crossover design and its variants [28]. In such situations, one might prefer a different data source than a GP-based system.

Conflicts of interest None.

Appendix

Table 5 ATC codes used to specify the drug subgroups presented in the bottom half of table 3

Anatomical subgroups	ATC codes
Proton pump inhibitors	A02BC
Antidiabetics	A10
Low-dose ASA	B01AC
Bendroflumethiazide with potassium chloride	C03AB01
Dihydropyridine derivates	C08C
ACE-inhibitors inclusive combination preparations	C09B
AT-II antagonists inclusive combination preparations	C09C and C09D
Statins	C10AA
β-Lactams	J01CA
NSAIDs	M01A excl. M01AX
Tramadol and codeine	N02AX02 and R05DA
Benzodiazepines (anxiolytics)	N05BA
SSRIs	N06AB
Bronchodilators	R03AC
Inhaled corticosteroids	R03BA

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