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Do patients initiate therapy? Primary non-adherence to statins and antidepressants in Iceland

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SUMMARY

Background: Primary non-adherence occurs when a drug has been prescribed but the patient fails to have it dispensed at the pharmacy. **Aims:** To assess primary non-adherence to statins and antidepressants in Iceland, the association of demographic factors with primary non-adherence, and the time from when a prescription is issued until it is dispensed. **Methods:** Data on patients receiving a new prescription for a statin or an antidepressant from the Primary Health Care database were linked with dispensing histories from The Icelandic Prescription Database. The proportion of patients who did not have their prescription dispensed within a year from issuing (primary non-adherent) was assessed, as well as the time from issue until dispensing. Associations between demographic factors and primary non-adherence were estimated using logistic regression. **Results:** The overall primary non-adherence was 6.3% and 8.0% for statins and antidepressants, respectively. The majority of patients had their prescription dispensed within 7 days (85% for statins, 87% for antidepressants). Being disabled and receiving a prescription for an expensive drug was associated with higher rates of primary non-adherence. **Conclusion:** The rate of primary non-adherence to statins and antidepressants in Iceland is low. Vulnerable groups such as the disabled should be given special attention when new drugs are prescribed.

What's known

Primary non-adherence has been less studied than secondary adherence. However, it is an important aspect of adherence. The increasing use of electronic medical records and the possibility to link prescription data with dispensing data has led to an increase in the number of studies on primary non-adherence. Studies on primary non-adherence use various definitions and have reported a wide range of proportions of primary non-adherence.

What's new

The proportion of patients who did not get their prescription for statins or antidepressants dispensed within a year after it being issued was 6.3% and 8.0%, respectively. The vast majority of patients had their prescriptions dispensed within 7 days (85–87%). Failing to have an antidepressant or statin prescription dispensed was more prevalent among certain subgroups such as the disabled and those receiving a prescription for a more expensive drug.

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None of the authors have anything to disclose.

Introduction

The term adherence has been defined as 'the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes, - corresponds with agreed recommendations from a healthcare provider' (1). Adherence to drug therapy can be divided into three phases: (i) Acceptance or initiation of treatment, (ii) Execution/implementation, i.e. how the drug is taken, and (iii) Discontinuation (2,3). The first phase involves having a prescription issued, getting it dispensed and initiating therapy. In this phase, primary adherence refers to patients getting their issued prescription dispensed at the pharmacy. The second phase concerns whether patients continue to use the drug correctly (4–6), often called secondary adherence. Secondary non-adherence has been extensively researched in the last decades, often using pharmacy dispensing databases (7,8). Although primary non-adherence has been less extensively studied, the prevalence of primary non-adherence has been reported to be between 2.4% and 30.7% (5,9–22).

One of the main reasons why primary non-adherence has been less extensively studied than secondary non-adherence is the fact that information on prescribing and dispensing are rarely stored in the same databases. Dispensing databases are convenient when measuring the execution phase of use, but they provide no information on those who do not accept and/or never start treatment. This leads to an underestimation of non-adherence in dispensing databases (14). Prescribing databases on the other hand contain information on all prescriptions, but without the corresponding dispensing data, it is impossible to distinguish those who accept treatment from those who do not. With the increasing use of electronic medical records and electronic prescribing, these two types of data are sometimes stored in the same database, or two different databases that can be linked together, which has opened up new opportunities in primary non-adherence research (10,12).

Measuring primary non-adherence is an important factor in assessing overall adherence, and in identifying patients who are at risk for primary non-adher-

ence, which may enable healthcare professionals to improve patient care. As adherence to drugs may depend on the type of drug (10,22–24), we chose two widely used but very different drug classes in our study. First, we looked at the use of statins, which are intended for long-term treatment of hyperlipidaemia, both in primary and secondary prevention of cardiovascular events. The prevalence of primary non-adherence for statins has been found to be between 5.2% and 15.4% (5,6,9,10,22). Second, we looked at the use of antidepressants, which are primarily used to treat anxiety and depression, but also used for other conditions (25). Clinical guidelines recommend a duration of at least 6 months for antidepressant treatment when treating depression (26). The prevalence of primary non-adherence for antidepressants has been reported to be between 4.2% and 32.6% (9,15,16,22).

The aim of this study was to assess primary non-adherence to statins and antidepressants in Iceland, the time elapsing from the issue of a prescription until its dispensing at the pharmacy, and investigate which patient and drug characteristics are associated with primary non-adherence.

Methods

Data sources

The Primary Health Care database contains all prescriptions issued by physicians at 16 primary healthcare centres in Reykjavik and nearby municipalities. In accordance with the law, every resident in Iceland is allocated a unique personal identifying number. The Primary Health Care database stores information using this personal identifying number. In addition, the Primary Health Care database stores information about patients' gender, residency, age and type of patient group which determines the level of co-payment for each individual, unique identifying number for the prescribing physician, date of issue as well as information about the prescribed drug, such as Anatomical Therapeutic Chemical (ATC) class, brand name, number of units prescribed and dosage instructions.

The Icelandic Prescriptions Database is a nationwide pharmacy dispensing registry which has been in operation since 2003 and contains data on practically all dispensed prescriptions from all pharmacies in the country. The dispensing database stores all information using the same personal identifying number as the Primary Health Care database, allowing for linkage with the complete history of dispensed drugs for all residents. In addition, the database stores information about patients' gender, residency and age at each dispensing, the unique identifying number for the prescribing physician, date of issue and date of dispensing, as well as information on the dispensed drug, such as number of units dispensed, strength and brand name, but it does not include dosage instructions. Drugs are categorised according to the ATC index, a hierarchical classification system developed by the WHO (27).

Population

Our data sources covered the adult population (18 years and older) of the capital area in Iceland in 2010, totalling 151,315 inhabitants in 2010 (28). We included all patients from this population who received a new prescription for a statin (ATC C10AA) or an antidepressant (ATC N06A) between January 1 2009 and December 31 2011 issued by a GP at a primary healthcare centre. The issue date of a new statin or antidepressant prescription was defined as the index date. A new prescription was defined as the first prescription for either an antidepressant or a statin in the Primary Health Care database within the study period, issued to a patient who had not received any drugs belonging to the respective drug group 1 year prior to the index date according to the prescription database.

Outcome

The primary study outcome was the proportion of primary non-adherence for statin and antidepressant drug treatment in 2009–2011. All new prescriptions extracted from the Primary Health Care database were linked with the dispensing database using the personal identifying number, the unique identifying number for the prescribing physician, date of issue and ATC class (5th level). For each prescription, the number of days from its issue to its dispensing was calculated. Primary non-adherence was defined as not having the prescription dispensed within 365 days after the index date. Our choice of using 365 days follow-up period is based on prescriptions in Iceland being valid for dispensing up to 365 days from the date of issue.

Analysis

Descriptive statistics were used to describe the characteristics of the population. The proportion of primary non-adherent patients was assessed. The time from issue until dispensing, was used to divide patients into three groups: 0–7 days (early adherence), 8–365 days (late adherence) and those who never had their prescription dispensed (primary non-adherence). Baseline characteristics associated with late adherence or primary non-adherence (as compared with early adherence) were estimated using logistic regression. These included gender, age (18–40 years, 41–66 years, 67 years and older), patient

group (general – large co-payment, pensioners – small co-payment, disabled – small co-payment (15)) and type of statin (simvastatin and atorvastatin) and antidepressant [non-selective monoamine reuptake inhibitors (TCA), selective serotonin reuptake inhibitors (SSRI), and the group of other antidepressants, mainly consisting of serotonin norepinephrine reuptake inhibitors (SNRI)]. Four regression models were created: one for each drug class and each outcome (late adherence and non-adherence, both compared with early adherence). Each of the baseline characteristics could enter any of the four models if a Fischer's exact test returned a p-value of less than 10%. For the resulting models we used multiple logistic regression to determine the OR (odds ratios) and 95% CI (confidence intervals) of late or primary non-adherence associated with the selected characteristics. All calculations were performed using STATA release 12.0 (StataCorp, College Station, TX).

Ethical approval

This study was approved in 2012 by The National Bioethics Committee (licence number: 10-062-S1), the Data Protection Authority in Iceland (licence number: 2010030201) and the Primary Health Care of the Capital Area (licence number: 1A3 g/14/845.1/LO/lo).

Results

Within the study period 2132 new prescriptions were issued for a statin and 8553 for an antidepressant. The majority of patients with a new prescription for a statin were female (52.2%), aged 41–66 years (69.3%) and general patients (55.8%). The majority of patients with a new prescription for an antidepressant were female (64.5%), 18–40 years old (48.2%) and general patients (72.5%) (Table 1).

Figure 1 shows graphically the percentage of patients who got their prescription dispensed from the pharmacy, from the day the prescription was issued until 365 days after its issue. Most patients had their prescription dispensed shortly after its issue, 66% of statin users and 75% of antidepressant users had their prescription dispensed on the same day it was issued. The rate of dispensing rose rapidly and 7 days after a prescription was issued 85% of statin users and 87% of the antidepressant users had had their prescription dispensed. The rate rose more slowly after day 7, and 30 days after issue 90% of both statin and antidepressant users had had their prescription dispensed. All in all, 93.5% of statin users and 92% of antidepressant users had had their prescription dispensed 365 days after it was issued, resulting primary non-adherence rate of 6.5% for new statin users and 8.0% for new antidepressant users.

Table 1 Baseline characteristics of patients receiving new prescriptions for a statin (ATC C10AA) or an antidepressant (ATC N06A) between January 1 2009 and December 31 2011

	Drug group	
Characteristics	**Statins *n* = 2132 (%)**	**Antidepressants *n* = 8553 (%)**
Gender		
Male	1020 (47.8)	3033 (35.5)
Female	1112 (52.2)	5520 (64.5)
Age (years)		
18–40	109 (5.1)	4127 (48.2)
41–66	1477 (69.3)	3332 (39.0)
67 and older	546 (25.6)	1094 (12.8)
Patient group*		
General	1190 (55.8)	6204 (72.5)
Pensioners	669 (31.4)	1.226 (14.3)
Disabled	246 (11.5)	968 (11.3)
Drug group†		
Simvastatin	1879 (88.1)	–
Atorvastatin	248 (11.6)	–
TCA	–	1688 (19.7)
SSRI	–	5678 (66.4)
Other antidepressants	–	1174 (13.7)

*Results for patients where information is missing are left out (*n* = 27 f or statins, *n* = 155 for antidepressants). †Results for the drug groups C10AA07 and N06AG are not shown because of a low number of users.

Factors associated with non-adherence to statins

The baseline factors associated with primary non-adherence to statins were patient group and drug group (Table 2), but neither was statistically significant in the multiple logistic regression model. Being a pensioner and disabled was associated with higher risk of non-adherence (OR = 1.10; 95% CI 0.74–1.64 and 1.29; 95% CI 0.74–2.29, respectively) and receiving a prescription for atorvastatin was associated with a higher risk of non-adherence compared with simvastatin (OR = 1.29; 0.95% CI 0.99–2.61). The factors associated with late adherence (dispensing a statin after 8–365 days) were gender, age and drug group (Table 2). Males had a higher risk of being late adherers (OR = 1.46; 95% CI 1.07–2.00). Patients 67 years of age and older were less likely to be in the late-adherence category (OR = 0.50; 95% CI 0.25–0.99). Other factors were not statistically significantly associated with primary or late adherence to statins.

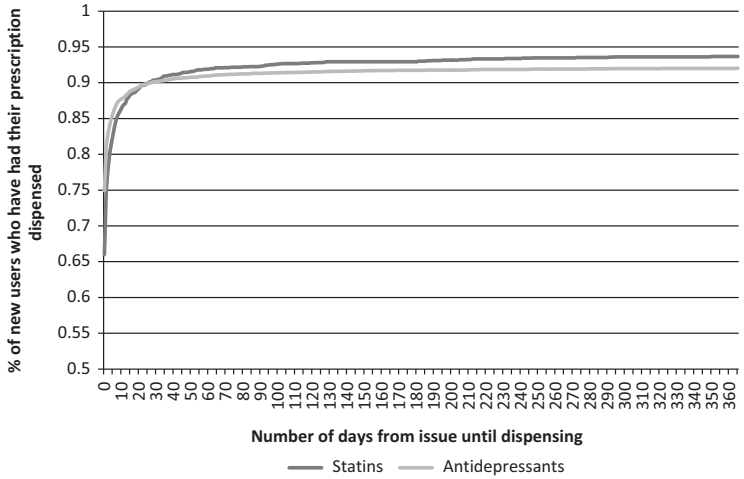

Figure 1 The percentage of new statin and antidepressant users who had their prescription dispensed 0–365 days after it was issued

Table 2 Baseline factors associated with primary non-adherence (patient and drug group) or later adherence (gender, age and drug group) for statins

	Days until dispensing				
	Early adherent (0–7 days)	Late adherent (8–365 days)		Primary non-adherent (not dispensed)	
Characteristics	***n* (%)**	***n* (%)**	**OR (95% CI)**	***n* (%)**	**OR (95% CI)**
Gender					
Female	961 (86.4)	77 (6.9)	Ref	74 (6.7)	
Male	852 (83.5)	107 (10.5)	1.46 (1.07–2.00)	61 (6.0)	
Age (years)					
18–40	85 (78.0)	13 (11.9)	Ref	11 (10.1)	
41–66	1253 (84.8)	139 (9.4)	0.76 (0.41–1.40)	85 (5.8)	
67 and older	475 (87.0)	32 (5.9)	0.50 (0.25–0.99)	39 (7.1)	
Patient group*					
General	1010 (84.9)	112 (9.4)		68 (5.7)	Ref
Pensioners	578 (86.4)	49 (7.3)		42 (6.3)	1.10 (0.74–1.64)
Disabled	208 (84.6)	20 (8.1)		18 (7.3)	1.29 (0.74–2.23)
Drug group†					
Simvastatin	1611 (85.7)	158 (8.4)	Ref	110 (5.9)	Ref
Atorvastatin	201 (81.0)	25 (10.1)	1.17 (0.75–1.84)	22 (8.9)	1.61 (0.99–2.61)

Number of users, percentage for each characteristic, odds ratios (OR) and 95% confidence intervals (95% CI). *Results for patients where information is missing are left out (n = 27). †Results for the drug group C10AA07 are not shown because of a low number of users.

Factors associated with non-adherence to antidepressants

Primary non-adherence to antidepressants was related to all the demographic factors that were tested (Table 3). Males had a lower risk of being primary non-adherent than females (OR = 0.79; 95% CI 0.67–0.94), those aged 41–66 years had a lower risk than those aged 18–40 years (OR = 0.70; 95% CI 0.59–0.84). Lastly, those receiving a prescription for other antidepressants (ATC class N06AX) had a higher risk of primary non-adherence compared with those receiving a prescription for SSRIs (OR = 2.06; 95% CI 1.67–2.54).

All the baseline factors, except gender, were associated with late adherence to antidepressants. Patients aged 67 years or older (OR = 0.35; 95% CI 0.16–0.76) had a lower risk of late adherence. The group of disabled (OR = 1.69; 95% CI 1.29–2.22), and

Table 3 Baseline factors associated with primary non-adherence (gender, age, drug group and patient group), or later adherence (age, patient group and drug group) for antidepressants

	Days until dispensing				
	Early adherent 0–7 days	Late adherent 8–365 days		Primary non-adherent Not dispensed	
Characteristics	***n* (%)**	***n* (%)**	**OR (95% CI)**	***n* (%)**	**OR (95% CI)**
Gender					
Female	4769 (86.4)	286 (5.2)		465 (8.4)	Ref
Male	2676 (88.2)	139 (4.6)		218 (7.2)	0.79 (0.67–0.94)
Age (years)					
18–40	3512 (85.1)	218 (5.3)	Ref	397 (9.6)	Ref
41–66	2910 (87.3)	177 (5.3)	0.89 (0.72–1.10)	245 (7.4)	0.70 (0.59–0.84)
67 and older	1023 (93.5)	30 (2.7)	0.35 (0.16–0.76)	41 (3.7)	0.71 (0.30–1.67)
Patient group*					
General	5378 (86.7)	301 (4.9)	Ref	525 (8.5)	Ref
Pensioners	1142 (93.1)	39 (3.2)	1.35 (0.69–2.66)	45 (3.7)	0.47 (0.21–1.05)
Disabled	802 (82.9)	75 (7.7)	1.69 (1.29–2.22)	91 (9.4)	1.19 (0.94–1.52)
Drug group†					
TCA	1485 (88.0)	73 (4.3)	0.95 (0.73–1.25)	130 (7.7)	1.18 (0.95–1.46)
SSRI	5003 (88.1)	263 (4.6)	Ref	412 (7.3)	Ref
Other antidepressants	945 (84.5)	32 (2.9)	1.82 (1.41–2.35)	141 (12.6)	2.06 (1.67–2.54)

Number of users, percentage for each characteristic, odds ratios (OR) and 95% confidence intervals (95% CI). *Results for patients where information is missing are left out (n = 155). †Results for the drug group N06AG are not shown because of a low number of users.

those receiving a prescription for other antidepressants (OR = 1.82; 96% CI 1.41–2.54) had a higher risk of late adherence.

Discussion

In this study of primary non-adherence to statins and antidepressants in Iceland, we found that the majority of patients in both groups had their prescription dispensed within the first 7 days after having it issued. The proportion of patients who had not retrieved their prescription after 365 days was 6.3% for statins and 8.0% for antidepressants.

The overall proportion of primary non-adherence was similar or lower than reported elsewhere (6,10,16,20,22). One of the possible explanations could be that many studies use shorter follow-up periods when assessing primary non-adherence (12,13). Another factor that could affect our results is that all the prescriptions were issued by primary healthcare physicians, while it has been reported that patients seeing specialists have their prescription dispensed to a greater extent than those seeing GPs (9,10). It is also important to consider that we assessed primary non-adherence in general practice, while many studies have reported primary non-adherence following discharge from hospital, where the proportion of primary non-adherence tends to be higher (9,19). Lastly, many studies define primary non-adherence as the proportion of all issued prescriptions that are never dispensed, instead of only prescriptions issued to new users, as in our study. Those studies tend to report lower rates of primary non-adherence, and are not directly comparable with our results (15,18,29).

If primary non-adherence had been defined as not having a prescription dispensed within the first 30 days after it was issued, primary non-adherence would have been 9.7% for statins and 9.9% for antidepressants which is within the range reported in other studies using a 30-day follow-up period (10,14). Our results indicate that having a follow-up period of 30 days would be adequate to capture primary non-adherent statin and antidepressant users.

Clinical relevance of our findings

We found that females and young people are more likely to be primary non-adherent which is in line with what others have reported (6,11,20,30). The results for the various patient groups, although not statistically significant, indicate that the disabled are more likely to be primary non-adherent than the general population, which is in line with findings

from another Icelandic study on primary non-adherence (15).

The type of drug had the strongest association with primary non-adherence. Patients receiving a prescription for the group of other antidepressants, mainly including SNRIs, and atorvastatin were more likely to be primary non-adherent than patients receiving a prescription for SSRIs and simvastatin respectively. This could be because the former drug classes include more expensive drugs, but it is also a likely result of changes in the reimbursement rules in Iceland. On the 1 March 2009, the reimbursement of statins was restricted to the cheapest available statin, which at the time was simvastatin (31). A similar change in reimbursement occurred on the 1 June 2010, where the reimbursement of SSRIs and the group of other antidepressants was restricted to the cheapest available drug in each class, a change that affected other antidepressants to a greater extent (32). This probably resulted in some patients with a new prescription for a drug that was not covered and therefore decided not to have that drug dispensed. Yet, those patients may have asked their physician for a new prescription for a reimbursed drug and thus initiated the treatment. Our results do not include those possible second prescriptions, and therefore our results could potentially overestimate the proportion of primary non-adherence.

Methodological relevance

Not knowing how or when an issued prescription is collected has the potential to cause misclassification bias, where researchers wrongly assume that drug use has been initiated when it may not be, and thus wrongly associate an outcome occurring during that time with the use of the drug being studied. We found that about 8% of new antidepressants and 6.7% of new statin prescriptions are not dispensed within a year from issue. How this might impact outcome research in antidepressant or statin users when healthcare data from prescribers are used, needs further investigation.

Strengths and limitations

The main strength of this study is the completeness of data for the patients included in our study. The unique personal identifying number used in both databases allows for reliable and secure linkage of information from the prescribing and dispensing databases. The main limitation of this study is the relatively small size of the study population, which resulted in the groups of late and non-adherers including very few patients. Another possible limitation is that the prescription data which were used only includes prescriptions from physicians working in healthcare centres in the capital city Reykjavik and nearby municipalities, but does not include prescriptions issued by other medical specialists, working outside the healthcare centres. Therefore, our results do not apply to patients receiving their first antidepressant or statin from specialists, such as cardiologists or psychiatrists.

Conclusion

The rate of primary non-adherence is low for statins and antidepressants in Iceland. Most patients have their new prescriptions dispensed within 7 days after having it issued, and only a small number of patients wait 8–365 days to have their prescription dispensed. Primary non-adherence is most notably associated with the more vulnerable group of disabled patients receiving a prescription for expensive drugs. It is therefore important to pay special attention to this patient group when treatment is initiated, and perhaps try to use a more affordable drug if possible.

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Author contributions

GTh, AP, KL, ABA and HG designed the study. AP performed the data analysis. GTh, AP, KL, ABA and HG interpreted the results. GTh drafted the manuscript, which was critically reviewed by AP, MH, KL, ABA and HG. All authors read and approved the final version of the manuscript.

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