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ORIGINAL RESEARCH ARTICLE

Effect of Information Intervention on Prescribing Practice for Neuropathic Pain in Older Patients: A Nationwide Register-Based Study

Iiro Ahomäki[1,2] · Petri Böckerman[1] · Jaakko Pehkonen[1] · Leena Saastamoinen[2]

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Abstract

Introduction Management of prescription medicines is challenging for older patients due to frail health and the prevalence of multiple chronic conditions. A salient policy challenge of prescribing practices is that all physicians are not well informed about the national clinical guidelines. A feasible policy intervention to mitigate the harms caused by Potentially Inappropriate Medications is to influence the frequency of prescribing and other prescribing attributes of the drugs by providing accurate and up-to-date information about the national clinical guidelines.

Objectives The objective of this study was to examine the effect of a nationwide information intervention on physicians' prescribing practices and patients' healthcare utilization.

Methods We used a quasi-experimental research design based on difference-in-differences variation and nationwide register data on prescribers and purchasers of pregabalin, nortriptyline, and amitriptyline combinations in Finland between January 2018 and May 2019. The study included 68,914 patients and 11,432 physicians.

Results We found that the information letter sent to all prescribers of pregabalin, nortriptyline, or amitriptyline combinations to patients aged 75 years or older decreased the probability of prescribing of these medications. The estimated effect of − 3.3 percentage points (95% confidence interval [− 0.041, − 0.024]) corresponds to a 29% reduction compared to the baseline mean of the outcome. The filled quantity, measured in Defined Daily Doses, of pregabalin, nortriptyline, and amitriptyline combinations per month was reduced by 11.7% [− 14.5% to − 8.9%] among patients aged 75 years or older. No effect on patients' healthcare utilization was observed.

Conclusions Findings of the study suggest that personal information intervention was an effective policy tool for nudging physicians to reduce prescribing of potentially inappropriate medicines, whereas the reduction in prescribing was not accompanied by improvements or adverse effects in patients' health.

1 Introduction

Management of prescription medicines is challenging for older patients due to frail health and the prevalence of multiple chronic conditions. For example, pregabalin (Anatomical Therapeutic Chemical (ATC)) code: N03AX16), nortriptyline (ATC: N06AA10), and amitriptyline (ATC: N06AA09) are drugs that are commonly used to treat neuropathic pain, which is a common complication of long-lasting conditions such as diabetes [1]. These drugs are recommended to be avoided, prescribed with caution, or, in case of even mild renal impairment, prescribed with decreased dosages for older adults [2–4]. Importantly, the Beers Criteria suggest avoiding prescribing or lowering the dose of pregabalin for older adults due to adverse health effects associated with the central nervous system, as well as avoiding prescribing of nortriptyline and amitriptyline because of their anticholinergic and sedative properties. All three of these drugs were also on the Finnish national list of drugs to be avoided for older adults during the study time [3].

A salient policy challenge of prescribing practices is that all physicians are not well informed about the national clinical guidelines. A feasible policy intervention to mitigate the harms caused by Potentially Inappropriate Medications (PIMs) is to influence the frequency of prescribing and other

✉ Iiro Ahomäki
iiro.l.j.ahomaki@jyu.fi

[1] School of Business and Economics, University of Jyväskylä, PO Box 35, 40014 Jyvaskyla, Finland

[2] The Social Insurance Institution of Finland, Helsinki, Finland

Key Points

Previous studies have found inconclusive evidence about the effects of information interventions on physicians' prescribing practices and on patients' health.

We used nationwide registry data and quasi-experimental design based on difference-in-differences variation to show that an information intervention decreased prescribing of potentially inappropriate medicines to patients aged 75+ years.

Our study shows that a physician-targeted information letter, providing feedback based on physicians' prescribing history as well as information about national clinical guidelines, reduces the scale of inappropriate prescribing.

prescribing attributes of the drugs by providing accurate and up-to-date information about the national clinical guidelines [5, 6].

Due to the large number of older patients using potentially inappropriate amitriptyline, nortriptyline, and pregabalin, the Social Insurance Institution of Finland (Kela) sent a letter to 7,801 physicians on 29 May 2018 (the content of the information letter is documented in the Online Supplementary Material (OSM)). Kela sent the information letter to all physicians in Finland who had prescribed pregabalin, nortriptyline, or amitriptyline and psycholeptic combinations (ATC: N06CA01) in 2017 to at least one patient aged 75 years or older (henceforth 75+ years). The explicitly stated objective of the letter was to draw attention to prescribing practices of the use of these medication in neuropathic pain. The information letter stated that the use of pregabalin, nortriptyline, or amitriptyline contains substantial health risks for older patients, and that prescribing these medications to patients aged 75+ years should be avoided. The letter explained that tricyclic antidepressants are highly anticholinergic, sedative, and have many interactions with other drugs. Moreover, pregabalin is sedative, addictive, and is associated with the risk of falls, according to the letter. In addition, the letter recommended paracetamol as first-line drug therapy for pain for older patients, and venlafaxine and duloxetine as second-line options if paracetamol is not effective enough in neuropathic pain.

Our study examined the effect of this information letter on physicians' prescribing practices, patients' healthcare utilization, and PIM-related diagnoses in a nationwide setting. We chose the diagnoses to be investigated based on prior research, for example, Hyttinen et al. [7], and the risks listed in the information letter. We also examined the possible substitution effects to gabapentin, venlafaxine, duloxetine, paracetamol, and anti-inflammatory drugs. We studied gabapentin because it is recommended as a first-line therapy for neuropathic pain in some guidelines [8]. Venlafaxine, duloxetine, and paracetamol were recommended as safer treatment options in the information letter. Anti-inflammatory drugs were chosen because they, especially ibuprofen, are widely used pain medications in Finland [9].

Our study contributes to the literature examining the effects of large-scale information interventions on physicians' prescribing behavior [10–13]. More generally, evidence on the effectiveness of educational or regulatory interventions on the prescribing behavior is, according to a recent review, relatively sparse [14]. However, there is more evidence that changing the default settings (e.g., lowering the number of tablets or using generic products as a default in electronic prescribing system), and providing social reference points (e.g., providing recommendations from an opinion leader or referring to social norms within the profession) are effective methods for changing physician behavior [15].

2 Data and Methods

2.1 Data Sources and the Study Sample

We used data from three nationwide registers maintained by Kela, the Finnish Institute for Health and Welfare, and Statistics Finland. To construct the balanced panel used in the empirical analyses, we aggregated prescription and discharge registers to patient-month level and linked them based on unique patient identifiers (see OSM for details).

The population under investigation, for which we retrieved the prescription and discharge data, consists of patients who filled a reimbursed pregabalin, nortriptyline, or amitriptyline combination prescription in a Finnish pharmacy between January 2018 and May 2019, and physicians who prescribed those drugs. We estimated all models using data from January 2018 onwards for two reasons. First, there was no meaningful comparison of the probabilities of patients aged 75+ years filling a prescription for the abovementioned drugs between the treatment and comparison groups before December 2017, because Kela chose the recipients of the information letter based on prescribing information from 2017. Second, there was a possibility of regression to the mean in the treatment group after the selection period, i.e., after December 2017 [16].

We excluded patients (n = 11,195) who had filled prescriptions from both the physicians who received the information letter and the physicians who did not receive the letter. In addition, we excluded patients who died during the study period (n = 3670).

2.2 Outcome Measures

For prescribing, the outcome variables were a logarithmic transformation of Defined Daily Doses (DDDs), and an indicator variable for patients aged 75+ years filling pregabalin, nortriptyline, or amitriptyline combinations during a given month (see OSM for details). For substitution analysis, we constructed five indicator variables taking the value of 1 if a patient filled a gabapentin (ATC: N03AX12), venlafaxine (ATC: N06AX16), duloxetine (ATC: N06AX21), paracetamol (ATC: N02BE01), or anti-inflammatory (ATC: M01) drug prescription during a given month. In addition, we constructed indicator variables for hospitalizations, outpatient primary care, and PIM-related diagnosis.

2.3 Other Measures

Kela provided us, together with the Prescription Registry data, an indicator variable taking the value of 1 if the prescription was issued by a physician who received the information letter. We also used information on the age, sex, and native language of physicians and patients, as well as the specialty of physicians.

To evaluate the coverage of the data, we calculated, from the retrieved data, the sum of filled pregabalin DDDs in 2018 per 1000 people per day in Finland.

2.4 Research Design and Statistical Analysis

The research design was based on a difference-in-differences (DiD) method and event study framework that use variation in outcomes before and after the intervention, and allow for a graphic representation of the effect of the intervention [17].

We compared the changes in outcomes between the patients of two distinct groups of physicians by estimating multivariable regressions in which the unit of observation was patient-month (see OSM for details). The treatment group ($N = 50{,}003$) consisted of patients whose pregabalin, nortriptyline, or amitriptyline combinations prescriptions were issued only by physicians ($N = 6569$) who received the information letter, and also prescribed these drugs during the study period, i.e., between January 2018 and May 2019. The comparison group ($N = 18{,}911$) consisted of patients who also filled a pregabalin, nortriptyline, or amitriptyline combination prescription during the study period but whose prescriptions were issued only by physicians ($N = 4863$) who had prescribed these drugs also in 2017 but did not receive the information letter. To illustrate the setting, if a physician prescribed pregabalin to only one patient in 2017, and the patient was 75 years old, all of his or her subsequent patients were assigned to the treatment group. On the contrary, if a physician prescribed pregabalin to only one patient in 2017, and the patient was 74 years old, his or her subsequent patients were assigned to the comparison group. Consequently, in advance, the only difference between the physicians who received the letter and those who did not was the patient age limit of 75 years, stated in the clinical guidelines.

Kela sent the letter to physicians on 29 May 2018. We used 1 June as the first treatment date, because there is a 1- to 2-day delay in delivering the letters by regular mail. In the DiD analysis, the first difference was the difference in outcomes between the treatment and comparison groups. The second difference was the comparison of before and after the receipt of the information letter.

Identification in the DiD method is based on the assumption of parallel outcome trends between the treatment and comparison groups in the absence of the information letter, i.e., confounders that varied across the groups were constant in time, and confounders that changed over time were group invariant [17, 18]. The assumption was not directly testable because the treatment group counterfactual is unobservable. The time gap between the intervention decision and the implementation of the intervention allowed us to use a pre-treatment period where the prescribing behavior and receiving the letter were unrelated. Because physicians were unaware of the delivery of the information letter beforehand, anticipatory effects of the intervention were very unlikely.

To illustrate the pre-treatment trends and the effect of the information letter graphically, we estimated event study models. The event study design has two advantages over the standard DiD method. First, by including the leads of the treatment, we were able to explicitly examine the pre-treatment trends, and provide support for the assumption that unobserved factors were not driving the outcome trends. Second, by including lags, we were able to assess the dynamics and time persistence of the effect [19].

We evaluated the sensitivity of the results to several different model specifications, variable transformations, and study population (see OSM for details).

3 Results

3.1 Descriptive Statistics

The sum of filled pregabalin DDDs in 2018 in the data retrieved from the Prescription Register was 9,548,412.5, which was 4.73 DDDs per 1000 people per day in Finland. For nortriptyline, and amitriptyline combinations, the sum of filled DDDs per 1000 people per day was 0.17 and 0.72, respectively. The descriptive statistics of the study sample, as well as the physicians who received the letter and

physicians whose patients constituted the comparison group, are presented in the OSM (Tables S2 and S3).

3.2 Effect of Information Letter on Prescribing

The information letter decreased the probability of filling a prescription of pregabalin, nortriptyline, or amitriptyline combinations among patients aged 75+ years. Figure 1 graphically presents the point estimates and corresponding 95% confidence intervals (CIs) for the coefficients on the interaction between month dummies and the treatment group. The effect depicted in Panel A of Fig. 1 converts to the DiD estimate of -0.033 (95% CI [− 0.041, − 0.241]), which corresponds to a 29% (=(− 0.033/0.115) × 100) decline compared to the baseline mean of the outcome (Table 1, column 1).

The estimates show no difference in the outcome trends before the treatment time, i.e., the coefficient estimates for pre-treatment months do not differ statistically from zero. This supports the identification assumption about the parallel outcome trends in the absence of the information letter. The estimated effect of the information letter on the filled quantity, measured using a logarithmic transformation of DDDs per month, of pregabalin, nortriptyline, and amitriptyline combinations per month was 11.7% [− 0.144, − 0.089] for patients aged 75+ years (Table 1, column 2).

3.3 Substitution Effects of Information Letter

We found no clear evidence of substitution from pregabalin, nortriptyline, and amitriptyline prescriptions to gabapentin, venlafaxine, duloxetine, paracetamol, or anti-inflammatory drugs (OSM Fig. S2 and Table S5). The DiD point estimates for gabapentin and paracetamol were statistically significant ($p < 0.05$), and, compared to the baseline prescribing of the drugs, the decreases of 64% and 20%, respectively, were large (OSM Table S5, columns 1 and 5). However, the significant differences in pre-treatment trends suggests that the

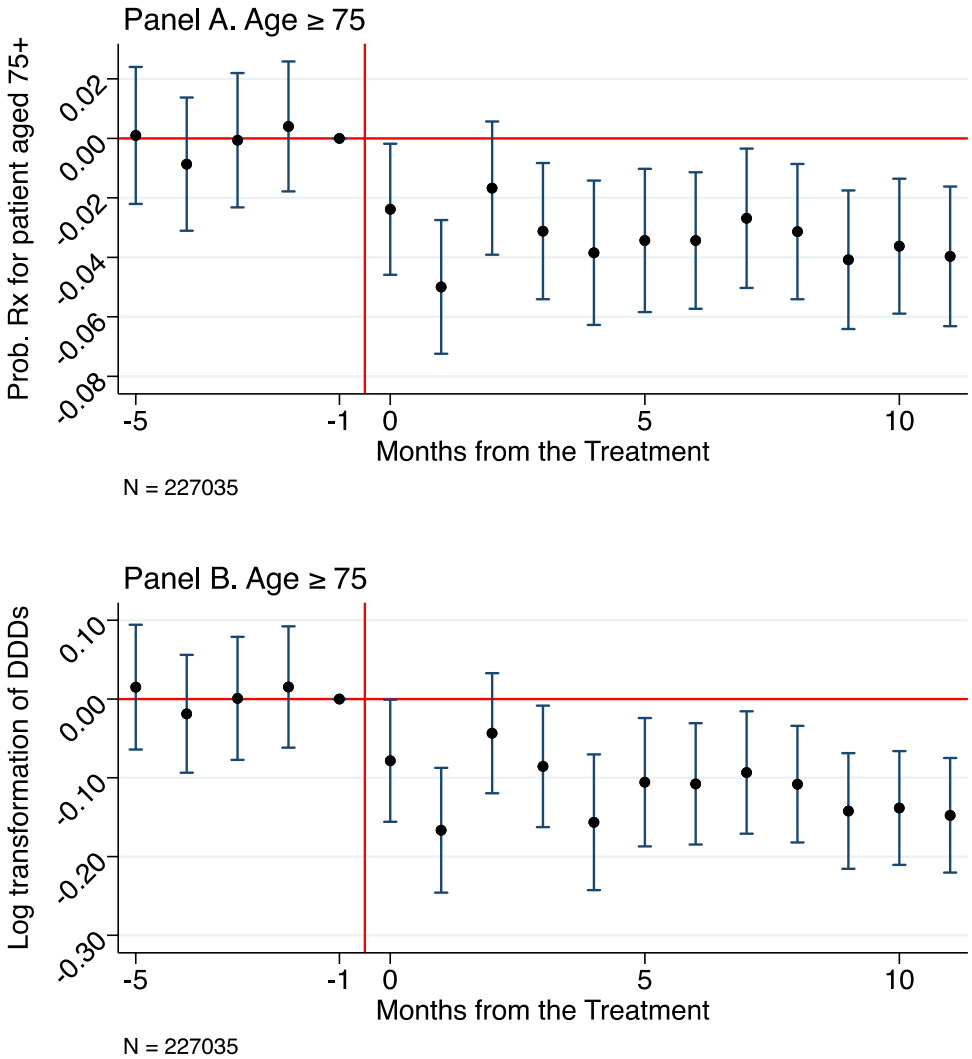

Fig. 1 Effect of information letter on prescribing pregabalin, nortriptyline, and amitriptyline combinations to patients aged 75+ years. *Notes:* Coefficients and 95% confidence intervals based on an event study regression (Equation (2) in the OSM). Estimated using patient-month level balanced panel data. The outcome is shown in the title of the vertical axis. Variable Rx for patient aged 75+ years takes the value of 1 if a patient aged 75+ years was issued a prescription in a given month. Logarithmic transformation of Defined Daily Doses (DDDs) is defined as Log(DDD+1). The vertical axes have different scales. The vertical line represents the treatment time (i.e., receipt of information letter). The regressions control for time and patient fixed effects. Standard errors are clustered at the patient level. The corresponding difference-in-differences (DiD) point estimates are reported in Table 1, columns 1 and 2

Table 1 Effect of information letter on prescribing pregabalin, nortriptyline, and amitriptyline combinations to patients aged 75+ years, difference-in-differences results

	(1) Prob. Rx for patient aged 75+	(2) Log transformation of DDDs
After × Treatment	− 0.0328***	− 0.1170***
	(0.0044)	(0.0141)
Observations	227,035	227,035
Number of unique patients	13,355	13,355
Time effects	Yes	Yes
Patient fixed effects	Yes	Yes
Outcome baseline mean	0.115	0.392

Notes: Standard errors are clustered at the patient level and presented in parentheses. All models estimated using difference-in-differences (DiD) specification (Equation (1) in the OSM) and patient-month level balanced panel data from January 2018 to May 2019. Variable Rx for patient aged 75+ years takes the value of 1 if a patient aged 75+ years was issued a prescription in a given month. Logarithmic transformation of Defined Daily Doses (DDDs) is defined as Log(DDD+1). *** $p < 0.01$, ** $p < 0.05$

decrease was driven by an unobserved factor (OSM Fig. S2, panel A).

3.4 Effect of Information Letter on Health

The results for healthcare utilization (Fig. 2) revealed no clear effect on the probability of being hospitalized for patients aged 75+ years. Correspondingly, the DiD estimate for patients aged 75+ years was not statistically different from zero (Table 2, column 1). The second measure for healthcare utilization was the probability of outpatient primary-care visits. The event study results for patients aged 75+ years revealed no consistent reduction in the probability of outpatient primary-care visits after the information letter (Fig. 2, panel B). The DiD estimate of − 0.0138 [− 0.0293, 0.0017] was not statistically significant (Table 2, column 2). The results showed no effect on the probability of PIM-related diagnoses (Table 2, column 3). The event study results did not show either a significant difference in pre-trends or effect of the treatment (Fig. 2, panel C). Figure S3 (OSM) presents the results for different diagnosis classes used in constructing the PIM-related diagnosis variable. The information letter also had no effect on these more specific diagnosis classes.

4 Discussion

The nationwide information letter to Finnish physicians about the national clinical guidelines for prescribing medications for neuropathic pain significantly decreased the probability of filling a prescription of pregabalin, nortriptyline, or amitriptyline combinations among patients aged 75+ years. The estimated effect was 3.3 percentage points. This corresponds to a 29% decline compared to the baseline mean of the outcome. The filled quantity of pregabalin, nortriptyline, and amitriptyline combinations per month was reduced by 11.7% for patients aged 75+ years. The results for prescribing outcomes showed that personal feedback and information had an effect on prescribing that prevailed over and above the general information available to all physicians from public information sources.

There was no clear substitution for gabapentin, venlafaxine, duloxetine, paracetamol, or anti-inflammatory drugs. We found no effect on the healthcare utilization or the potentially inappropriate medicine-related diagnoses for patients aged 75 years or older.

Recent research examining the effects of large-scale information interventions on opioid [10, 11] and antipsychotic prescribing [13] has found significant decreases in prescribing. Ahomäki et al. [10], Doctor et al. [11], and Sacarny et al. [13] studied the effects of an information intervention, a personal letter informing physicians that their patient had died from an overdose of a controlled substance, and a peer comparison letter accompanied by a notification that physicians' prescribing was under review, respectively. Sacarny et al. [12] evaluated the effect of a peer comparison intervention on over-prescribing of a more wide-ranging class of controlled substances (including, e.g., opioids, amphetamines, and methylphenidate). Our results for prescription outcomes are of the same quantitative magnitude as those of Ahomäki et al. [10], Doctor et al. [11], and Sacarny et al. [13]. However, the null effects of a rather similar large-scale information intervention found by Sacarny et al. [12] stand in contrast to our results.

The absence of substitution to medications recommended in the information letter (venlafaxine, duloxetine, and paracetamol) and to gabapentin is consistent with previous studies that have found no substitution from codeine prescribing to other opioids [10], or only a small substitution from quetiapine prescribing to other antipsychotics [13] after similar information interventions. We found no statistically significant reduction in healthcare utilization. This result is consistent with the results of Sacarny et al. [13], who detected no effects on healthcare utilization or mortality.

Inaccurate knowledge and information of all stakeholders, including physicians and patients, regarding effective and ineffective care has been identified as a key driver of

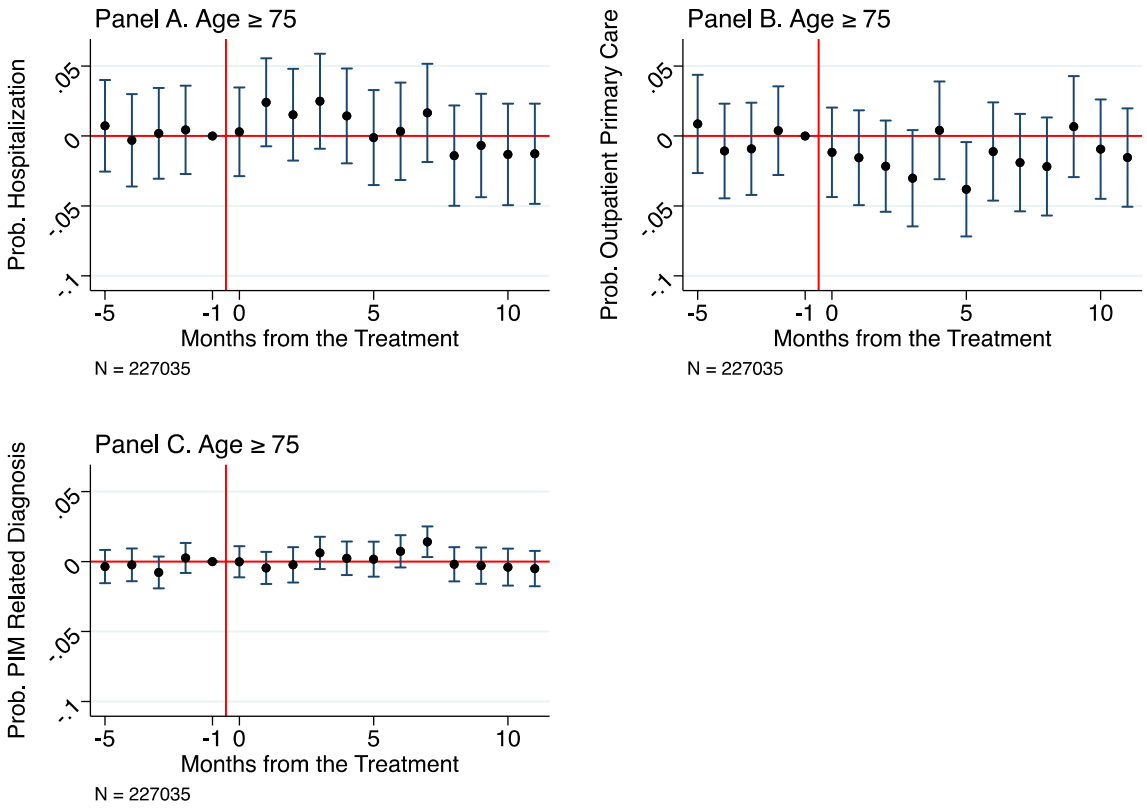

Fig. 2 Effect of information letter on health outcomes of patients aged 75+ years. *Notes:* Coefficients and 95% confidence intervals based on an event study regression (Equation (2) in the OSM). Estimated using patient-month level balanced panel data. The outcome is shown in the title of the vertical axis. The vertical line represents the treatment time (i.e., receipt of information letter). The regressions control for time and patient fixed effects. Standard errors are clustered at the patient level. The corresponding difference-in-differences (DiD) point estimates are reported in Table 2. *PIM* Potentially Inappropriate Medications

Table 2 Effect of information letter on health outcomes of patients aged 75+ years, difference-in-differences results

	(1) Prob. hospitalization	(2) Prob. outpatient primary care	(3) Prob. PIM-related diagnosis
	Age ≥ 75 years	Age ≥ 75 years	Age ≥ 75 years
After × Treatment	0.0024	− 0.0138	0.0031
	(0.0085)	(0.0079)	(0.0030)
Observations	227,035	227,035	227,035
Number of patients	13,355	13,355	13,355
Time effects	Yes	Yes	Yes
Patient fixed effects	Yes	Yes	Yes
Outcome baseline mean	0.260	0.671	0.0349

Notes: Standard errors are clustered at the patient level and presented in parentheses. All models estimated using difference-in-differences (DiD) specification (Equation (1) in the OSM) and patient-month level balanced panel data from January 2018 to May 2019. PIM-related diagnosis consists of fractures, adverse drug effects, fall-related diagnosis, and memory-related diagnosis. *PIM* Potentially Inappropriate Medications. *** p <0.01, ** p <0.05

inadequate healthcare [6]. Our study shows that a physician-targeted information letter, providing feedback based on physicians' prescribing history as well as information about national clinical guidelines, reduces the scale of inappropriate prescribing. However, when evaluating the generalizability of the findings, it should be emphasized that Finland

has recently attempted to improve the quality of drug treatment through other methods as well. These approaches, which may be utilized in other nations in a different manner, include the national Rational Pharmacotherapy Action Plan [20], the supervisory authority access to prescription register data, and the national potentially inappropriate medications database (Meds75+ published by the Finnish Medicines Agency) [3].

The prescribing of PIMs to older patients is related to an elevated risk of adverse drug effects, and consequent hospitalizations [21–24]. There are no previous nationwide studies of the prevalence of hospitalizations caused by adverse drug effects in Finland. In local settings, it has been estimated that 14–23% of emergency department visits of older patients were related to adverse drug effects [25, 26].

4.1 Strengths and Limitations

The intervention implemented by the Social Insurance Institution of Finland in sending the information letters to the prescribers of pregabalin, nortriptyline, and amitriptyline combinations for older adults in a single country provided a nationwide quasi-experimental research setup. The setting enabled the use of the DiD method to tease out the effects of the intervention. DiD models have been used in the medical literature, for example, to study the effects of Medicaid expansions on uninsurance rates and healthcare utilization, as well as the effect of insurance expansion on the use of elective surgical procedures and healthcare utilization in the USA [27, 28]. The event study regressions provided support for the parallel outcome trends between the treatment and comparison groups, which is the most important identifying assumption of the research method. However, in an ideal research setting the recipients of the information letter would have been assigned randomly into treatment and control groups.

A key strength of our study was the use of nationwide register data covering all filled outpatient prescriptions reimbursed under the national health insurance scheme and healthcare records for all patients in Finland. The study sample did not contain information on drugs administered in hospitals, or on medicines that were not reimbursed under the national health insurance scheme. However, the coverage of the data was still very high. The overall use of pregabalin, the most commonly used medicine under investigation in our study, was 5.19 DDDs per 1,000 people per day in Finland in 2018 [9]. The corresponding quantity in the data we retrieved for the study was 4.73, i.e., 91% of the total amount of pregabalin used in Finland in 2018.

We did not observe if the physicians to whom the information letter was sent read it. Thus, the estimates can be interpreted as the intention-to-treat (ITT) effects of the information letter. In addition, the physicians who did not receive the letter might have been aware of its content from other sources, because the core content of the letter was published in The Finnish Medical Journal and on the Social Insurance Institution web page simultaneously with the delivery of the personal letter. Hence, we estimated the effect of receiving the information personally compared to not receiving it at all or receiving it from public sources.

The 12-month follow-up period, together with the fixed-effects specifications, may not be long enough to detect the effect on diagnosis classes (i.e., adverse drug effects, fall-related, fractures, memory-related, and PIM-related health diagnoses) that have low incidence rates (0.06–1.7%). We were not able to distinguish between pre-existing PIM-related health diagnoses and those diagnosed for the first time during the study period. The long-term health effects of the decreased availability of pregabalin, nortriptyline, or amitriptyline and psycholeptic combinations for patients aged 75+ years is an important topic for future research.

5 Conclusion

Our results support the conclusion that personal information letters are an effective policy tool for nudging physicians to reduce prescribing of potentially inappropriate medicines. The reduced prescribing did not lead to a lower probability of PIM-related adverse health conditions. After the intervention, the targeted patient healthcare utilization neither reduced nor increased, indicating that the decreased availability of PIMs had no health advantages or adverse effects.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-022-00993-4.

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Declarations

Author contributors IA analyzed the data and wrote the first draft of the manuscript. All authors designed the study, critically revised the manuscript, and gave final approval of the version to be published.

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Conflict of interest IA and LS receive salary from the Social Insurance Institution of Finland, which also provided funding for the research, collects and maintains part of the data used in the research, as well as implemented the intervention under investigation in the study. PB and JP declare that they have no conflicts of interest.

Consent to participate Not applicable.

Consent for publication Not applicable.

Ethics approval Not needed for a register-based study due to the Finnish legislation.

Data sharing The data used in the study cannot be shared due to legal restrictions. The data can be obtained by sending a direct request to the Social Insurance Institution of Finland and the Finnish Institute for Health and Welfare.

Code availability Not applicable.

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