DISCUSSION PAPER SERIES

Effect of an Information Intervention on Opioid Prescribing: A Preregistered Nationwide Randomized Experiment

Iiro Ahomäki
Petri Böckerman
Jaakko Pehkonen
Leena Saastamoinen

DISCUSSION PAPER SERIES

Effect of an Information Intervention on Opioid Prescribing: A Preregistered Nationwide Randomized Experiment

Iiro Ahomäki
Jyväskylä University and The Social Insurance Institution of Finland

Petri Böckerman
Jyväskylä University and IZA

Jaakko Pehkonen
Jyväskylä University

Leena Saastamoinen
Finnish Medicines Agency

ABSTRACT

Effect of an Information Intervention on Opioid Prescribing: A Preregistered Nationwide Randomized Experiment

We study the impact of an information intervention on opioid prescribing using a preregistered research design and comprehensive nationwide register data. The intervention involved a personal letter sent to all Finnish physicians who had prescribed oxycodone or fentanyl to a patient who had purchased at least three months' supply of these medications in the previous year. These physicians were randomized into the treatment and control groups. The letter was sent to physicians in the treatment group in May 2019, and the control group received the same letter six months later. The intervention letter contained information about opioid use and proper pain treatment using opioids based on national clinical guidelines. While the intervention showed no significant effects in the whole study population, we detected heterogeneity in effect with respect to preregistered physician characteristics. We observed a 22% reduction in fentanyl and oxycodone prescriptions to new patients among physicians receiving their first information letter, a 4.8% reduction in any opioid prescriptions among high-volume prescribers as well as an increase of 7% in nonopioid analgesic prescribing among low-volume prescribers. These results highlight the challenges policymakers encounter when attempting to sustainably reduce opioid prescriptions and mitigate harmful clinical practices through repeated information-based interventions.

JEL Classification:	I10, I12, I19
Keywords:	opioid prescribing, information intervention, randomized experiment

Corresponding author:
Iiro Ahomäki
School of Business and Economics
PO Box 35 FI-40014
University of Jyväskylä
Jyväskylä, FI 40014
Finland
E-mail: iiro.l.j.ahomaki@jyu.fi

1   Introduction

Opioids have caused considerable health harms and excess deaths in many high-income countries. For example, in the U.S., the number of drug overdose deaths has quadrupled since 1999, reaching approximately 92,000 in 2020. The estimated increase in the age-adjusted death rate from 2019 was 31%. Notably, opioids were associated with 70% of these deaths. Since 1999, nearly 500,000 people have died prematurely due to opioid overdoses in the U.S., including those involving prescription and illicit opioids (CDC 2022a; Hedegaard and Warner 2021).

Cutler and Glaeser (2021) and Ruhm (2019) have found that demand-side factors, such as physical and mental pain, despair, local economic conditions, and the opportunity cost of time, explain only a small fraction of the increased use of opioids and the subsequent surge in deaths in the U.S. On the supply side, major innovations initially occurred within the legal market. Physicians increased their opioid prescribing following the introduction of OxyContin and the effective marketing that accompanied its launch (Alpert et al. 2022).

Opioid prescribing has declined since 2012 (CDC 2022b). However, the introduction of fentanyl and its increased import to the U.S. from China and other countries (Maclean et al. 2022), coupled with a rise in heroin use (Alpert, Powell, and Pacula 2018), have offset the decrease in the prescribing rates (CDC 2022b). These factors have significantly contributed to the ongoing opioid epidemic (Cutler & Glaeser 2021).

Opioid use is a salient public health concern not only in the U.S. but also in many other high-income countries. Opioid prescribing increased in most European countries until 2016. For instance, in the UK, opioid-related deaths per population in 2019 were comparable to those in the U.S. in 2018. (Bosetti et al. 2019; Häuser et al. 2021). Opioids

are also widely prescribed in the Nordic countries. For example, in 2019, 378 000 individuals purchased opioids reimbursable under the national health insurance scheme in Finland, the country our study focusses on. Of them, 59,000 purchased oxycodone or fentanyl (Kela 2024). Rönkä et al. (2020) have estimated that almost 1% (approximately 24,000–30,000 individuals) of the working-age population in Finland were problem users of opioids in 2017. Moreover, Finland has been identified as one of the European countries where opioid-related deaths increased between 2000 and 2018. (Häuser et al. 2021).

A straightforward policy to mitigate the harms caused by opioids is for doctors to prescribe fewer of them (Samet and Kertesz 2018). In particular, the amount of opioids prescribed to new patients has been closely linked to long-term use due to the highly addictive nature of these substances (Barnett, Olenski, and Jena 2017; Shah, Hayes, and Martin 2017). Possible policy interventions to influence opioid prescribing include providing physicians with information about national clinical guidelines, offering peer comparisons, and manipulating the default settings in electronic prescribing systems (Wang and Groene 2020).

In this paper, we estimate the causal impact of an information intervention on opioid prescribing outcomes. Our results are based on a preregistered study design utilizing nationwide register data and the randomization of physicians into the treatment and control groups. The information intervention under investigation is a letter (discussed in Section 2.3 and described in detail in Appendix B) sent by the Social Insurance Institution of Finland (Kela) to physicians of patients who had purchased more than three months' supply of oxycodone or fentanyl in 2018. Patients whose purchases of these opioids was reimbursed based on a cancer diagnosis were excluded. The physicians were randomized to receive the letter either in May or December 2019.

4

Our research design has three strengths: First, our data set offers extensive register-based information spanning several years and encompassing all opioid prescriptions issued in outpatient settings in Finland as well as health-care contacts for individuals to whom the prescriptions were issued. Second, the staggered timing of the information intervention was based on randomization in a nationwide context, covering the entire relevant patient population. Third, our study setting allows us to document responses to repeated use of physician-targeted information interventions, which is a considerable advantage in contrast to previous studies. This advantage stems from the fact that a fraction of the research population's physicians had already received one or two similar interventions previously, and those who received an additional intervention were, in effect, selected at random.

Our research contributes to the literature studying the impacts of large-scale information interventions on the opioid prescribing behavior of physicians (Ahomäki et al. 2020; Doctor et al. 2018; Navathe et al. 2022; Sacarny et al. 2016). The results of earlier empirical research remain inconclusive. Doctor et al. (2018) found that information letters reduced opioid prescribing and the probability of prescribing opioids to new patients. Ahomäki et al. (2020) found that the information letter reduced opioid prescribing to new patients. Conversely, Sacarny et al. (2016) did not find a significant effect on prescribing controlled substances, including opioids. Navathe et al. (2022) found that peer comparison feedback reduced opioid prescribing both as a separate intervention and when combined with individual audit feedback. Moreover, they found that individual audit feedback alone did not have an effect on prescribing. In a broader context, evidence on the effectiveness of educational or regulatory interventions in influencing prescribing behavior is relatively limited, as highlighted in a recent review of the literature (Suleman and Movik 2019). There is stronger evidence suggesting that

changing the default settings, such as reducing the default number of tablets, establishing generic products as the default option in electronic prescribing systems, or employing social reference points are effective strategies for changing physicians' behavior (Wang and Groene 2020).

Our study is also connected to the literature that examines the long-term effects or repeated implementation of behavioral interventions (e.g., Allcott and Rogers (2014) and references therein). These studies have shown that behavioral interventions induce more persistent reductions in behaviors such as energy use when the interventions are used repeatedly. To the best of our knowledge, there are no previous studies examining the repeated use of information interventions in the context of opioid prescribing. Moreover, we study the differences in responses to the intervention between physicians working in the private and public sectors. Physicians' incentives to provide a certain quantity and quality of care may differ between private and public sector health care (Biglaiser and Albert Ma 2007). In addition, empirical findings suggest considerable variation in prescribing between physicians employed in the public and private sectors in Finland (Jussila, Kotakorpi, and Verho 2023). Consequently, we hypothesized that the response to information interventions can also be different for physicians working in different sectors.

We contribute to the literature by addressing the following research questions: First, what was the effect of the information letter on physician-level opioid prescribing outcomes? Second, what was the effect of repeated use of physician-targeted information letters? Third, was there a difference in response to the intervention between physicians prescribing opioids in the private and public sectors? Moreover, we examine the differences in the effects between high- and low-volume opioid prescribers, substitution

to other common pain medicines, and the impact on prescribing to non-cancer patients. The latter analysis is not based on preregistration.

2   Preregistered experimental design

We preregistered the outcomes and econometric analyses at the AEA Trial Registry (AEARCTR-0008439) before gaining access to the data we use to evaluate the causal impacts of the intervention. As we report our results, we flag all unregistered analyses.

Kela identified all physicians (n=7,109) who had prescribed strong opioids (oxycodone or fentanyl) to a patient who had purchased more than three months' supply of these opioids in Finland in 2018. Patients with a cancer diagnosis in the national special reimbursement eligibility register were excluded. In addition to identifying the physicians, Kela was responsible for the randomization and sending the letters in May 2019 (n=3,563) and in December 2019 (n=3,546).

2.1   Data sources

We use four administrative nationwide registers as data sources for this study. First, we use prescription data from Kanta Prescription Centre. These data allow us to track all prescriptions and the related dispensing of the drugs nationwide. Second, we use information on physician characteristics from Digital and Population Data Services Agency. Finally, to identify patients with a cancer diagnosis, we use data from Finnish Care Register for Health Care and the Register of Primary Health Care Visits maintained by the Finnish Institute for Health and Welfare. In addition to register data, Kela provided us with unique identification numbers for physicians to whom the information letter was sent in 2019, 2018, and/or 2017, allowing us to link physicians who received these interventions to prescription data.

2.2   *Study sample and outcomes*

To construct the study sample that we use in the main analysis, we link the aforementioned datasets and calculate the preregistered outcomes. The unit of observation in the analysis is a physician. We study the period between June 1, 2019, and November 30, 2019 (November is the last full month before the information letter was sent to the control group and the experiment ended). We also calculate the outcome variables for the six-month period prior to the intervention (from December 2018 to May 2019). Hereafter, we will refer to these quantities as the baseline values of the variables. For prespecified primary outcomes, we also analyze the short-term effects of the information letter by looking at time periods of one and three months. In the study sample, there are 7,109 physicians (treatment group n=3,563 and control group n=3,546). During the study period, they prescribed opioids to 180,750 patients of whom 29,769 were prescribed oxycodone or fentanyl.

For fentanyl and oxycodone prescribing, the primary outcome that we use is the number of fentanyl (ATC[1]: N01AH01 and N02AB03) and oxycodone (ATC: N02AA05) prescriptions. For opioid prescribing, the primary outcome is the number of opioid (ATC: N02A, N01AH, N07BC) prescriptions. Moreover, we preregistered the quantity of prescribed drugs (Morphine Milligram Equivalent (MME)) as an outcome. Of the 304,761 observations (opioid prescriptions issued during the study period) in the raw data, 22,167 were prescribed for a certain time period (e.g., one week) Therefore, we have no information on the number of prescribed units and were unable to study this outcome.

---

[1] The ATC Index (Anatomical Therapeutic Chemical Classification System) is a standardized system used to classify drugs based on their therapeutic use and chemical characteristics (WHO 2021).

To study different margins and heterogeneity of the possible effect, we construct the following variables: prescriptions issued to new patients (who had no opioid or fentanyl prescriptions in the preceding 365 days), number of previous information letters sent to the physician, number of fentanyl and oxycodone prescriptions the physicians have issued in the public and private sectors, and a dummy variable based on which sector (public or private) the physicians issued more fentanyl and oxycodone prescriptions.

To identify the possible substitution effects of the information letter, we calculate the number of nonopioid analgesic (NOA) (ATC: M01, N02BE01) prescriptions the physicians in the study population issued during the study period.

2.3 Information letter

Out of the 7,109 physicians who prescribed oxycodone or fentanyl to patients[2] who purchased at least a three-month supply of these opioids in 2018, 3,563 were randomly allocated to receive a letter with national clinical guidelines on proper pain management and opioid prescribing recommendations in May 2019. The letter contained a cover letter and an expert article. The explicitly stated objective of the letter was to draw the physician's attention to their prescribing practices regarding strong opioids, and the adverse effects related to the long-term use of these medications were highlighted in the cover letter. Moreover, the cover letter stated that the physician receiving the letter had prescribed opioids for a patient receiving a three month's supply of fentanyl or oxycodone in the previous year. The expert article provided background information on the

---

[2] Patients who were entitled to special reimbursement from the national health insurance based on a cancer diagnosis were excluded by Kela.

development of the opioid epidemic in the U.S., discussed the use of strong opioids in Finland and the adverse effects of opioids, as well as instructed on the use of strong opioids in the management of long-term, non-cancer-related pain. The English translation of the information letter is documented in Appendix B.

Physicians randomized into the control group (n=3,546) did not receive any direct communication during the experiment. However, Kela issued a press release describing the content of the letter at the same time the letters were sent to the treatment group. The key contents of the letter were also published in the Finnish Medical Journal (Kalso et al. 2019) and on Kela's website. The same personal letter was sent to physicians in the control group when the experiment ended six months later.

2.4 Empirical approach and identification

We compare opioid prescribing between the treatment and control groups. Since the physicians were randomized into the two groups, we use linear regression models to estimate the causal impact of the information letter on the outcomes. We report both unadjusted and regression-adjusted results, adjusting for relevant physician covariates. These characteristics include the lagged value of the outcome, age, sex, and indicators for native language. Although the straightforward comparison of outcome means is sufficient for identifying the causal impact on the intervention due to randomization to the treatment and control groups, adjusting for covariates may improve the precision of the point estimates and also makes it possible to evaluate the heterogeneity of the effects (Athey and Imbens 2017). We estimate the following regression models for physician-level outcomes:

$$Y_i = \beta_0 + \beta_1 Letter_i + X_i'\beta_3 + \varepsilon_i, \tag{1}$$

in which Y_i is the outcome of interest for physician i, β_0 is a constant, Letter$_i$ is an indicator

for the treatment (i.e., the information letter), X_i is a vector of physician-level covariates. Provided that the randomization is properly conducted, β_1 offers the unbiased least squares estimate of the average causal effect on the outcome. We report heteroscedasticity-corrected robust standard errors for physician-level outcomes and, as a sensitivity check, p-values based on randomization inference (Athey and Imbens 2017; Heß 2017). We did not observe whether the physicians read the letters sent to them. As a result, the estimates based on the model (1) are the intention-to-treat (ITT) effects of the information letter. As mentioned in Section 2.3, the physicians in the control group might have been aware of the letter's content from other public sources. Hence, we estimate the effect of receiving the information personally compared to not receiving it at all or receiving it from public sources.

2.5   *Heterogeneity and robustness analysis*

As described in the pre-analysis plan, we conduct subgroup analyses to evaluate potential heterogeneity in the treatment effect. To study the different margins of the overall effect, we analyze prescriptions issued to new patients (no oxycodone or fentanyl prescriptions in the preceding 12 months or no opioid prescription in the preceding 12 months) and patients continuing (oxycodone or fentanyl or any opioid) treatment separately.

To examine the heterogeneity of the effect, we include interaction terms to the model described in equation (1). First, to check if the repeated use of information letter diminishes or amplifies their effectiveness, we add interaction terms between $Letter_i$ and dummy variables indicating whether a physician received one or two of the 2017 and 2018 information letters (equation (A1) in the appendix). This approach allows us to study if there is notable heterogeneity in the treatment effect between physicians who received one, two, or three of these letters. The content of the 2017 and 2018 letters is documented,

11

and their effects are analyzed in Ahomäki et al. (2020) and Ahomäki et al. (2023), respectively.

Second, to study different responses to personal information between physicians working in different sectors, we add an interaction term between $Letter_i$ and a dummy variable indicating if a physician issued more prescriptions in the private sector at baseline (equation (A2)).

Third, we examine the potential heterogeneity in the effects of the intervention based on the number of prescriptions issued for opioids or fentanyl and oxycodone six months before the intervention. In this analysis, we divide the physician population into high-prescribers and low-prescribers, based on median as a cut-off value, and add an interaction term between the high-prescriber dummy and $Letter_i$ in the regressions (equation (A3)).

Finally, to study if physicians reduced prescribing that does not adhere to clinical guidelines and recommendations in the information letter, we estimate the effects separately for patients who did not have a cancer diagnosis in the Finnish Care Register for Health Care or in the Register of Primary Health Care. We identified all health-care contacts that recorded a cancer diagnosis between January 2017 and November 2019 (i.e., before the intervention and during the study period), flagged all patients that did not have a cancer diagnosis, and calculated the number of issued prescriptions to these patients. Cancer-related ICD-10 diagnosis codes were adopted from Pitkäniemi et al. (2018) and are documented in Table A 1 along with corresponding ICP-2 codes.

3   Results

3.1   Descriptive statistics and covariate balance between the treatment arms

Moving on to the findings of our study, we first confirm that the randomization was correctly implemented. Table 1 reports the descriptive statistics of physician characteristics and variables used to study heterogeneity for the treatment and control groups separately. We find that 86% of physicians in the treatment group were native Finnish speakers, 57% were female, and the mean age of the physicians at baseline was 42 years. In addition, 23% of the physicians had received Kela's information letters both in 2017 and 2018, and 35% prescribed more fentanyl and oxycodone in the private sector.

Moreover, we test for the differences between the groups by regressing each of the baseline characteristics on the treatment status. Differences between the treatment and control groups are quantitatively small, and none of the estimates are statistically significant at the standard 5% level, confirming that the randomization was effective in creating balanced groups.

Table A 2 shows descriptive statistics and differences between the treatment and control groups for the baseline outcomes. There are no statistically significant differences between the groups with respect to the baseline outcomes.

Table A 3 reports the characteristics of patients to whom physicians prescribed opioids during the study period by physicians' treatment status, excluding patients who received prescriptions from both study arms. Due to the large sample size, there are some statistically significant differences between the patient groups, quantitively the groups are very similar. The largest difference is that there are 0.6 percentage points more native Finnish speakers among the patients of the treatment group physicians.

13

Table 1 Mean characteristics of physicians by treatment status

	(1)	(2)	(3)
Variable	Control group	Treatment group	Difference
Finnish	0.86	0.86	-0.00
	(0.3)	(0.3)	{0.886}
Swedish	0.04	0.04	-0.00
	(0.2)	(0.2)	{0.657}
Other	0.09	0.10	0.00
	(0.3)	(0.3)	{0.637}
Female	0.56	0.57	0.01
	(0.5)	(0.5)	{0.621}
Age	42.2	42.3	0.0
	(12.9)	(12.7)	{0.890}
Second letter	0.47	0.48	0.01
	(0.5)	(0.5)	{0.433}
Third letter	0.23	0.23	0.00
	(0.4)	(0.4)	{0.888}
Private (opioids)	0.22	0.22	0.00
	(0.4)	(0.4)	{0.947}
Private (oxycodone and fentanyl)	0.34	0.35	0.01
	(0.5)	(0.5)	{0.652}
High prescriber (opioids)	0.50	0.52	0.02
	(0.5)	(0.5)	{0.063}
High prescriber (oxycodone and fentanyl)	0.54	0.55	0.01
	(0.5)	(0.5)	{0.572}
Observations	3,546	3,563	7,109

Notes: Physician-level data from December 2018 to June 2019. Columns (1) and (2) show means and, in parentheses, standard deviations. Column (3) shows coefficients and p-values from a t-test of the coefficient on treatment status from a regression of the characteristic on treatment. Finnish takes the value of 1 if physician's native language is Finnish. Swedish takes the value of 1 if physician's native language is Swedish. "Other" takes the value of 1 if physician's native language is other than Finnish or Swedish. Private variables are dummies for physicians who prescribed more opioids or fentanyl and oxycodone in the private sector. High-prescriber variables are dummies for physicians who prescribed more opioids or fentanyl and oxycodone than the median physician.

3.2 Effect on physician-level outcomes

3.2.1 Effect of information on prescribing outcomes

Descriptive outcome trends from 12 months before and after Kela's information letter was sent to physicians do not show a clear difference between the groups. Panel A in Figure 1 depicts the number of issued oxycodone and fentanyl prescriptions relative to

baseline for both the treatment group and the control group. There is no significant difference in the prescribing of these drugs between the groups before or after receiving the information letter. Panel B shows the number of issued opioid prescriptions relative to baseline. The illustrated trends are similar to those observed with fentanyl and oxycodone, revealing no significant differences between the groups. The data also show a seasonal trend, with fewer prescriptions issued during the summer, aligning with the intervention's timing.

Figure 1 Monthly number of issued prescriptions relative to baseline

Notes: The outcome is shown in the title of the vertical axis. The solid vertical line represents the treatment time (i.e., receipt of information letter), and the dashed vertical line shows when the control group received the letter. The vertical bars represent the 95% confidence intervals. The vertical axes have different scales.

Figure 2 shows the same comparison between the treatment group and control group as Figure 1 but specifically focusing on new patients. The data indicate that there is no

significant difference between the two groups in terms of issued opioid or fentanyl and oxycodone prescriptions to new patients, either before or after the information letter was introduced.

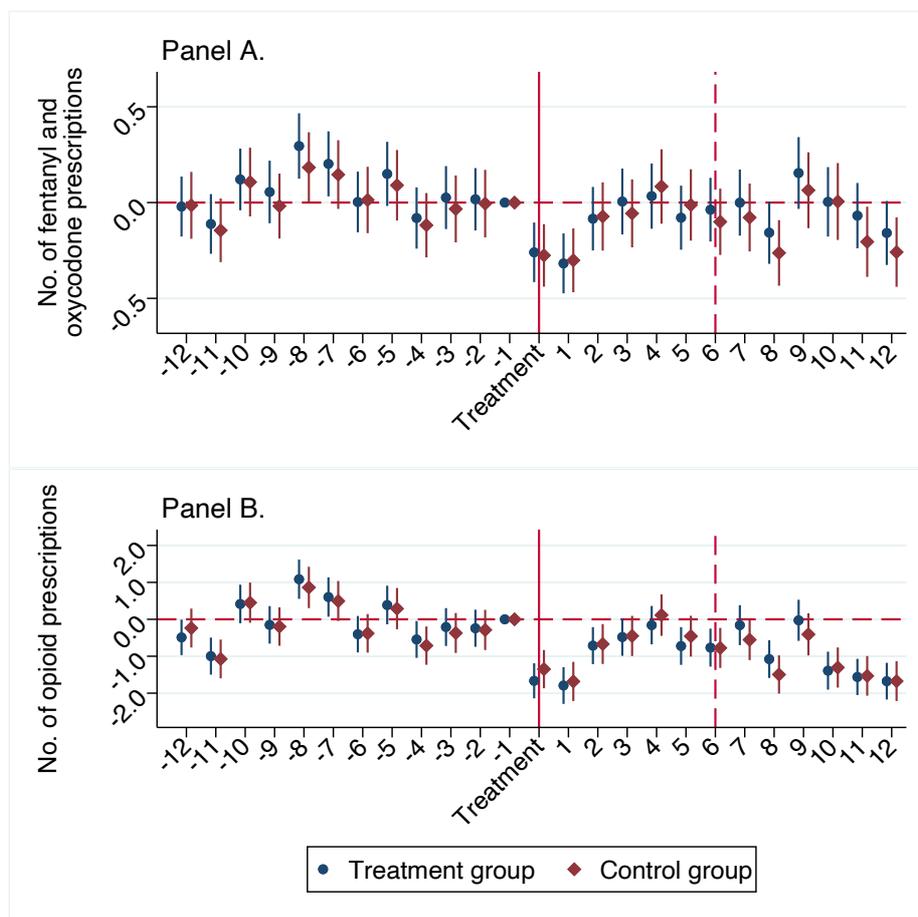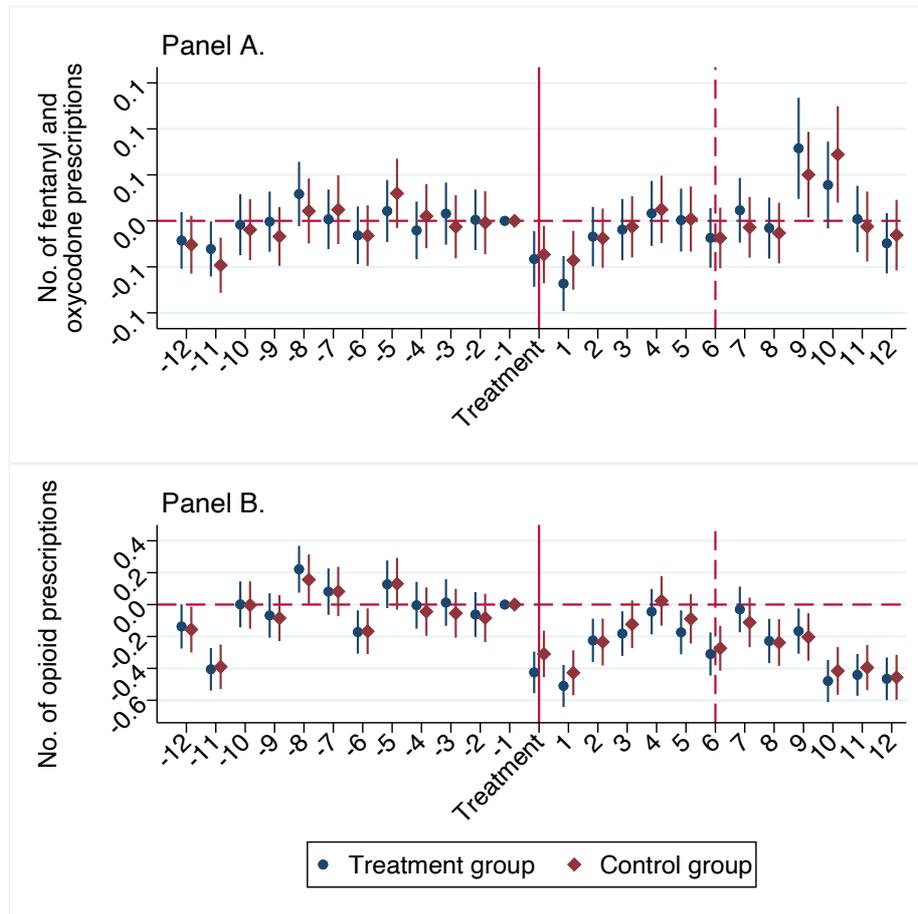Figure 2 Monthly number of prescriptions issued to new patients relative to baseline.

Notes: The outcome is shown in the title of the vertical axis. The solid vertical line represents the treatment time (i.e., receipt of information letter), and the dashed vertical line shows when the control group received the letter. The vertical bars represent the 95% confidence intervals. The vertical axes have different scales.

Table 2 presents the ordinary least squares (OLS) estimates based on the specification (1) for preregistered physician-level outcomes. Each row displays the results from a separate regression. These estimates support the findings from the graphical analysis, i.e., the information intervention had no significant effect on opioid prescribing in the full study population. We find a statistically insignificant decrease of 1.21 in the number of issued opioid prescriptions and a 0.37 prescription decrease in prescribing to new patients, which is also statistically insignificant at the standard 5% level. The decrease for all patients is 2.6% compared to the control group mean of the outcome. The relative decrease for new patients was 3.6%. At the 95% confidence level, we can rule out that the letters reduced opioid prescribing by more than 2.7 prescriptions for all patients and 0.8 prescriptions for new patients in the six-month time period under study. Other physician-level outcomes, as examined and reported in Table 2, support the main conclusion that the information letter had no significant effect on prescribing opioids, including fentanyl and oxycodone in the full study population. All point estimates are negative but close to zero and, importantly, all statistically insignificant at the 5% level. The p-values obtained using heteroscedasticity-robust standard errors closely match those obtained from randomization inference (Figure A 1). The unadjusted estimates corresponding to the regression-adjusted results in Table 2 are reported in Table A 4. The sign and magnitude of the estimates are stable to the exclusion of covariates.

Table 2 Treatment effects of the information letter

Outcome	Treatment	SE	P-value	Control mean
No. of opioid prescriptions	-1.21	0.78	0.12	46.69
No. of opioid prescriptions (new patients)	-0.37	0.20	0.06	10.30
No. of fentanyl and oxycodone prescriptions	-0.26	0.25	0.29	9.28
No. of fentanyl and oxycodone prescriptions (new patients)	-0.03	0.05	0.62	1.05

Notes: n=7,097. Standard errors (SE) are heteroscedasticity-robust. Outcomes are calculated using physician-level data from June 2019 to November 2019. Control variables include lagged value of the outcome, physician's age, as well as dummies for Finnish, Swedish, and other native languages.

Table A 5 and Table A 6 present the estimates for periods of one month and three months after the intervention, respectively. These estimates suggest that the effect of the intervention for the whole study population was quantitatively similar, i.e., close to zero, in shorter post-intervention periods than in the six-month period used in the main analysis.

To study if the intervention induced physicians to adhere to clinical guidelines and recommendations in the information letter more closely, we graphically evaluate fentanyl and oxycodone prescribing to non-cancer patients. This analysis was not preregistered. Figure A 3 plots the kernel-smoothed distributions of issued prescriptions both at baseline and during the outcome period for both physician groups. The distributions are very similar during both periods and show almost perfect overlap, suggesting that physicians did not reduce prescribing to non-cancer patients due to the information letter.

3.2.2 Effect of repeated use of information interventions on prescribing outcomes

So far, we have established that physicians in the treatment group did not prescribe less opioids on average than physicians in the control arm. We also explore the potential variation in the intervention's effects based on the preregistered characteristics of physicians. First, we show differences in the information letter's effects by the number of similar information interventions received in previous years. In Table 4, each column

reports the treatment effects from a single regression of the outcome on treatment status interacted with subgroup indicators. Here, subgroups are based on the number of information interventions the physicians received before the May 2019 letter. The reported treatment effects are calculated as follows: First Letter is the main effect from equation (A1), i.e., γ_1. Second Letter is the sum of the main effect and the coefficient (γ_2) for the interaction term between treatment arm and a dummy variable for the physicians who received an information letter in either 2017 or 2018. Third Letter is the sum of the main effect and the coefficient (γ_3) for the interaction term between treatment arm and a dummy variable for the physicians who received an information letter in 2017 and 2018. First three columns show that the differences in the effect are statistically indistinguishable between the subgroups. Treatment group physicians in all subgroups prescribed less opioids and fentanyl and oxycodone than control group physicians but the point estimates are not statistically significant (Columns (1)-(3)). More notably, the physicians in the treatment group who received their first letter in May 2019 prescribed 22% (point estimate in column (4): -0.13 and SE: 0.06) less fentanyl and oxycodone to new patients than physicians in the control group. At the 95% confidence level, we can rule out reductions larger than 44% (95% CI: -44% to -2%). The corresponding randomization inference p-value for this outcome is 0.03 (Figure A 2).

Table 3 Treatment effects of the information letter by number of previous letters

	(1) No. of opioid prescriptions	(2) No. of opioid prescriptions (new patients)	(3) No. of fentanyl and oxycodone prescriptions	(4) No. of fentanyl and oxycodone prescriptions (new patients)
First letter	-0.85	-0.54	-0.38	-0.13
	(1.26)	(0.34)	(0.32)	(0.06)
	[30.39]	[8.30]	[4.96]	[0.58]
Second letter	-0.96	-0.28	-0.22	-0.01
	(1.08)	(0.29)	(0.39)	(0.08)
	[45.31]	[9.93]	[10.01]	[1.18]
	{0.947}	{0.556}	{0.737}	{0.214}
Third letter	-2.11	-0.33	-0.24	0.06
	(1.93)	(0.43)	(0.62)	(0.13)
	[70.38]	[13.59]	[13.35]	[1.41]
	{0.582}	{0.700}	{0.833}	{0.166}
F-test p-value	0.846	0.835	0.938	0.256
N	7,109	7,109	7,109	7,109

Notes: Standard errors are heteroscedasticity-robust and reported in parentheses. Control means for subgroups in brackets. P-value from test of subgroup compared to reference subgroup (First Letter) in curly brackets. Outcomes are calculated using physician-level data from June 2019 to November 2019. Second Letter is the sum ($\gamma_1 + \gamma_2$ from equation (A1) of the main effect and the coefficient for the interaction term between treatment arm and a dummy variable for those physicians who received an information letter in either 2017 or 2018. Third Letter is the sum ($\gamma_1 + \gamma_3$ from equation (A1)) of the main effect and the coefficient for the interaction term between treatment arm and a dummy variable for the physicians who received an information letter in 2017 and 2018. Control variables include lagged value of the outcome, physician age as well as dummies for Finnish, Swedish, and other native languages. F-test jointly tests the significance of the treatment-by-subgroup interactions.

To further investigate this, we plotted the kernel-smoothed distributions of the number of fentanyl and oxycodone prescriptions for new patients issued by physicians who received their first information letter from Kela in May 2019. Panel A in Figure 3 displays the smoothed densities of issued prescriptions at baseline, which are similar across the distribution. As depicted in Panel B of Figure 3, the distribution for the treatment group shifted left following the intervention, indicating more physicians issuing zero prescriptions to new patients. In this subgroup, the unadjusted number of prescriptions in the treatment group was 0.17 (29%) lower than in the control group (Figure 3). This

20

finding suggests that the information letter was effective in reducing the already infrequent prescribing of fentanyl and oxycodone to new patients by physicians who received their first intervention.
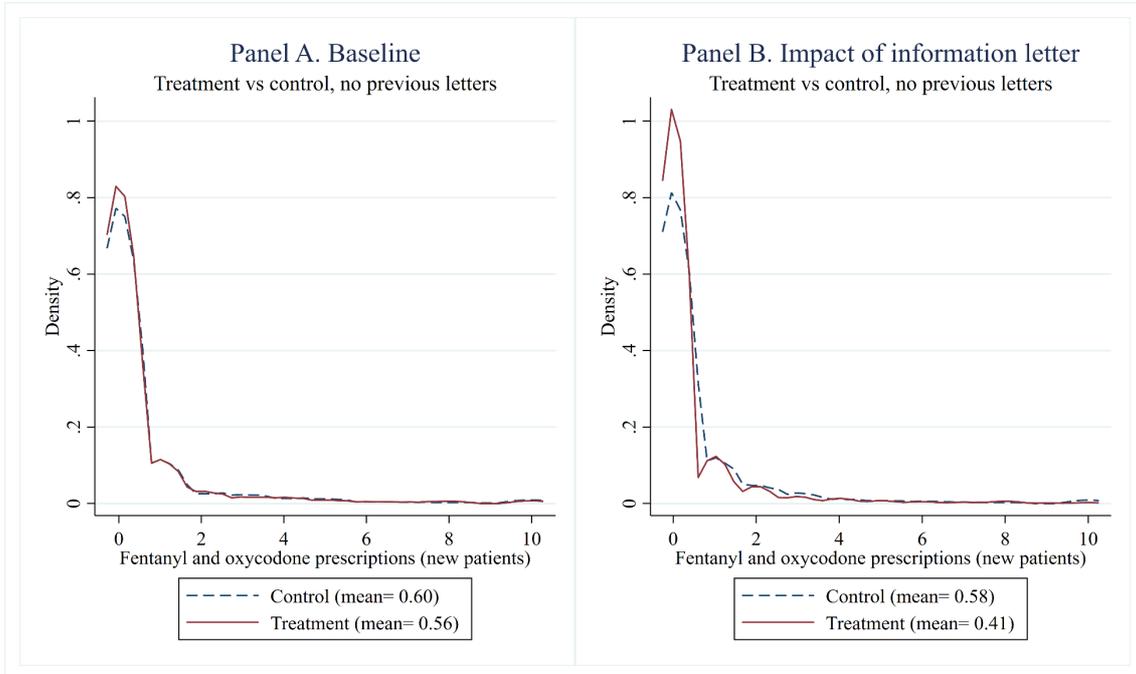
Figure 3 Treatment effects of the information letter for physicians receiving their first letter from Kela

Notes: The densities are smoothed using an Epanechnikov kernel.

Table A 7 displays descriptive statistics by the number of previous information letters. The share of physicians receiving the May 2019 letter is very similar in all groups (between 49% and 51%), further supporting the conclusion that the randomization was effective in creating balanced groups. The most notable differences between physicians receiving the information letter for the first time and other physicians are age, private sector prescribing, and the baseline volume of opioid prescribing. Physicians receiving their first letter were younger, a larger percentage of them was prescribing more opioids in the private sector than in the public sector at baseline, and overall prescribed fewer opioids at baseline.

3.2.3 *Effect of information intervention on prescribing outcomes by sector of employment*

In this section, we examine whether the causal effect varies by physicians' sector of employment (refer to Table 4 for regression estimates). This analysis reveals no clear difference in the response to the information letter between the sectors. Opioid prescribing to all patients decreased more in the public sector, whereas prescribing opioids to new patients decreased more in the private sector. Prescribing fentanyl and oxycodone decreased more among public sector physicians. However, all estimates are statistically indistinguishable from zero at the 5% significance level, and the differences between these subgroups are also not statistically significant.

Table 4 Treatment effects of the information letter by physician sector.

	(1) No. of opioid prescriptions	(2) No. of opioid prescriptions (new patients)	(3) No. of fentanyl and oxycodone prescriptions	(4) No. of fentanyl and oxycodone prescriptions (new patients)
Public	-1.76	-0.36	-0.48	-0.07
	(1.08)	(0.25)	(0.36)	(0.07)
	[55.86]	[10.94]	[12.16]	[1.36]
Private	-0.23	-0.40	0.14	0.06
	(0.92)	(0.31)	(0.26)	(0.06)
	[29.31]	[9.07]	[3.81]	[0.46]
	{0.282}	{0.937}	{0.159}	{0.184}
N	7,109	7,109	7,109	7,109

Notes: Standard errors are heteroscedasticity-robust and reported in parentheses. Control means for subgroups in brackets. P-value from test of subgroup compared to reference subgroup (public) in curly brackets. Outcomes are calculated using physician-level data from June 2019 to November 2019. Private is the sum ($\delta_1 + \delta_2$ from equation (A2)) of the main effect and the coefficient for the interaction term between treatment arm and a dummy variable for the physicians who prescribed more fentanyl and oxycodone in the private sector. Control variables include lagged value of the outcome, physician age, as well as dummies for Finnish, Swedish, and other native languages.

3.2.4 *Effect of information on prescribing by the physicians' baseline prescribing volume*

Next, we explore heterogeneity in the effects of the intervention by the physicians' baseline prescribing volume. We find that the reduction in prescribing is larger for high-volume prescribers across all outcomes, with decreases in this subgroup ranging from -0.08 to -3.19 prescriptions. However, the difference in effect between low and high prescribers is only statistically significant at the 5% level for prescribing to all patients. The estimates reported in Table 5, Column (1) suggest that the high prescribers reduced opioid prescribing to all patients by 3.19 prescriptions (95% CI: -5.63 to -0.73) or by roughly 4.8%. The impact on fentanyl and oxycodone prescribing to all patients (Column (3)) is more nuanced. While the results suggest that the impact is larger for high-volume prescribers, the treatment effect is statistically indistinguishable from zero for both groups.

Table 5 Treatment effects of the information for high- and low-volume prescribers

	(1)	(2)	(3)	(4)
	No. of opioid prescriptions	No. of opioid prescriptions (new patients)	No. of fentanyl and oxycodone prescriptions	No. of fentanyl and oxycodone prescriptions (new patients)
Low prescribers	1.18	-0.02	0.29	0.03
	(0.80)	(0.26)	(0.17)	(0.03)
	[23.64]	[7.27]	[1.89]	[0.19]
High prescribers	-3.19	-0.66	-0.71	-0.08
	(1.25)	(0.29)	(0.44)	(0.09)
	[66.16]	[12.85]	[15.52]	[1.78]
	{0.003}	{0.098}	{0.034}	{0.267}
N	7,109	7,109	7,109	7,109

Notes: Standard errors are heteroscedasticity-robust and reported in parentheses. Control means for subgroups in brackets. P-value from test of subgroup compared to reference subgroup (low prescribers) in curly brackets. Outcomes are calculated using physician-level data from June 2019 to November 2019. Treatment effect for high prescribers is the sum ($\rho_1 + \rho_2$ from equation (A3)) of the main effect and the coefficient for the interaction term between treatment arm and a dummy variable for the physicians who prescribed more fentanyl and oxycodone than the median physician at baseline. Control variables include lagged value of the outcome, physician age, as well as dummies for Finnish, Swedish, and other Native languages.

Figure 4 displays the distributions of issued prescriptions at baseline and during the study period for high prescribers. Again, the baseline distributions are very similar, and there is a small shift towards zero in the treatment group distributions following the intervention. For opioid prescriptions, the unadjusted difference between the study arms was -2.81 (Panel B) and for fentanyl and oxycodone prescriptions -1.13 (Panel D).
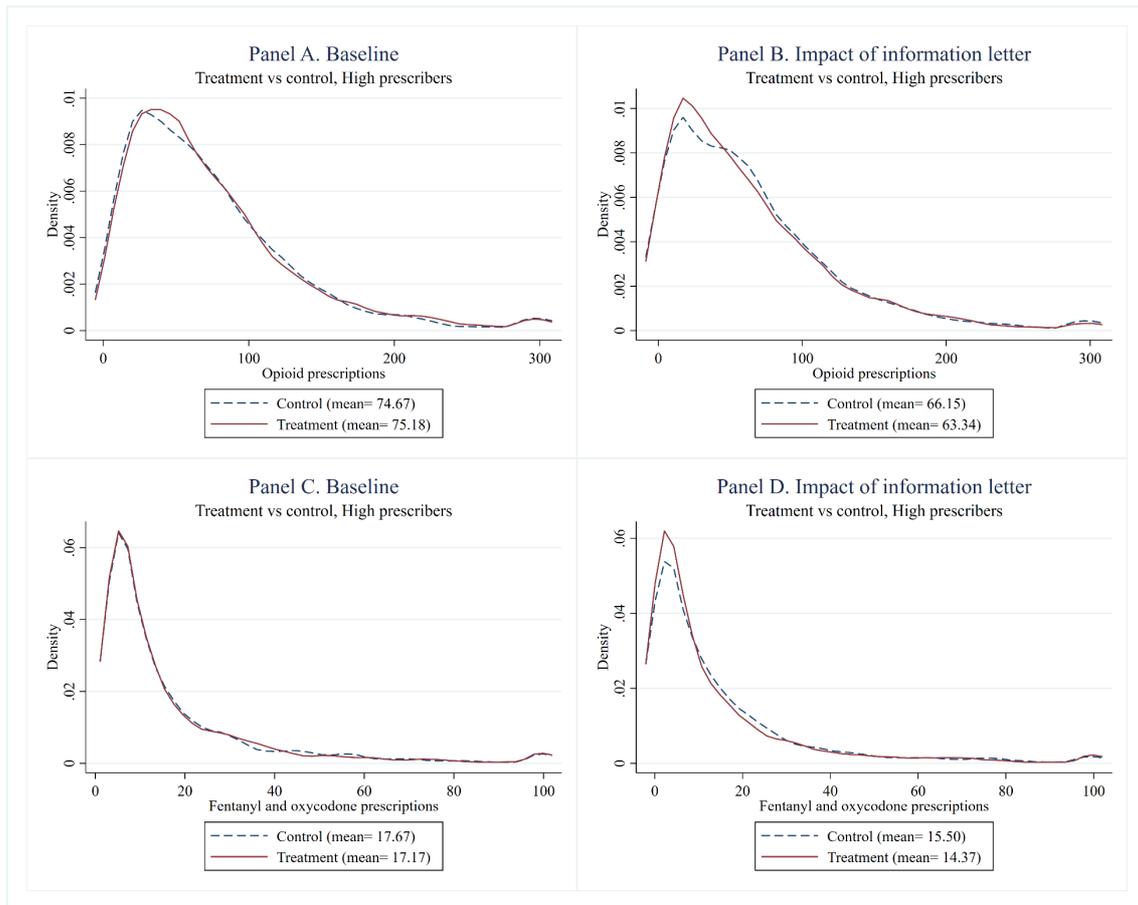
Figure 4 Treatment effects of the information letter for the high prescribers of fentanyl and oxycodone

Notes: The densities are smoothed using an Epanechnikov kernel.

3.2.5 Substitution effect of the information letter

Finally, to study if the physicians diverted from opioid prescribing to other common pain medicines as a response to the intervention, we studied the changes in the number of issued NOA prescriptions. As seen in Table 6, column (1), in the full study population, the prescribing of NOAs increased slightly among the treatment arm physicians: there was an increase of 0.65 prescriptions compared to the control group. In addition to being quantitively small, this effect is statistically indistinguishable from zero. Furthermore, we find no evidence of heterogeneity in effect with respect to either the number of previous letters (column (2)) or physician's sector of employment (column (3)). However, the baseline low prescribers of fentanyl and oxycodone increased the prescribing of NOAs

by 3.09 prescriptions (95% CI: 0.64 to 5.55), or nearly 7% as a result of the information letter (column (4) and Figure 5).

Table 6 Substitution effects of the information letter

	(1)	(2)	(3)	(4)
		No. of NOA prescriptions		
Treatment	0.65			
	(0.99)			
	[61.74]			
	{ 0.52}			
First letter		-0.12		
		(1.82)		
		[48.40]		
Second letter		1.54		
		(1.40)		
		[58.81]		
		{0.472}		
Third letter		-0.02		
		(2.17)		
		[84.74]		
		{0.972}		
Public			0.06	
			(1.32)	
			[68.03]	
Private			1.63	
			(1.41)	
			[49.83]	
			{0.414}	
Low prescribers				3.09
				(1.25)
				[44.35]
High prescribers				-1.38
				(1.49)
				[76.44]
				{0.021}
F-test p-value		0.717		
N	7,109	7,109	7,109	7,109

Notes: Standard errors are heteroscedasticity-robust and reported in parentheses. Control means for subgroups in brackets. P-value from test of subgroup compared to reference subgroup in curly brackets. Outcome is calculated using physician-level data from June 2019 to November 2019. Control variables include lagged value of the outcome, physician age, as well as dummies for Finnish, Swedish, and other Native languages. NOA stands for nonopioid analgesic.

Panel A. Baseline
Treatment vs control, Low prescribers

Panel B. Impact of information letter
Treatment vs control, High prescribers

Control (mean= 40.78)
Treatment (mean= 42.54)

Control (mean= 44.36)
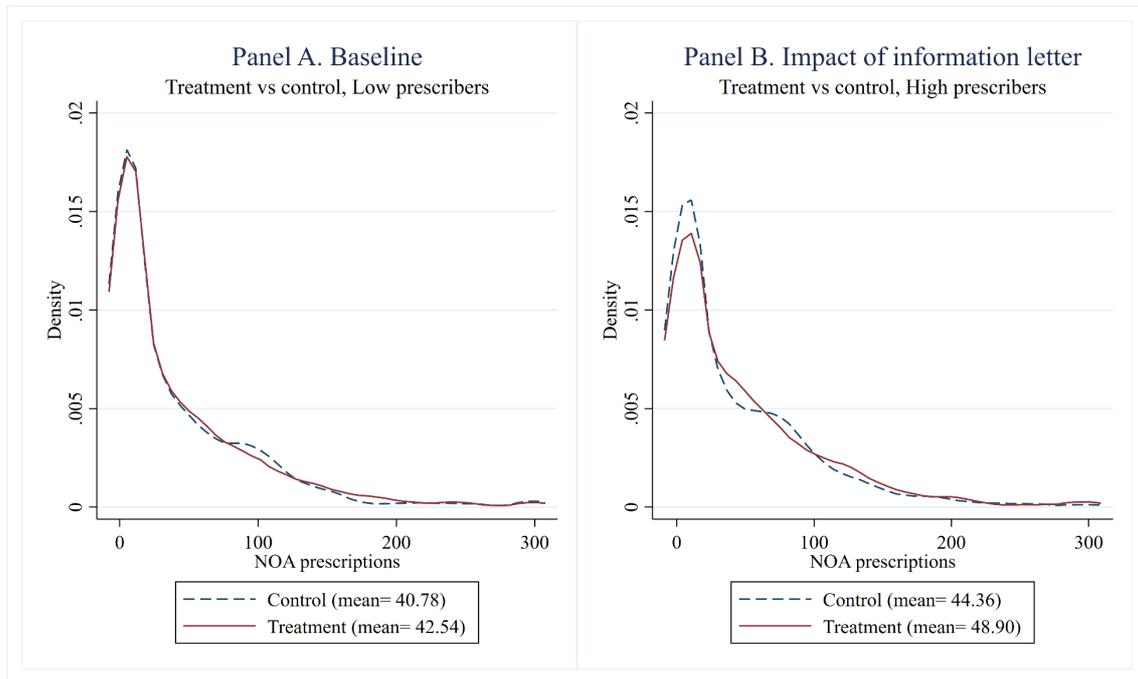Treatment (mean= 48.90)

Figure 5 Substitution effects of the information letter for low prescribers of fentanyl and oxycodone

Notes: The densities are smoothed using an Epanechnikov kernel. NOA stands for nonopioid analgesic.

4 Discussion

In this paper, we document four policy-relevant findings based on a preregistered nationwide randomized experiment. First, we found that, on average, physicians who received the information letter did not significantly reduce opioid prescribing compared to the control group. Second, when focusing on physicians who received their first information letter, we observed that physicians in the treatment group issued 22% fewer fentanyl and oxycodone prescriptions to new patients compared to those in the control group. However, the level of prescribing was already relatively low prior to the intervention in this group. Third, we found a 4.8% reduction in the number of issued prescriptions for any opioid among the high-volume prescribers. Fourth, we found an increase of 7% in NOA prescribing among low-volume baseline prescribers. Our analysis revealed no meaningful difference in the response to the information letter between public and private sector physicians.

27

The overall null effect of the information intervention on opioid prescribing aligns with the findings of Sacarny et al. (2016). However, Ahomäki et al. (2020), Doctor et al. (2018) and Navathe et al. (2022) documented significant effects when studying similar large-scale information campaigns aiming to reduce opioid prescribing. Because the exact mechanism at play is unclear, we cannot definitively explain why some information interventions are effective, while others are not. However, there are some notable similarities among the effective interventions. First, effective interventions were related to the physicians' past behavior and included, for example, notifying them of their patient's fatal overdose, providing evidence-based treatment alternatives, or combining individual audit feedback and peer comparison. Second, the interventions were characterized by their straightforward and simple message. For example, the physicians were told they had previously prescribed 100 tablets of codeine to a new patient even though the recommended package size is 10-30, or they were told that they have prescribed more opioids than their peers and given information on the percentage of patients with new opioid prescriptions in the last month. Third, the interventions were targeted at a very specific set of medications.

In contrast, the intervention studied by Sacarny et al. (2016) and the intervention under investigation in this paper concerned either a broad range of controlled substances (including opioids) or provided general recommendations,[3] along with partially conflicting guidance (tips 3 and 5 in the letter (Appendix B)) for managing chronic pain. In the intervention under study, there was no direct peer-comparison. Therefore,

---

[3] The objective (stated in the cover letter (Appendix B)) of the information letter was to draw the physician's attention to prescribing practices of strong opioids and adverse effects related to the long-term use of these medications.

individual feedback might have been difficult to understand, as the prescribing behavior and recommendations were discussed separately in the beginning and at the end of the letter, respectively. The target group of this study's intervention likely also includes physicians who have treated patients suffering from severe pain strictly according to national clinical guidelines. The inconclusive findings in the literature highlight that additional research is required to identify the exact mechanisms through which the effective information interventions operate.

In behavioral economics, previous research has found that the effect of information letters becomes more persistent when used repeatedly (Allcott and Rogers 2014). To the best of our knowledge, our study is the first to analyze the potentially different responses to physician-targeted information campaigns regarding opioids by the number of previous interventions in a nationwide setting. Navathe et al. (2022) study multiple interventions as well, but their analysis does not separately examine physicians who have received multiple interventions. Our study setting does not allow us to analyze the long-term persistence of the effect.

However, we found evidence of a larger effect on physicians who received their first intervention letter. These physicians' baseline opioid prescribing volume was lower compared to those who had already received interventions in previous years. Taken together, our results suggest that physician-targeted information letters can change the prescribing behavior for physicians who occasionally deviate from clinical guidelines, even when the peer-comparison or recommended guidelines are somewhat ambiguous. The physicians receiving their first intervention were also younger on average. Some prior research suggests that older physicians are slower to respond to new information (Howard and Hockenberry 2019).

When discussing information provision to physicians, Currie et al. (2024) raise the question of whether physicians respond to the information provided to them or to the fact that an authority is monitoring their prescribing practices. Our finding that only physicians who received their first letter responded by reducing the prescribing of fentanyl and oxycodone to new patients may suggest the latter. This could be because physicians become accustomed to the communications and realize that there are no consequences for receiving the letters or being monitored. While they do not study the effects of repeated use of information letters Sacarny et al. (2018) also briefly discuss the possibility that the magnitude of effects may decline if they are used repeatedly. The fact that among first-time receivers of the letters, an effect was only observed in prescriptions for new patients may be attributed to the relative ease with which the physicians can refrain from starting an opioid treatment as opposed to discontinuing one. Previous studies have also found that the size and duration of the first prescription are associated with prolonged opioid use (Shah, Hayes, and Martin 2017). Therefore, reducing the initiation of opioid treatments may be a desirable goal for the authority providing physicians with information.

We also observed a larger effect among physicians who were high-volume prescribers of opioids prior to the intervention. This finding is consistent with earlier results by Ahomäki et al. (2020).

The staggered implementation of the intervention, i.e., sending information letters based on randomization, provided a nationwide experimental research setup. This setting enabled a reliable estimation of the causal effects of the information intervention. To further enhance the reliability of the results, we used comprehensive, nationwide register data on outpatient opioid prescriptions combined with a preregistered analysis plan. A limitation of the study is that the dataset did not include all the necessary information to

examine the intensive margin response to the intervention, which was one of the original objectives in our preregistered analysis plan. This limitation offers a possible explanation for the substitution effect towards prescribing more NOAs in the low-volume prescribers of oxycodone and fentanyl we found. It is possible that the low-volume prescribers responded to the information letter by reducing the quantity of opioids per prescription and substituting this reduction by increasing the prescribing of NOAs.

To conclude, sending information letters to Finnish physicians did not significantly impact the overall opioid prescribing patterns among the whole study population. Our results indicate that although information interventions have effectively reduced opioid prescribing in some contexts, they are not effective when the goal is to decrease the prescribing of strong opioids in a nationwide context and when the provided information and recommendations lack simplicity and specificity. Fox et al. (2020) reached a similar conclusion when describing the details of successful nudges in the context of medical decision-making. The detected heterogeneity in the impact of the intervention highlights the challenges policymakers face in relying on repeated use of information-based interventions to sustainably reduce opioid prescriptions and mitigate the potentially harmful clinical practices. For example, the authority needs to take into account the characteristics of the targeted physician and patient populations. Our results contribute to the growing body of empirical research (Suleman and Movik 2019; Wang and Groene 2020) on behavioral interventions in health care. The findings provide valuable insights for policymakers and health-care authorities striving to align health-care practices more closely with clinical guidelines.

REFERENCES

Ahomäki, Iiro, Petri Böckerman, Jaakko Pehkonen, and Leena Saastamoinen. 2023. "Effect of Information Intervention on Prescribing Practice for Neuropathic Pain in Older Patients: A Nationwide Register-Based Study." *Drugs & Aging* 40 (1): 81–88. https://doi.org/10.1007/s40266-022-00993-4.

Ahomäki, Iiro, Visa Pitkänen, Aarni Soppi, and Leena Saastamoinen. 2020. "Impact of a Physician-Targeted Letter on Opioid Prescribing." *Journal of Health Economics* 72 (July):102344. https://doi.org/10.1016/j.jhealeco.2020.102344.

Allcott, Hunt, and Todd Rogers. 2014. "The Short-Run and Long-Run Effects of Behavioral Interventions: Experimental Evidence from Energy Conservation." *American Economic Review* 104 (10): 3003–37. https://doi.org/10.1257/aer.104.10.3003.

Alpert, Abby, William N Evans, Ethan M J Lieber, and David Powell. 2022. "Origins of the Opioid Crisis and Its Enduring Impacts*." *The Quarterly Journal of Economics* 137 (2): 1139–79. https://doi.org/10.1093/qje/qjab043.

Alpert, Abby, David Powell, and Rosalie Liccardo Pacula. 2018. "Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids." *American Economic Journal: Economic Policy* 10 (4): 1–35. https://doi.org/10.1257/pol.20170082.

Athey, S., and G. W. Imbens. 2017. "Chapter 3 - The Econometrics of Randomized Experiments." In *Handbook of Economic Field Experiments*, edited by Abhijit Vinayak Banerjee and Esther Duflo, 1:73–140. Handbook of Field Experiments. North-Holland. https://doi.org/10.1016/bs.hefe.2016.10.003.

Barnett, Michael L., Andrew R. Olenski, and Anupam B. Jena. 2017. "Opioid-Prescribing Patterns of Emergency Physicians and Risk of Long-Term Use." *New England Journal of Medicine* 376 (7): 663–73. https://doi.org/10.1056/NEJMsa1610524.

Biglaiser, Gary, and Ching-to Albert Ma. 2007. "Moonlighting: Public Service and Private Practice." *The RAND Journal of Economics* 38 (4): 1113–33. https://doi.org/10.1111/j.0741-6261.2007.00128.x.

Bosetti, Cristina, Claudia Santucci, Silvia Radrezza, Juliana Erthal, Stefano Berterame, and Oscar Corli. 2019. "Trends in the Consumption of Opioids for the Treatment of Severe Pain in Europe, 1990–2016." *European Journal of Pain* 23 (4): 697–707. https://doi.org/10.1002/ejp.1337.

CDC. 2022a. "Understanding the Epidemic | Drug Overdose | CDC Injury Center." February 9, 2022. https://www.cdc.gov/drugoverdose/epidemic/index.html.

———. 2022b. "U.S. Opioid Dispensing Rate Maps | Drug Overdose | CDC Injury Center." October 19, 2022. https://www.cdc.gov/drugoverdose/rxrate-maps/index.html.

Currie, Janet, W. Bentley MacLeod, and Kate Musen. 2024. "First Do No Harm? Doctor Decision Making and Patient Outcomes." Working Paper 32788. Working Paper Series. National Bureau of Economic Research. https://doi.org/10.3386/w32788.

Cutler, David M., and Edward L. Glaeser. 2021. "When Innovation Goes Wrong: Technological Regress and the Opioid Epidemic." *Journal of Economic Perspectives* 35 (4): 171–96. https://doi.org/10.1257/jep.35.4.171.

Doctor, Jason N., Andy Nguyen, Roneet Lev, Jonathan Lucas, Tara Knight, Henu Zhao, and Michael Menchine. 2018. "Opioid Prescribing Decreases after Learning of a Patient's Fatal Overdose." *Science* 361 (6402): 588–90. https://doi.org/10.1126/science.aat4595.

Fox, Craig R, Jason N Doctor, Noah J Goldstein, Daniella Meeker, Stephen D Persell, and Jeffrey A Linder. 2020. "Details Matter: Predicting When Nudging Clinicians

Will Succeed or Fail." *BMJ*, September, m3256. https://doi.org/10.1136/bmj.m3256.

Häuser, Winfried, Eric Buchser, David P. Finn, Geerd Dom, Egil Fors, Tarja Heiskanen, Lene Jarlbaek, et al. 2021. "Is Europe Also Facing an Opioid Crisis?—A Survey of European Pain Federation Chapters." *European Journal of Pain* 25 (8): 1760–69. https://doi.org/10.1002/ejp.1786.

Hedegaard, Holly, and Margaret Warner. 2021. "Drug Overdose Deaths in the United States, 1999–2020," no. 428.

Heß, Simon. 2017. "Randomization Inference with Stata: A Guide and Software." *The Stata Journal* 17 (3): 630–51.

Howard, David H., and Jason Hockenberry. 2019. "Physician Age and the Abandonment of Episiotomy." *Health Services Research* 54 (3): 650–57. https://doi.org/10.1111/1475-6773.13132.

Jussila, Elina, Kaisa Kotakorpi, and J Verho. 2023. "Prescription Behavior of Physicians in the Public and Private Sector." *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.4324209.

Kalso, Eija, Katariina Klintrup, Helena Kastarinen, Leena Saastamoinen, Sari Helminen, and Jari Välimäki. 2019. "Oksikodonin Ja Fentanyylin Käyttö Avohoidossa." *Suomen Lääkärilehti* 74 (23): 1512–14.

Kela. 2024. "Tilastotietokanta Kelasto." 2024. https://raportit.kela.fi/ibi_apps/WFServlet.

Maclean, Johanna Catherine, Justine Mallatt, Christopher J. Ruhm, and Kosali I. Simon. 2022. "The Opioid Crisis, Health, Healthcare, and Crime: A Review of Economic Studies." Working Paper 29983. Working Paper Series. National Bureau of Economic Research. https://doi.org/10.3386/w29983.

Navathe, Amol S., Joshua M. Liao, Xiaowei S. Yan, M. Kit Delgado, William M. Isenberg, Howard M. Landa, Barbara L. Bond, et al. 2022. "The Effect Of Clinician Feedback Interventions On Opioid Prescribing." *Health Affairs* 41 (3): 424–33. https://doi.org/10.1377/hlthaff.2021.01407.

Pitkäniemi, J, N Malila, A Virtanen, H Degerlund, S Heikkinen, and K Syöpä Seppä. 2018. "Tilastoraportti Suomen Syöpätilanteesta." *Suomen Syöpäyhdistyksen Julkaisuja Nro* 93.

Rönkä, Sanna, Jukka Ollgren, Hannu Alho, Henrikki Brummer-Korvenkontio, Teemu Gunnar, Karoliina Karjalainen, Airi Partanen, and Tiina Väre. 2020. "Amfetamiinien Ja Opioidien Ongelmakäytön Yleisyys Suomessa Vuonna 2017." *LÄÄKETIETEELLINEN AIKAKAUSKIRJA DUODECIM*, 2020. https://www.duodecimlehti.fi/duo15450.

Ruhm, Christopher J. 2019. "Drivers of the Fatal Drug Epidemic." *Journal of Health Economics* 64 (March):25–42. https://doi.org/10.1016/j.jhealeco.2019.01.001.

Sacarny, Adam, Michael L. Barnett, Jackson Le, Frank Tetkoski, David Yokum, and Shantanu Agrawal. 2018. "Effect of Peer Comparison Letters for High-Volume Primary Care Prescribers of Quetiapine in Older and Disabled Adults: A Randomized Clinical Trial." *JAMA Psychiatry* 75 (10): 1003–11. https://doi.org/10.1001/jamapsychiatry.2018.1867.

Sacarny, Adam, David Yokum, Amy Finkelstein, and Shantanu Agrawal. 2016. "Medicare Letters To Curb Overprescribing Of Controlled Substances Had No Detectable Effect On Providers." *Health Affairs* 35 (3): 471–79. https://doi.org/10.1377/hlthaff.2015.1025.

Samet, Jeffrey H., and Stefan G. Kertesz. 2018. "Suggested Paths to Fixing the Opioid Crisis: Directions and Misdirections." *JAMA Network Open* 1 (2): e180218. https://doi.org/10.1001/jamanetworkopen.2018.0218.

Shah, Anuj, Corey J. Hayes, and Bradley C. Martin. 2017. "Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies." *The Journal of Pain* 18 (11): 1374–83. https://doi.org/10.1016/j.jpain.2017.06.010.

Suleman, Fatima, and Espen Movik. 2019. "Pharmaceutical Policies: Effects of Educational or Regulatory Policies Targeting Prescribers." *Cochrane Database of Systematic Reviews*, no. 11. https://doi.org/10.1002/14651858.CD013478.

Wang, Sophie Y., and Oliver Groene. 2020. "The Effectiveness of Behavioral Economics-Informed Interventions on Physician Behavioral Change: A Systematic Literature Review." *PLoS ONE* 15 (6). https://doi.org/10.1371/journal.pone.0234149.

WHO. 2021. "WHOCC - ATC/DDD Index." WHO. 2021. https://www.whocc.no/atc_ddd_index/.

Appendix A

Table A 1 Cancer-related ICD-10 and ICP-2 codes

ICD-10 codes	ICP-2 codes
Cancer	
C00-96	A79
D09.0-1	B72
D32-33	B73
D41-43	B74
D45-47	B75
D76	D74, D75, D76, D77, F74, H75, K72, L71, N74, N75, N76, R84, R85, S77, T71, T73, U75, U76, U77, U79, W72, X75, X76, X77, X80, Y77, Y78

Notes: Table shows ICD-10 diagnosis codes and the related ICP-2 codes used in identifying individuals with cancer.

Heterogeneity analysis methods

To study the possible heterogeneity in effect, we estimate the following models by ordinary least squares:

$$Y_i = \gamma_0 + \gamma_1 Letter_i + \gamma_2 SecondLetter_i \times Letter_i \qquad (A1)$$

$$+ \gamma_3 ThirdLetter_i \times Letter_i + X_i' \gamma_4 + \varepsilon_i$$

$$Y_i = \delta_0 + \delta_1 Letter_i + \delta_2 Private_i \times Letter_i + X_i' \delta_3 + \varepsilon_i \qquad (A2)$$

$$Y_i = \rho_0 + \rho_1 Letter_i + \rho_2 HighPrecriber_i \times Letter_i + X_i' \delta_3 + \varepsilon_i, \qquad (A3)$$

in which Y_i is an outcome of interest for physician i. The variable $Letter_i$ is an indicator equal to 1 if the physician was randomized to receive the information letter in May 2019. X_i is a vector of covariates. $SecondLetter_i$ is an indicator equal to 1 if the physician received Kela's information letter in either 2017 or 2018. $ThirdLetter_i$ is an indicator

equal to 1 if the physician received Kela's information letter in 2017 and 2018. $Private_i$ is an indicator equal to 1 if the physician issued more fentanyl and oxycodone prescriptions in the private sector at baseline. $HighPrecriber_i$ is an indicator equal to 1 if the physician issued more fentanyl and oxycodone prescriptions than the median physician. We use heteroscedasticity-robust standard errors in all specifications.

Additional results

Table A 2 Mean baseline outcomes by treatment status

Variable	(1) Control group	(2) Treatment group	(3) Difference
No. of opioid prescriptions	49.74	50.91	1.17
	(60.8)	(57.5)	{0.41}
No. of opioid prescriptions (new patients)	11.25	11.76	0.51
	(16.9)	(15.4)	{0.18}
No. of fentanyl and oxycodone prescriptions	9.85	9.69	-0.16
	(19.7)	(18.0)	{0.71}
No. of fentanyl and oxycodone prescriptions (new patients)	1.15	1.13	-0.02
	(3.5)	(3.1)	{0.81}
Observations	3,546	3,563	7,109

Notes: Physician-level data from December 2018 to June 2019. Columns (1) and (2) show means and, in parentheses, standard deviations. Column (3) shows coefficients and p-values from a t-test of the coefficient on treatment status from a regression of the characteristic on treatment.

Table A 3 Mean characteristics of patients by treatment status

| Variable	(1) Control group	(2) Treatment group	(3) Difference
Finnish	0.93	0.93	0.0064
	(0.26)	(0.25)	{0.0000006}
Swedish	0.04	0.04	-0.0052
	(0.20)	(0.19)	{0.0000001}
Other	0.03	0.03	-0.0012
	(0.17)	(0.17)	{0.1519656}
Female	0.57	0.57	-0.0001
	(0.50)	(0.50)	{0.9733533}
Cancer diagnosis	0.68	0.69	0.0050
	(0.47)	(0.46)	{0.0338631}
Age	62.7	62.9	0.1177
	(18.9)	(19.0)	{0.2213969}
Observations	77,841	77,656	155,497

Notes: Characteristics of patients to whom physicians prescribed opioids during the study period by the physicians' treatment status, excluding patients who received prescriptions from both study arms. Columns (1) and (2) show means and, in parentheses, standard deviations. Column (3) shows coefficients and p-values from a t-test of the coefficient on treatment status from a regression of the characteristic on treatment. Finnish takes the value of 1 if patient's native language is Finnish. Swedish takes the value of 1 if patient's native language is Swedish. "Other" takes the value of 1 if patient's native language is other than Finnish or Swedish. Cancer diagnosis takes the value of 1 if the patient has a cancer diagnosis between January 2017 and November 2019 (i.e., before the intervention and during the study period).

Table A 4 Unadjusted treatment effects on the information letter

Outcome	Treatment	SE	P-value	Control mean
No. of opioid prescriptions	-0.32	1.33	0.81	46.70
No. of opioid prescriptions (new patients)	-0.01	0.35	0.98	10.30
No. of fentanyl and oxycodone prescriptions	-0.40	0.44	0.37	9.27
No. of fentanyl and oxycodone prescriptions (new patients)	-0.04	0.07	0.60	1.05

Notes: n=7,109. Standard errors (SE) are heteroscedasticity-robust. Outcomes are calculated using physician-level data from June 2019 to November 2019.

Figure A 1 Treatment effects of the information letter: Randomization inference

Panel A.
No. of opioid prescriptions

Randomization inference p-value: 0.11

Panel B.
No. of opioid prescriptions (new patients)

Randomization inference p-value: 0.06

Panel C.
No. of fentanyl and oxycodone prescriptions

Randomization inference p-value: 0.30

Panel D.
No. of fentanyl and oxycodone prescriptions (new patients)

Randomization inference p-value: 0.61
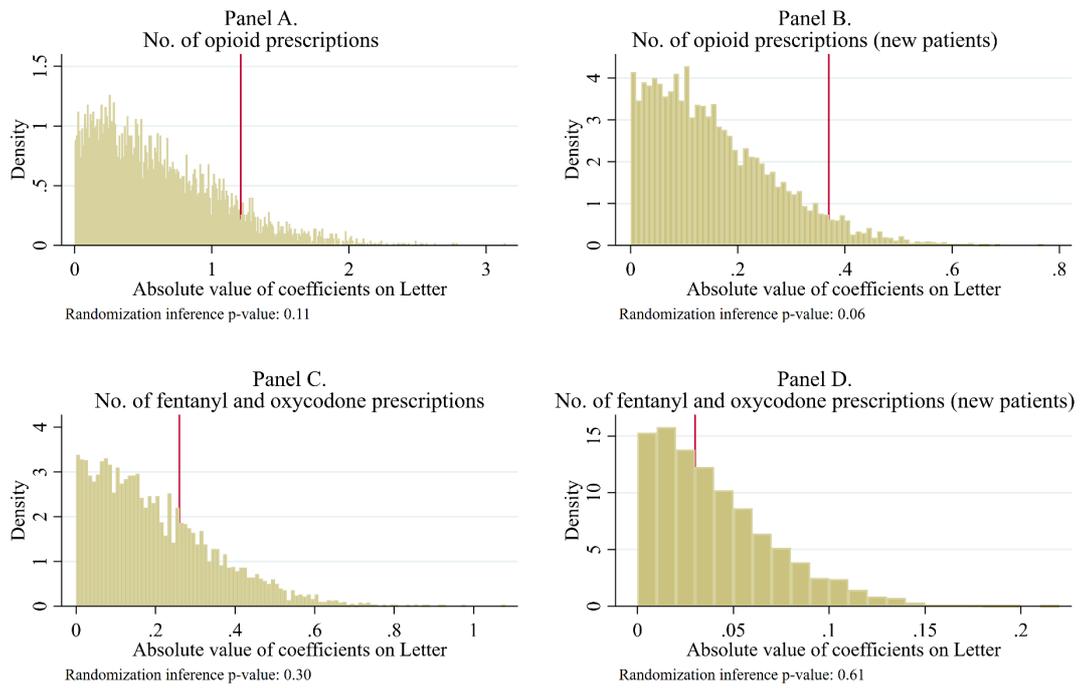
Notes: This figure shows the density of estimates of Letter for the main outcomes. Keeping the number of physicians in the Letter group fixed, we randomly allocate each physician in the study population to the Letter group 5,000 times. The vertical line displays the estimated effect from Table 2. Panels depict the absolute value of the coefficients because we use a two-sided test of significance.

Table A 5 Effect of the intervention on the number of issued opioid and fentanyl and oxycodone prescriptions during the three-month post-intervention period

| Outcome	Treatment	SE	P-value	Control mean
No. of opioid prescriptions	-0.48	0.40	0.23	21.89
No. of opioid prescriptions (new patients)	-0.16	0.11	0.14	4.75
No. of fentanyl and oxycodone prescriptions	-0.12	0.13	0.35	4.31
No. of fentanyl and oxycodone prescriptions (new patients)	-0.03	0.03	0.25	0.47

Notes: n=7,097. Standard errors (SE) are heteroscedasticity-robust. Outcomes are calculated using physician-level data from June 2019 to August 2019. Control variables include lagged value of the outcome, physician age, as well as dummies for Finnish, Swedish, and other native languages.

Table A 6 Effect of the intervention on the number of issued opioid and fentanyl and oxycodone prescriptions during the one-month post-intervention period

| Outcome	Treatment	SE	P-value	Control mean
No. of opioid prescriptions	-0.26	0.16	0.10	7.18
No. of opioid prescriptions (new patients)	-0.08	0.05	0.10	1.60
No. of fentanyl and oxycodone prescriptions	-0.004	0.05	0.94	1.38
No. of fentanyl and oxycodone prescriptions (new patients)	-0.001	0.01	0.94	0.15

Notes: n=7,097. Standard errors (SE) are heteroscedasticity-robust. Outcomes are calculated using physician-level data from June 2019. Control variables include lagged value of the outcome, physician age, as well as dummies for Finnish, Swedish, and other native languages.

Figure A 2 Treatment effect of the information letter on physicians receiving their first letter from Kela: Randomization inference

No. of fentanyl and oxycodone prescriptions (new patients)

Randomization inference p-value: 0.03
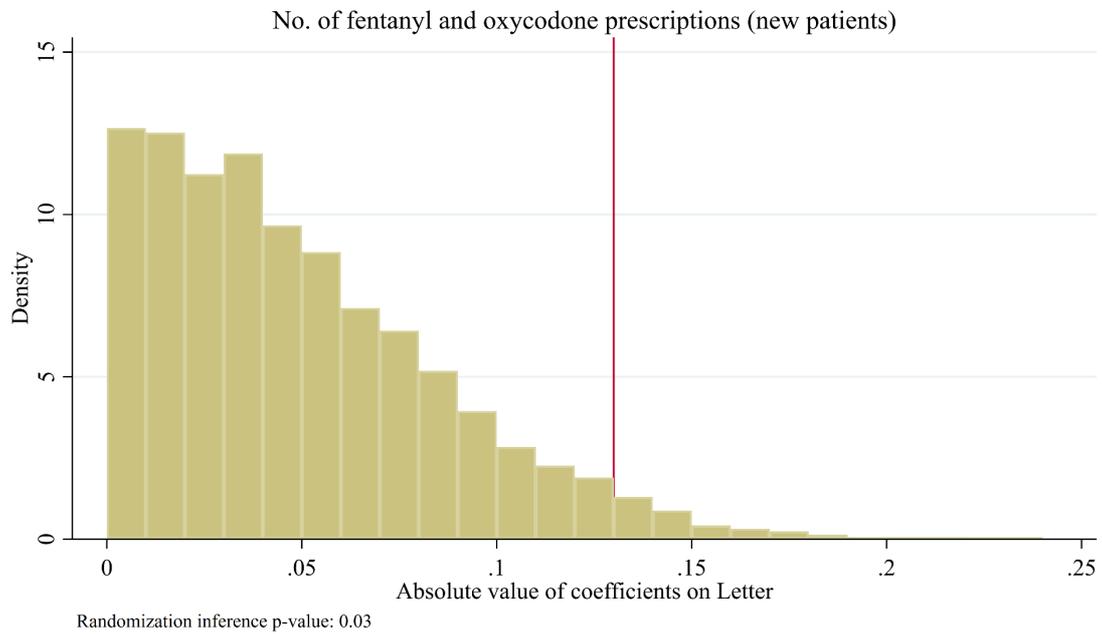
Notes: This figure shows the density of estimates of Letter when using the number of issued fentanyl and oxycodone prescriptions to new patients as the outcome. Keeping the number of physicians in the Letter group fixed, we randomly allocate each physician in the study population to the Letter group 5,000 times. The vertical line displays the estimated effect from Table 3. Figure depicts the absolute value of the coefficients because we use a two-sided test of significance.

Figure A 3 Treatment effects of the information letter on prescribing to non-cancer patients
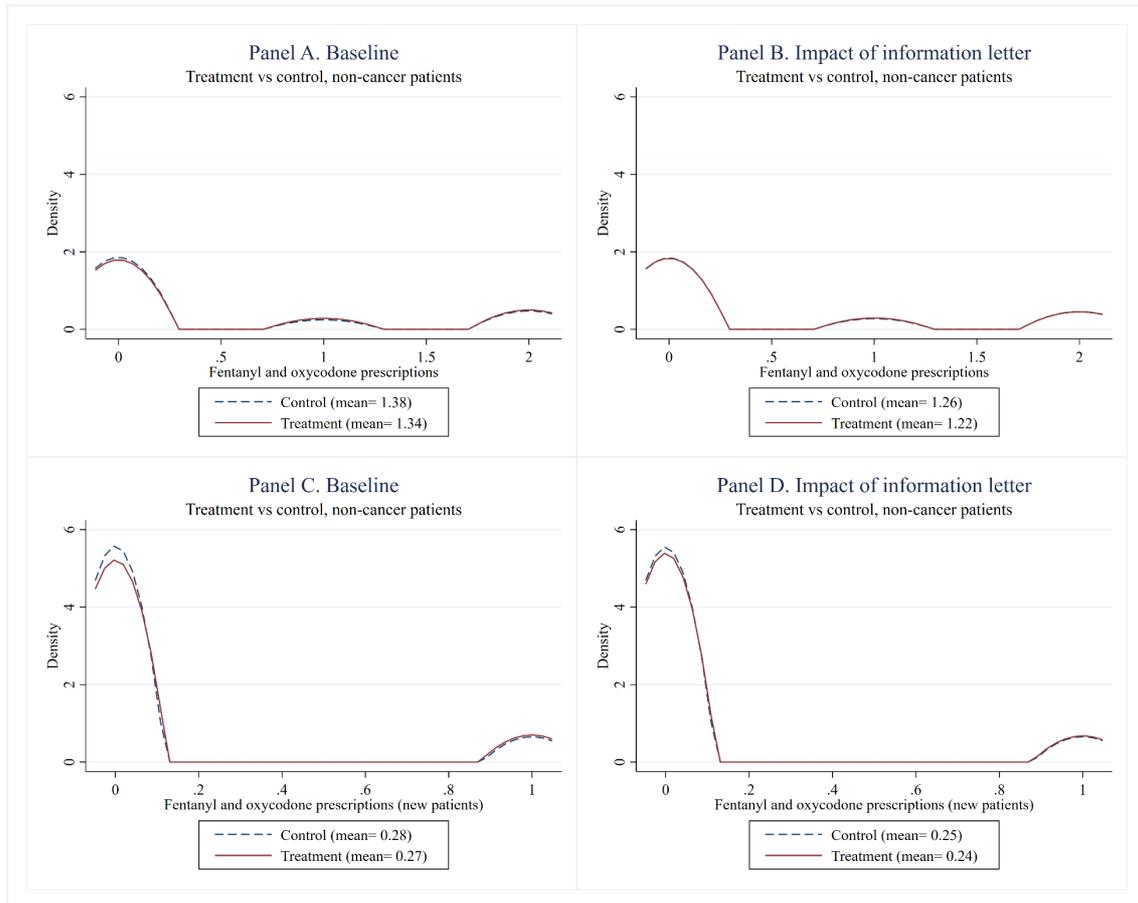
Notes: The densities are smoothed using an Epanechnikov kernel. This analysis was not preregistered.

Table A 7 Mean characteristics of physicians and baseline outcomes by number of previous letters

	(1)	(2)	(3)
Variable	First letter	Second letter	Third letter
Treatment	0.49	0.51	0.50
	(0.50)	(0.50)	(0.50)
Finnish	0.88	0.86	0.85
	(0.33)	(0.35)	(0.36)
Swedish	0.04	0.05	0.03
	(0.20)	(0.21)	(0.18)
Other	0.08	0.10	0.12
	(0.27)	(0.30)	(0.32)
Female	0.55	0.60	0.50
	(0.50)	(0.49)	(0.50)
Age	39.31	42.19	46.02
	(12.74)	(12.27)	(12.78)
Private (opioids)	0.26	0.20	0.20
	(0.44)	(0.40)	(0.40)
Private (oxycodone and fentanyl)	0.45	0.31	0.29
	(0.50)	(0.46)	(0.45)
High prescriber (opioids)	0.31	0.53	0.70
	(0.46)	(0.50)	(0.46)
High prescriber (oxycodone and fentanyl)	0.38	0.58	0.68
	(0.49)	(0.49)	(0.47)
No. of fentanyl and oxycodone prescriptions	4.73	10.56	14.53
	(10.34)	(19.40)	(23.89)
No. of opioid prescriptions	28.43	50.54	77.43
	(37.44)	(53.39)	(78.13)
No. of fentanyl and oxycodone prescriptions (new patients)	0.58	1.29	1.56
	(1.97)	(3.57)	(3.98)
No. of opioid prescriptions (new patients)	8.33	11.27	15.97
	(15.84)	(15.35)	(17.10)
Observations	2,095	3,349	1,665

Notes: Physician-level data from December 2018 to June 2019. Columns show means and, in parentheses, standard deviations by the number of Kela's information letters the physicians have received. Finnish takes the value of 1 if physician's native language is Finnish. Swedish takes the value of 1 if physician's native language is Swedish. "Other" takes the value of 1 if physician's native language is other than Finnish or Swedish. Private variables are dummies for physicians who prescribed more opioids or fentanyl and oxycodone in the private sector. High prescriber variables are dummies for physicians who prescribed more opioids or fentanyl and oxycodone than the median physician.

Appendix B

Translation of the information letter

Insurance   Medical
Unit
PL 450
00056 KELA

Dear Doctor/Dentist,

Kela is sending this letter to all doctors and dentists who, during the year 2018, prescribed oxycodone or fentanyl to patients who were not suffering from cancer and purchased at least three months' supply of medication.

The purpose of this targeted prescription feedback is to advance rational pharmacotherapy. The final report of the Rational Pharmacotherapy Implementation Programme was published in March 2018 (https://stm.fi/rationaalinen-laakehoito/julkaisut). Rational pharmacotherapy is based on the individual's health condition and aims to be effective, safe, economical, high-quality, and equitable. The Rational Pharmacotherapy Implementation Programme has evaluated the means to promote appropriate prescribing and use of medications through informational guidance.

The topic selected for the targeted prescription feedback in 2019 is the use of strong opioids in outpatient care. This topic was chosen based on awareness of the opioid crisis in the United States and the significant increase in the number of individuals in Finland who have purchased oxycodone reimbursable under the NHI scheme since 2017. The recipients of this feedback (approximately 7,000 individuals) were identified based on the health insurance reimbursement data for oxycodone and fentanyl from 2018. Purchases of oxycodone and fentanyl prescribed for cancer patients have been excluded from the feedback selection.

This targeted feedback is sent only to the individual doctors themselves. The feedback has been generated automatically. The purpose of the feedback is to encourage doctors and dentists to reflect on the prescribing of strong opioids and the issues associated with their long-term use. Half of the selected doctors will receive this feedback letter in May, and the remaining half will receive it in the fall. Attached is an article by Professor Eija Kalso on the use of oxycodone and fentanyl in outpatient care.

All the medications reimbursable under the NHI scheme prescribed by each doctor can be viewed at www.kela.fi/reseptit, where they can be accessed at any time. The service can be logged into using a certificate card (known as a VRK card) or online banking credentials. In this service, you can also compare your own prescription data with the average data by hospital district or by specialization.

We welcome feedback and suggestions for improvements regarding the electronic system and prescription feedback at laake.palaute@kela.fi.

Additionally, you can explore Kela's medicine search at www.kela.fi/laakehaku. The medicine search provides up-to-date information on medication prices, reimbursement statuses, and interchangeable products.

THE SOCIAL INSURANCE INSTITUTION

The use of oxycodone and fentanyl in outpatient care

Background factors of the increasing opioid use

Morphine, oxycodone, and fentanyl are strong opioids. Previously, these were only used in injectable form for perioperative pain management or in emergency departments. For cancer patients, opioids were administered subcutaneously or into the epidural space if oral morphine solution was insufficient or inappropriate.

The availability of opioid tablets was a significant advancement in the treatment of cancer pain. Morphine tablets entered the market in the late 1980s, followed by oxycodone tablets and transdermal fentanyl for cancer patients who could not take oral opioids. Subsequently, fentanyl was also developed into formulations that could be rapidly absorbed through the oral and nasal mucosa, and they were used for severe acute postoperative pain and cancer pain spikes.

Since the 1990s, more attention has been paid to the treatment of chronic pain other than cancer pain. The pharmaceutical industry soon recognized that the common issue of chronic pain presented a larger market opportunity than cancer pain. As a result of aggressive and misleadingly positive marketing, opioid consumption surged, particularly in the United States. The massive opioid crisis was primarily caused by oxycodone. Currently, over 200 people die from opioid overdose in the United States every day. Initially, most of the problems were related to prescription opioids. It wasn't until 2015 that illegal opioids (such as heroin and synthetic opioids, especially fentanyl) surpassed prescription opioids as the leading cause of opioid-related deaths (Kiang et al. 2019). Since 2012, the consumption of doctor-prescribed opioids has been on the decline in the United States. Opioids cause fatalities by depressing the respiratory center. Neither tolerance nor pain can protect against opioid-induced respiratory depression if the dose is sufficiently high. Some opioid-related deaths are suicides, the risk of which increases with the opioid dose (Ilgen et al. 2016).

Changes in postoperative pain management have partly contributed to problematic opioid use. Oral opioids have become common on wards for postoperative pain management, and they have been easy to prescribe to patients once they have been discharged. With the advent of short-stay surgery, patients have been discharged faster, and some have needed opioids for pain relief. The continuation of opioid medication has sometimes transferred from one doctor to another, leading to a break in the care continuum. The increase in opioid use has also been promoted by perhaps exaggerated fears of the side effects of nonsteroidal anti-inflammatory drugs.

A recent study from the United States found that in postoperative pain management, 0.6% of patients developed opioid misuse. Each additional week of opioid medication increased the risk of misuse by 34.2% (Brat et al. 2018). Other risk factors included bariatric surgery, smoking, preoperative chronic pain conditions, benzodiazepine use, severe depression, and the use of oxycodone as an analgesic, in this order.

There are significant differences between doctors in the prescribing of opioids, for example, in emergency departments. Doctors in the top quartile of opioid prescribing ordered doses more than three times higher than the doctors in the bottom quartile with similar patients at the same workplace (Barnett et al. 2017). Patients of the doctors who prescribed the most opioids had statistically significantly more hospital visits related to fractures and opioid overdoses.

The Use of Strong Opioids in Finland

Europe has not experienced an opioid crisis similar to that in the United States, and, hopefully, such a crisis will never arise. In Finland, the overall consumption of opioids prescribed by doctors in outpatient care began to decline in 2012, and this trend appears to be continuing (Figure 1). The most

significant reduction has been observed in the use of codeine. However, the consumption of oxycodone and fentanyl continues to increase.

Approximately one in four persons who purchased oxycodone in 2018 were entitled to medicine reimbursement at a special rate for medications related to cancer. For patients without the entitlement to special reimbursement rate, a total of 143,851 oxycodone purchases were reimbursed in 2018. Nearly 12,500 more prescriptions were reimbursed than in 2017. In 2018, doctors who prescribed the most oxycodone to this patient group were those without a specialty (62.8%), general practitioners (12.0%), orthopedic surgeons (3.0%), geriatricians (2.6%), and internists (2.0%).

The statistics on very large doses of oxycodone (e.g., 80 mg extended-release tablets) suggest that individual doctors are prescribing dangerously high doses of opioids for non-cancer-related pain. The harms caused by opioids increase in proportion to the dose size and the duration of treatment.

Adverse effects of opioids

The pharmacology of opioids has not changed over the years, but improper usage has concretized their associated dangers. Opioids are effective and safe analgesics when used correctly. They are still the key medications for treating severe acute and cancer-related pain. In the management of other chronic pain, it has not been demonstrated that patients gain more benefit than harm from opioids. Some research findings indicate that long-term opioid therapy can increase pain sensitivity and decrease functional capacity.

Long-term use of opioids leads to a decline in health-related quality of life (Becker et al. 1997). The most common adverse effects include constipation, sedation, mood depression, hormonal changes (e.g., decreased testosterone levels and adrenal insufficiency), weakened immune system, and cardiovascular issues. In the elderly, opioid medication quadruples the risk of fractures (Solomon et al. 2010). Opioids can cause dependence and drug misuse (Volkow and McLellan, 2016). In primary health care, 3.8% of patients who received opioid medication developed opioid dependence (Fleming et al. 2007). Some chronic pain patients have psychological conditions related to their illness (such as anxiety disorders, depression, personality disorders), which predispose them to opioid misuse. Anxiety, catastrophizing, and fear of pain can also lead to prolonged opioid use if not addressed (Martel et al. 2013).

Withdrawing from opioids can be challenging, but the patients' quality of life improves afterwards: pain, depression, and anxiety are alleviated, functional capacity improves (Huffman et al. 2017). Reducing opioid doses and employing more appropriate pain management methods (safer medications, psychological interventions, and physiotherapy) can be further supported by online therapies in the future.

The use of strong opioids for chronic (over 3 months) non-cancer pain – six tips to avoid problems

1. Postoperative pain rarely requires opioid medication for more than a week. The management of ongoing postoperative pain at home should be the responsibility of the surgical unit, not primary health care. Strong opioids should be prescribed judiciously and in the smallest possible dose. Problematic patients (e.g., those with preoperative opioid medication or chronic pain) can be referred to an acute postoperative pain clinic (Tiippana et al. 2016). At discharge, the patient should be informed about whom to contact in pain-related questions.

2. The decision to start opioids is the most critical point in potentially developing an opioid problem. This decision must be made carefully. If necessary, specialists (multidisciplinary pain clinics) should be consulted. For some patients, opioids are not an option, even if no other treatment seems

to help (e.g., patients with personality disorders, severe depression or anxiety, or those clearly seeking opioids).

3. Strong opioids are not recommended for the treatment of any chronic pain. They should be avoided especially in certain pain conditions (e.g., headaches, fibromyalgia, unclear back pain). Strong opioids should be used short-term (1–2 months) to alleviate pain until other pain management methods can be initiated. Tissue injury or inflammatory pain should be treated primarily with nonsteroidal anti-inflammatory drugs and neuropathic pain with low-dose amitriptyline or nortriptyline, dual-action antidepressants, or gabapentinoids. Multidisciplinary pain management also includes psychological treatments, physiotherapy, and lifestyle guidance.

4. Starting strong opioids should be discussed with the patient. Patient should be informed about opioid medication being a temporary treatment option associated with significant side effects that are proportional to dose size and duration, that it has an upper dose limit, and that medications will be prescribed from a single point of care.

5. For a small subset of patients suffering from chronic pain, long-term strong opioid medication may be justified. These patients experience pain relief from opioids and have no absolute contraindications, while other medication options are not possible or effective. The highest recommended daily dose of morphine for long-term use is 50–60 mg (Dowell et al. 2016), for oxycodone 30–40 mg, and for fentanyl 12–25 micrograms/hour. If you believe a higher dose is beneficial for your patient, consult a multidisciplinary pain clinic. Fast-acting fentanyl preparations should never be prescribed for anything other than a cancer patient's breakthrough pain.

6. If you decide to discontinue a patient's opioid medication (e.g., due to significant side effects, decreased quality of life, increasing doses, lost prescriptions, or non-compliance with other treatments), do so gradually (e.g., 10% dose reduction per week). The longer the opioid treatment and the higher the doses, the longer the weaning period will take. The patient will need substantial support during withdrawal. Cognitive-behavioral therapy can effectively reduce opioid doses while improving pain relief. Pain patients with opioid dependence should primarily be referred to multidisciplinary pain clinics for a better pain management plan. Opioid withdrawal can be managed through collaboration between primary health care and multidisciplinary pain clinics.