Pharmacological Treatment of Mild and Moderate Pain in Primary Care – A Danish Registry-based Study

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VIVE

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Preface

In this paper, we address an important question regarding the pharmacological aspect of chronic pain management. Pain management often starts with paracetamol, and with increasing pain intensity, supplemented by NSAIDs and Opioids. While this course of treatment, also known as the analgesic ladder, has been used for years, there is a possibility that different formulae of paracetamol might reduce the need for NSAIDs and opioids by improving the pain management in the lower end of the pain intensity domain.

In the absence of a traditional randomised control trial, we propose exploiting the natural experiment that arises from first-time analgesics prescription. While it is not possible, a priori, to assess the validity of this strategy, it is the second best solution and in accordance with traditional economic research.

As you read through this paper, you will find that the proposed strategy failed, and therefore the findings are to be considered associative rather than causal. While this is considered a setback in the study, the data does provide some interesting insights into the prescription patterns of the various kinds of analgesics.

This paper is written by Research Assistant Serkan Korkmaz (MSc in Economics), Senior Research Analyst Morten Sall Jensen (PhD) and Chief Research Analyst Eskild Klausen Fredslund (PhD) in close collaboration with Jonas Strunge (MD). We would like to thank Professor Jørgen T. Lauridsen for his highly valued comments and suggestions, which significantly improved the quality of this paper.

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Mickael Bech
Head of Research and Analytics, VIVE Health
May, 2022

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Summary

In this paper, we examine the use of extended release paracetamol (ERP) and its associated effects on chronic pain management, exploiting a natural experiment in a propensity score matching framework. We argue that the prescription of analgesics is as good as randomly assigned at the initial treatment stage of chronic pain, conditional on a set of observable characteristics if the pharmacological intervention is considered a supportive element in this process.

Using Danish registries hosted by Statistics Denmark, we identify a study population using various classes of analgesics in the years 2014-2018. Although the evidence from this population challenges the conditionally random nature of the analgesics prescriptions, thus rendering any causal interpretation void, there is suggestive evidence of systematic geographical variation across analgesics use.

We partially ascribe the violation of the conditionally random nature of analgesics prescription to the non-pharmacological aspect of the biopsychosocial model of chronic pain management. Empirical evidence suggests that non-pharmacological interventions at, and before, primary care visitation play a significant role, and information on this aspect of the treatment is not readily available from these registries. This introduces confounders, which consequentially distort causal inference.

There are, however, pronounced differences in the prescription of ERP relative to immediate-release paracetamol (IRP). For example, relative to The Capital Region of Denmark, patients in the North Denmark and Central Denmark Regions are less likely to be prescribed ERP, while patients in the remaining regions (Region Zealand and The Region of Southern Denmark) are more likely to be so.

A similar pattern appears in the prescription of ERP as the only class of analgesics prescribed. Relative to The Capital Region of Denmark, patients in Region Zealand and The Region of Southern Denmark are more likely to end their pharmacological intervention with ERP, while patients in The North Denmark Region are less likely to end their intervention with this medicine.

1 Introduction

Pain and discomfort are a problem for a considerable share of the Danish adult population. In the Danish health profile of 2022, 57% replied that they had experienced very troublesome pain or discomfort in the past 14 days (Jensen et al., 2022). While the majority of these respondents were relieved of their pain within the first month, some develop chronic pain, e.g. pain persisting for at least six months. Evidence suggests that chronic pain in primary care settings accounts for, on average, a loss of five quality-adjusted life years per 100,000 citizens and a 0.08 decrease in health-related quality of life (Fernández et al., 2010). A study from 2006 found that 16% of the respondents in a representative sample of approximately 2,000 Danes had chronic pain, which is considered a major driver of loss of function, decreased quality of life and loss of work ability (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Sundhedsstyrelsen, 2015).

Chronic pain management in general is an interdisciplinary and, predominantly, behavioural intervention across biomedical, psychological and social domains. See Hylands-White et al. (2017) for an overview of these interventions. This doctrine, the biopsychosocial model, has shown improvement in various outcomes and is adopted by the clinical guidelines of chronic pain management in Denmark (Mills, Torrance, & Smith, 2016; Sundhedsstyrelsen, 2018). In this paper, we focus on the first domain of the model, the pharmacological intervention.

Chronic pain severity in Denmark is commonly measured using Numerical Rating Scales, and can be classified as Mild, Moderate and Severe. See Hawker et al. (2011) for an introduction to the various pain measurements and Karcioglu (2018) for a recent review on the validity of these measures. Mild and moderate pain are usually treated in primary care, while severe and acute cases may require specialised treatment in secondary or palliative care.

The pharmacological treatment of chronic nociceptive pain in primary care consists of different classes of drugs, of which the following are of immediate interest in this paper:

1. Paracetamol (ATC code: N02BE01)
2. Non-Steroidal Anti-Inflammatory(NSAID), with the active component being either ibuprofen (ATC code: M01AE01), diclofenac (ATC code: M02AA15) or acetylsalicylic acid, with or without codeine (ATC code: N02BA)
3. Opioids with (ATC-code: R05DA04) or without, codeine (ATC ode: N02A).

The national guidelines on pain treatment in malignant and non-malignant chronic pain favour paracetamol as the primary treatment, while NSAIDs and opioids are considered as supplementary treatment options for increasingly severe cases (Sundhedsstyrelsen, 2019).

Immediate release paracetamol (IRP) should be taken every six hours to maximise pain coverage, while extended release paracetamol (ERP) should be taken every eight hours and therefore, arguably, provides the patient with a stable pain management option, especially during the night, as well as reducing the probability of moving up the analgesic ladder (Ortiz, Calcino, & Dunagan, 2016).

1.1 Objectives

In this paper, we examine the use of analgesics among patients with mild to moderate nociceptive pain and its associated effects on the pain management. There are two leading objectives of interest:

1. Characterising variation in the prescription pattern, and use, of ERP[1]
2. Estimating the causal effect of ERP prescriptions on the pain management relative to alternative prescriptions.

We collect demographic, socioeconomic and health-related data on a patient level grouped by analgesics use in a descriptive analysis. We extend this analysis to a progression analysis of the analgesics use with Sankey diagrams to depict possible patterns across time. See Lamer et al. (2020).

Using a linear regression, we compare the intervention group, patients receiving ERP, with a matched sample of controls. Four outcomes are of interest:

1. The probability of moving to another class of analgesics (e.g. NSAIDs or opioids)
2. Primary care contacts
3. Secondary care contacts
4. Long-term sick leave.

The main hypothesis is that ERP improves pain management and therefore reduces all outcomes.

[1] More specifically, we use the ERP Panodil 665.

2 Research Methodology

2.1 Study Design

This paper is based on a quasi-randomised case-control study using first-time ERP prescription as the source of random variation. Using this source, we statistically construct an intervention group and a control group using propensity score matching.

2.2 Data Sources

The data is collected from the national registries hosted by Statistics Denmark. All registries include unique identifiers at the patient level to join the data across these registries.

The Danish National Prescription Registry (Lægemiddelstatistikregisteret)

The Danish National Prescription Registry contains information on prescription redemption, redemption date and amount.

The National Health Insurance Service Registry (Sygesikringsregistret)

The National Health Insurance Service Registry contains information on healthcare provision covered by the National Health Insurance in the private sector.

The Danish National Patient Registry (Landspatientregistret)

The Danish National Patient Registry contains detailed information on public health care usage, diagnoses and associated costs.

The DREAM database

The DREAM database contains welfare transactions listed by week from 1991 onwards and is updated quarterly.

2.3 Study Population

The study population consists of patients who in the years 2014-2018[2] received a new prescription, with a two-year washout period, for:

- Paracetamol (ATC code: N02BE01)
- NSAIDs (ATC code: M01AE01, N02BA)
- Opioids (ATC code: N02A)
- Codeine (ATC code: R05DA04)
- Pregabalin (ATC code: N03AX16)
- SNRI (ATC code: N06AX16, N06AX21)

[2] We restrict the lower sampling limit to the year 2014 as OTC sale of stronger OTC analgesics became illegal in 2013. For paracetamol, this means that purchase of packages above 10 grams requires a prescription from a healthcare professional.

- Muscle Relaxants (ATC code: M03BB03).

We exclude patients with prescriptions for psychiatric disorders from the study population.

2.4 Quantitative Method

Descriptive analysis

For each class of analgesic, paracetamol (ATC code: N02BE01), NSAIDs (ATC code: M01AE01, N02BA) and opioids (ATC code: N02A), we conduct a descriptive analysis of the average analgesic recipient in the study population. We extend this analysis to estimate the probability of being prescribed ERP as the only class of analgesics relative to the remaining class of analgesics. Furthermore, we estimate the odds ratio of being prescribed ERP relative to IRP.

Progression analysis of analgesics use

For each class of analgesic, paracetamol (ATC code: N02BE01), NSAIDs (ATC code: M01AE01, N02BA) and opioids (ATC code: N02A), we construct a Sankey diagram to depict the course of treatment in the period 2015-2017, using 2016 as the reference.

Regression analysis: A matched control difference-in-differences design

To study these effects causally, we propose using first-time ERP prescription as the source of random variation in a quasi-randomised experiment. In the absence of a controlled environment, this strategy rests on the assumption that the first-time prescription of ERPs is as good as randomly assigned, conditional on a set of observable characteristics. For a non-exhaustive list of similar strategies see Meyer (1995). While the majority of these studies exploit the natural experiments created by external factors, such as government interventions, our study exploits the natural experiment that occurs during the initial prescription of analgesics by the general practitioner (GP).

It can be argued that the first-time prescription is as good as randomly assigned, under the leading assumption that the GP is equally likely to prescribe ERP and IRP, conditional on a set of observable characteristics. This assumption holds true if, for example, the non-pharmacological interventions are considered the main driver of the initial pain management, while the pharmacological intervention serves as a predominantly supportive intervention. The latest evidence supporting the use of first-time prescription as a source of random variation is found in the latest survey of chronic pain in Europe. In this survey, 70% of the respondents received non-pharmacological interventions only (Breivik et al., 2006). This suggests that non-pharmacological treatment in the mild and moderate pain domains is the main driver of the initial pain management, which, in turn, renders the prescription of paracetamol a supportive intervention rather than a crucial element of the treatment, in accordance with the biopsychosocial model[3] (Bodenheimer, Wagner, &

[3] More formally, we claim that the intervention assignment, T, is mean independent of intervention type once conditioned on a set observable characteristics, $E[T|NP, P, X] = E[T|X]$

.

Grumbach, 2002). However, to our knowledge no other studies use this strategy, and therefore, in this aspect, this paper is novel.

Using first-time ERP prescription as the intervention assignment, we construct statistically balanced intervention and control groups in a two-step propensity score matching procedure with a probit regression to mimic a simple randomised clinical trial (Rosenbaum & Rubin, 1983). We start by exact matching on year and month variables, and then re-estimate the propensities of being assigned in the intervention group. Based on these propensities, we proceed with the matching based on the nearest neighbour algorithm without replacement. Using a two-step propensity score matching procedure removes possible residual imbalances from the first step (Nguyen et al., 2017). See, for example, Sun et al. (2022) for a similar approach.

Under the leading assumption that first-time prescription of ERP is random conditional on a set of observable characteristics, it immediately follows that the derived propensities of the intervention assignment conditional on the same set of observable characteristics are conditionally independent of the intervention assignment (Rosenbaum & Rubin, 1983).

From the Danish National Prescription Registry we identify subjects who have redeemed an ERP prescription for the first time, while redeeming at least two prescriptions of IRP during the six months preceding the ERP redemption.

Using this identifier as the intervention allocator we construct a statistically balanced intervention and control group in a propensity score matching framework. To calculate the propensity of receiving the intervention, we run a probit regression on the form:

$$\Pr(T = 1|X) = \phi(\beta X)$$

where $\Pr(T = 1|X)$ is the intervention propensity, β is a vector of coefficients, and X is a matrix of observable characteristics. These include gender, age, education, income, labour market affiliation, industry code, marital status, residence at municipality level, previous drug consumption, date and primary and secondary health care contacts. Using these propensities, we create an auxiliary dataset by exact matching based on year and month.

From this auxiliary data, we re-estimate the propensities and perform nearest neighbour matching without replacement and finalise the matched dataset for further analysis.

In their final form, the data constitute a panel data set with unique identifiers across year and month. To estimate the effect of using ERP over time, we propose running a difference-in-differences regression:

$$Y = \beta_0 + \beta_1 Intervention + \beta_2 Time + \beta_3 Intervention * Time + \beta X + \varepsilon$$

where Intervention is the identifier of the intervention assignment, Time represents intervention date, and X is a matrix of observable characteristics, as described above. β represents coefficients, and a vector of coefficients where subscripts are excluded.

The coefficient of interest is β_3, which, under the assumption of first-time ERP prescription being as good as randomly assigned, is the causal effect of receiving ERP on the outcome Y. To account for possible biases in the standard error, we use heteroscedasticity and autocorrelation-consistent standard errors (Bertrand, Duflo, & Mullainathan, 2004).

2.5 Outcome Measures

To assess the pain management that ERP provides, we use the following measures as proxies:

1. Consumption of analgesics
    a. Measured in defined daily dosages (DDD)
2. Primary care contacts
    a. All-cause GP contacts
    b. All-cause physiotherapist contacts
    c. All-cause psychologist contacts
    d. All-cause anaesthesiologist contacts
3. Secondary care contacts
    a. All-cause inpatient contacts
    b. All-cause outpatient contacts.

As an additional outcome, we examine the effect of ERP on sick leave. The leading hypothesis is that ERP use reduces all outcome measures.

The consumption of analgesics is measured in defined daily dosages (DDD), while primary and secondary care contacts are measured in all-cause contacts during the study period.

3 Results

We analyse the results in three separate subsections. Though presented separately, these results are to be considered in relation to one another. All non-essential tables and figures can be seen in the appendix. The first subsection is the descriptive analysis, the second subsection is the course of treatment, and the third subsection is the regression analysis.

3.1 Descriptive Analysis

There are approximately 200,000 patients with a first-time prescription for any class of analgesic. Of these, 32% received IRPs, 2% received ERPs, 46% received NSAIDs, and 20% received opioids as the highest step on the analgesic ladder.[4] In the first part of the descriptive analysis, we evaluate the distribution of various characteristics within, and across, each class of analgesics.

The gender distribution across the analgesic ladder is skewed towards females in the lower steps and becomes increasingly equal as we move up the ladder. Whether the increasingly equal distribution reflects a higher proportion of men using, for example, opioids or, conversely, a lower proportion of women using opioids is not revealed by the data. The age distribution in the higher steps of the analgesic ladder is relatively uniform, while the lower steps reveals that the vast majority are in the 70+ age group (See appendix).

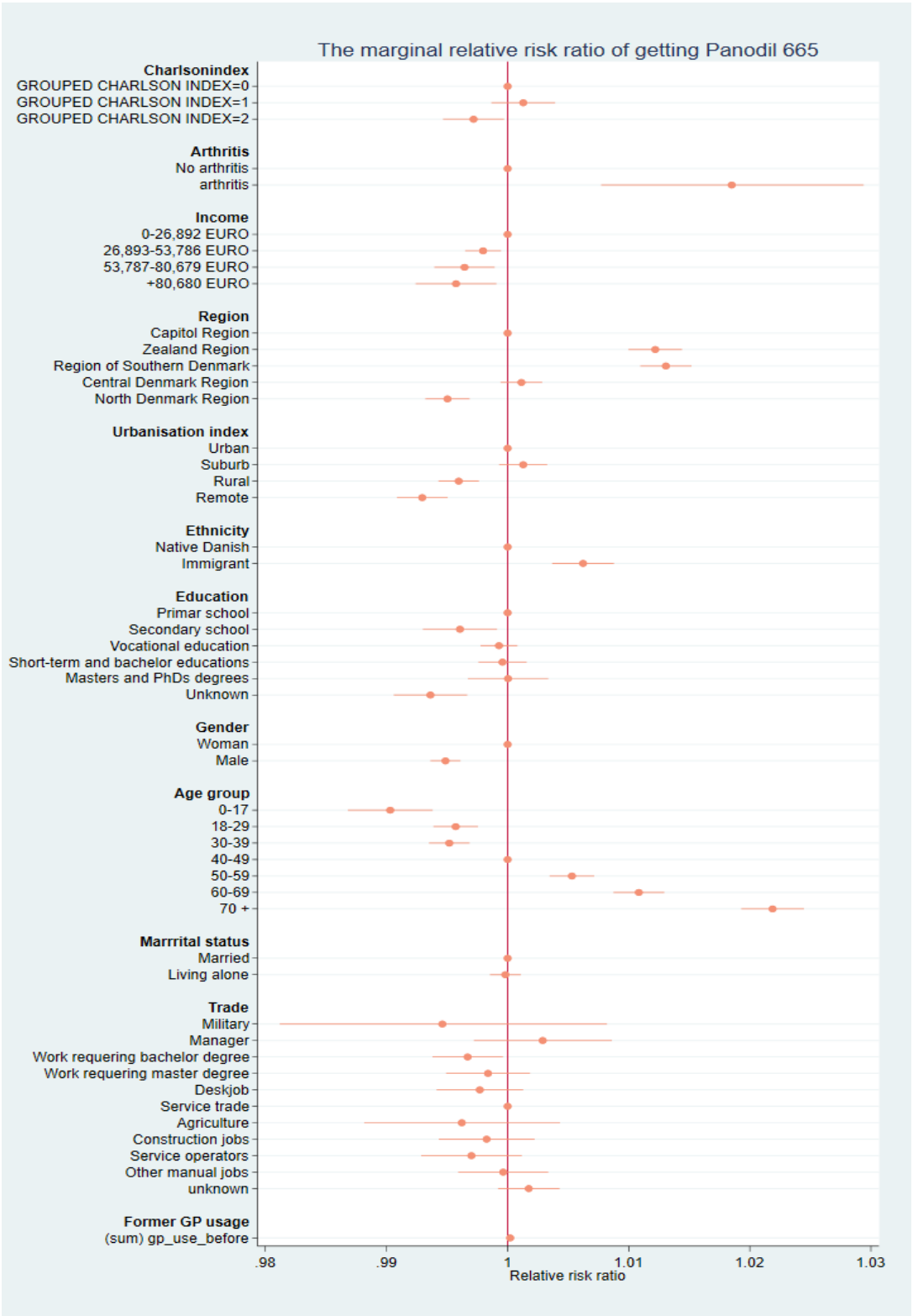
Although the data reveals no obvious pattern across the analgesic ladder with regard to education or income, the distribution is skewed towards lower schooling and consequentially by lower income brackets within each step. This is true for the geographical factors as well, where there are no obvious pattern across the analgesic ladder, but each step is dominated by urban and rural areas. While the steps of the analgesic ladder are barely determined by regional factors, there is a tendency of The Region of Southern Denmark to utilise ERP more intensively (See appendix).

We extend the descriptive analysis and, conditional on a set of observable characteristics, estimate the probability of ERP prescription as the last step of the analgesic ladder, using a Multinomial Logistic Regression. The data suggests that regional factors, socioeconomic factors and co-morbidities statistically affect the probability of being prescribed ERP (Figure 3.1). At face value, this implies that while Region Zealand and The Region of Southern Denmark show a tendency to keep patients on ERP, patients in The North Denmark Region show more movement across the analgesic ladder relative to patients in The Capital Region of Denmark. A similar interpretation can be made for patients in remote and rural areas, who show more movement across the analgesic ladder relative to patients in urban areas. To determine whether this is a chance finding or due to systematic regional variation would require in-depth analysis, which is beyond the scope of this paper.

[4] For narrative simplicity, we will refer to IRP and ERP as the first step in the analgesic ladder, and opioid as the last step.

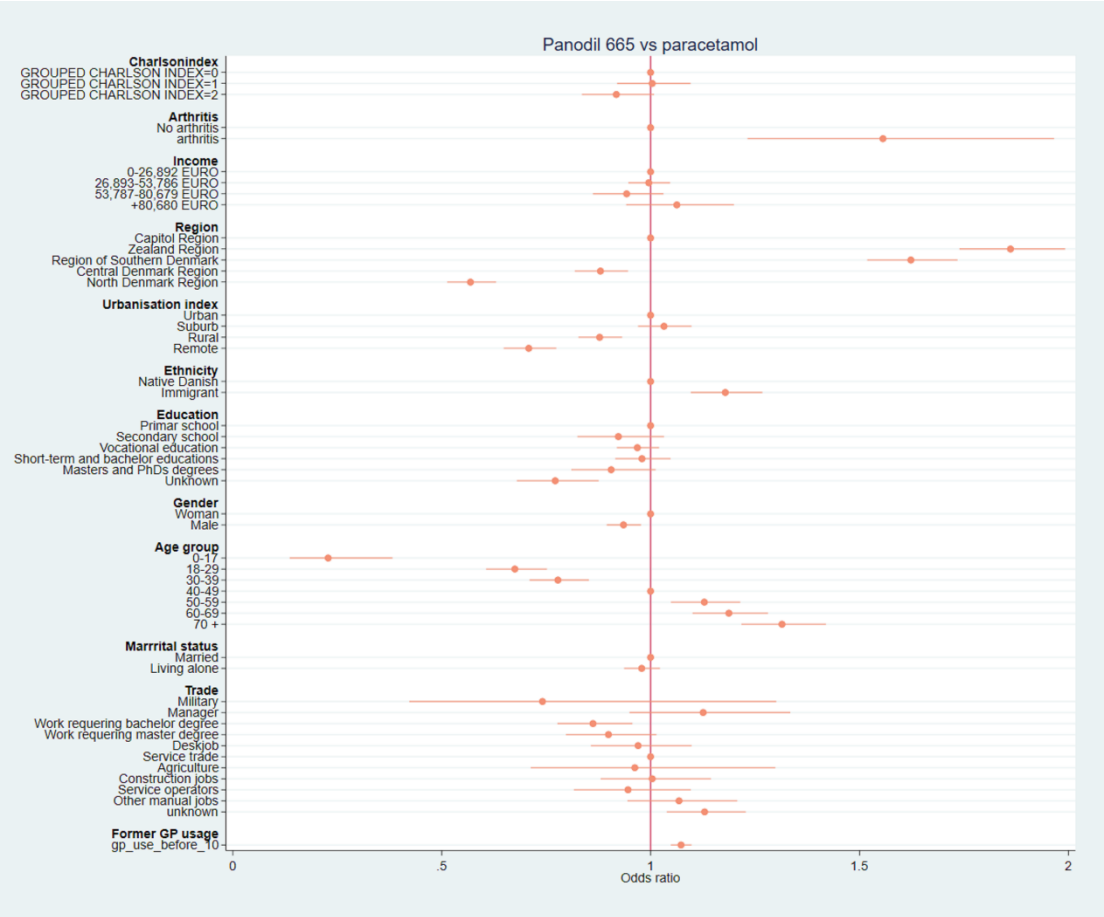
To examine the use of ERP vs. IRP (in possible combination with other analgesics), we ran a logistic regression, and while the results are similar to those of the multinomial regression, the geographical factors are more elaborate (Figure 3.2). Patients in Region Zealand and The Region of Southern Denmark are more likely to receive ERPs, while patients in the Central Denmark and North Denmark Regions are more likely to receive IRP relative to patients in the Capital Region of Denmark. This is also true for rural and remote areas.

Figure 3.1 Risk ratios of ERP prescription characteristics



Note: Relative risk ratios of ERP being the only class of analgesics prescribed, relative to NSAIDs and opioids. Estimated by a multinomial logistic regression. Each value is relative to the initial, or middle, value in each category. Based on 203,286 patients. Values above 1 indicate a higher probability of staying on ERP.

Figure 3.2 Odds ratio of being prescribed ERP



Note: Odds ratio of receiving ERP vs. IRP (in possible combination with other analgesics). Estimated by a logistic regression. Each value is relative to the initial, or middle, value in each category. Based on 114,383 patients. Values above 1 favour Panodil 665.

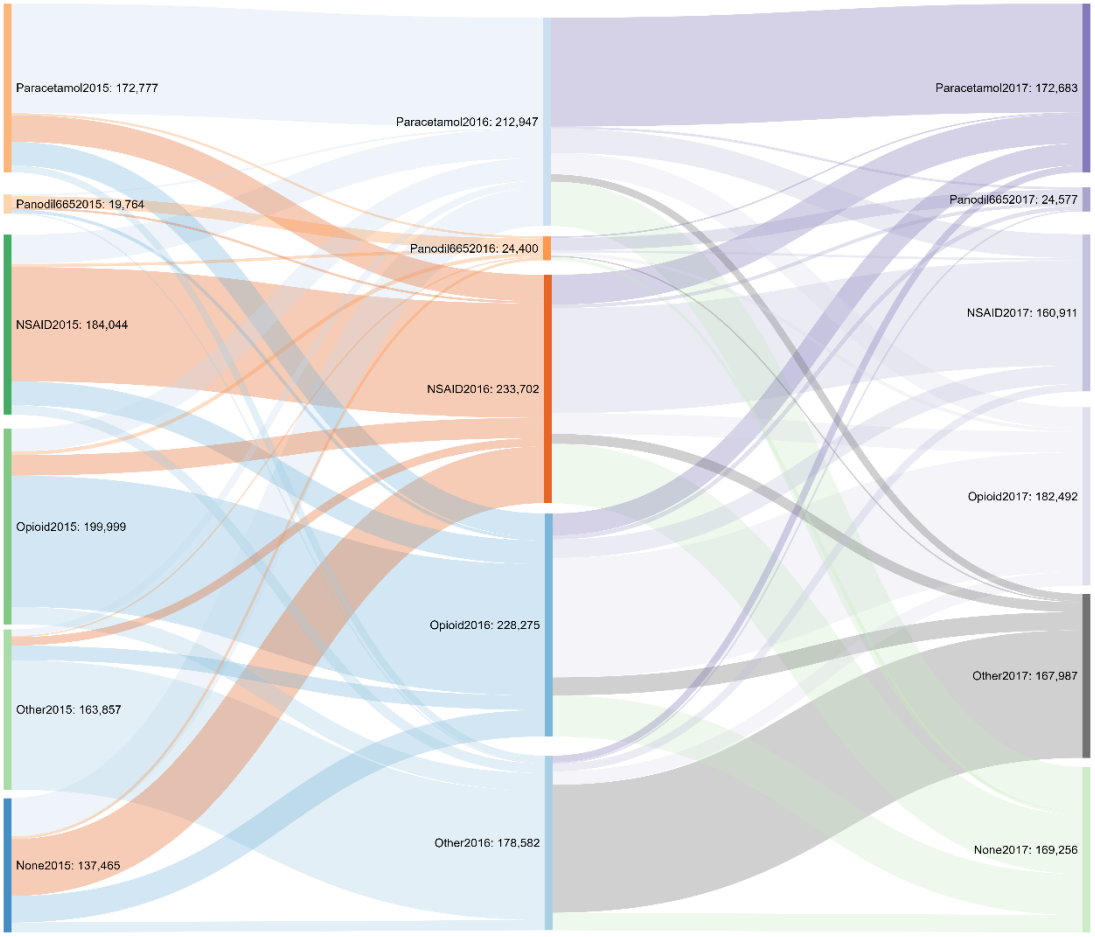
3.2 The Course of Treatment

In this section, we use Sankey diagrams to depict the course of treatment for patients receiving pharmacological interventions in the period between 2015 and 2017, using 2016 as reference. While the majority of patients continue with the initial prescription, there are predictable movements along the analgesic ladder, as is the case for the movement from paracetamol to NSAIDs, and from NSAIDs to opioids

From the reference year, there are some differences between IRPs and ERPs. More patients in the IRP group continue to no treatment (22% vs. 13% in the ERP group), and more patients move to the NSAID group (12% vs. 9% in the ERP group). The opposite is the case for moving to the opioid group, where 13% move from the ERP group to opioids compared to 11% of the IRP group (Figure 3.3).

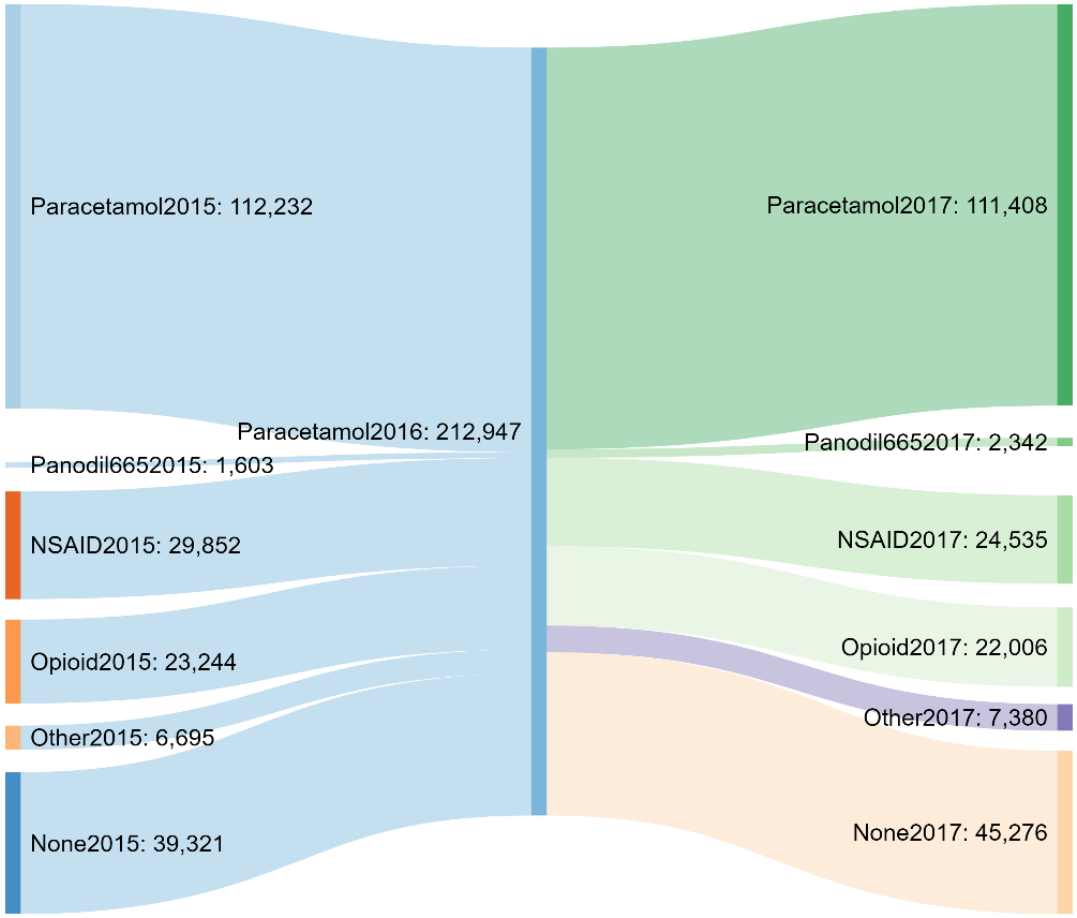
In Figures 3.4 and 3.5, patients prescribed IRP and ERP, respectively, show a similar pattern. Once patients have been prescribed either of these analgesics, moving across the analgesic ladder is less likely. The majority of the patients that switched analgesics were on opioids before they were prescribed ERP (15%), while the majority either stopped use of analgesics completely (13%) or were prescribed opioids (13%). For the patients prescribed IRP in 2016, the majority were either prescribed NSAIDs (11%) or opioids (10%) the following year, while 1% were prescribed ERP.

Figure 3.3 Courses of treatment for patients identified on the analgesic ladder in 2016



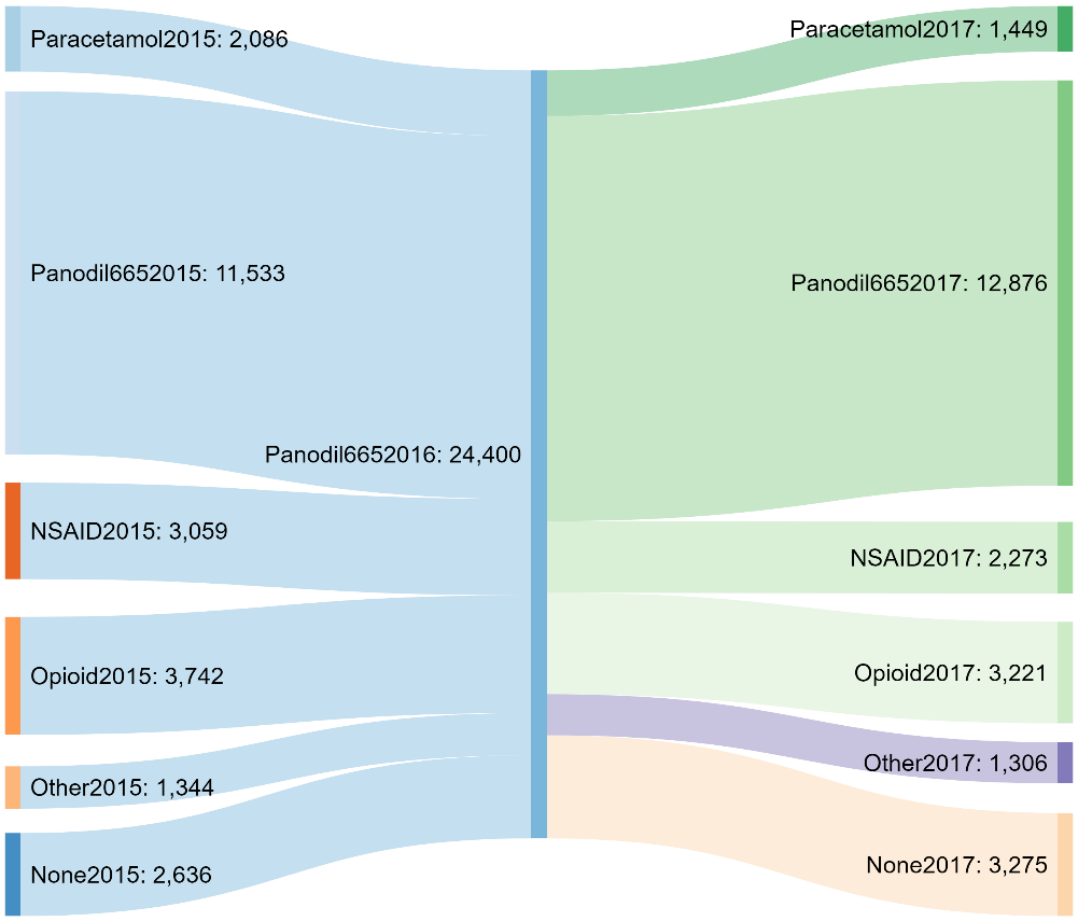
Note: The diagram shows the courses of treatment between 2015 and 2017 across the analgesic ladder. Moving from left to right, the figure shows the initial analgesic class and the terminal analgesic class. Sankey diagram produced using SankeyMATIC

Figure 3.4 Courses of treatment for patients receiving IRP



Note: The diagram shows the courses of treatment between 2015 and 2017 for patients receiving IRP in 2016. Moving from left to right shows the transition to and from IRP.

Figure 3.5 Courses of treatment for patients receiving ERP



Note: The diagram shows the courses of treatment between 2015 and 2017 for patients receiving ERP in 2016. Moving from left to right shows the transition to and from ERP.

3.3 Regression Analysis

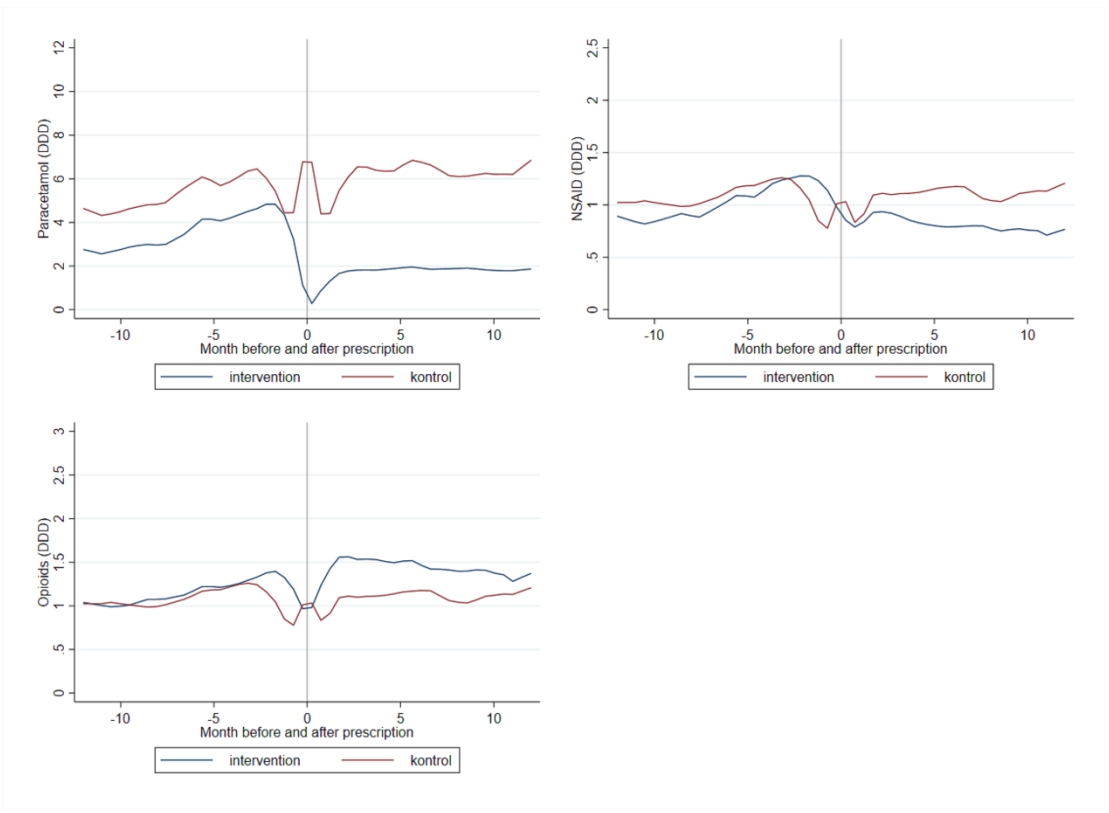
In this section, we analyse the results of the propensity score matching at face value and provide a brief description of the findings. The descriptive statistics of the final matched data can be seen in the appendix. By construction, all descriptive characteristics are statistically balanced.

This section is divided between analgesics use, primary care contacts and secondary care contacts before and after ERP prescription. The various results share some common overall characteristics that are suggestive of some unobserved health shock in the close vicinity of the ERP prescription date. While this health shock challenges the notion of ERP prescription being as good as randomly assigned, the interpretation of these results should be considered associative rather than causal.

The largest changes in absolute values are found for visits to outpatient clinics and anaesthesiologists, which supports the existence of an unspecified health shock prior to ERP prescription. More specifically, there is a divergence in all outcomes prior to the ERP prescription date, suggesting systematic differences between the groups that cannot be ascribed solely to the prescription, which complicates inference. This divergence is pronounced in the close vicinity of the ERP prescription date and serves as a strong indication of some unobserved health shock.

3.3.1 Analgesics Use

Figure 3.6 Analgesics use before and after ERP prescription

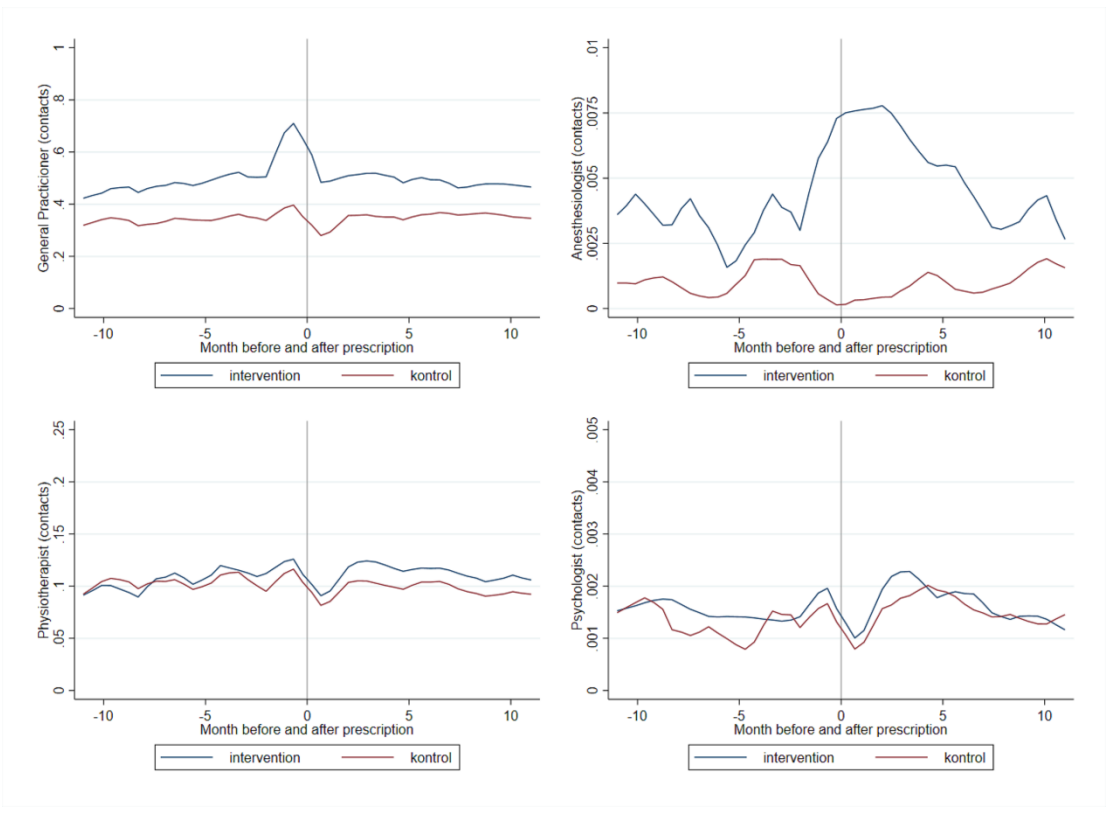


Note: For each figure the outcomes for the intervention group (blue) and control group (red) are plotted. The intervention date is set to 0, and positive values along the x-axis show outcomes months before and after ERP prescription. All values are given in averages.

The change in use of analgesics in the vicinity of ERP prescription may reflect a transition towards another class of analgesic, as is the case for immediate-release paracetamol. However, the unobserved health shock necessitates caution in the interpretation of these outcomes as it complicates inference beyond direct visual inspection. Any movement, or change, in these outcomes on either side of the ERP prescription may reflect various factors that are not observable, and hence not adjusted for accordingly.

3.3.2 Primary Care Contacts

Figure 3.7 Primary care contacts before and after ERP prescription

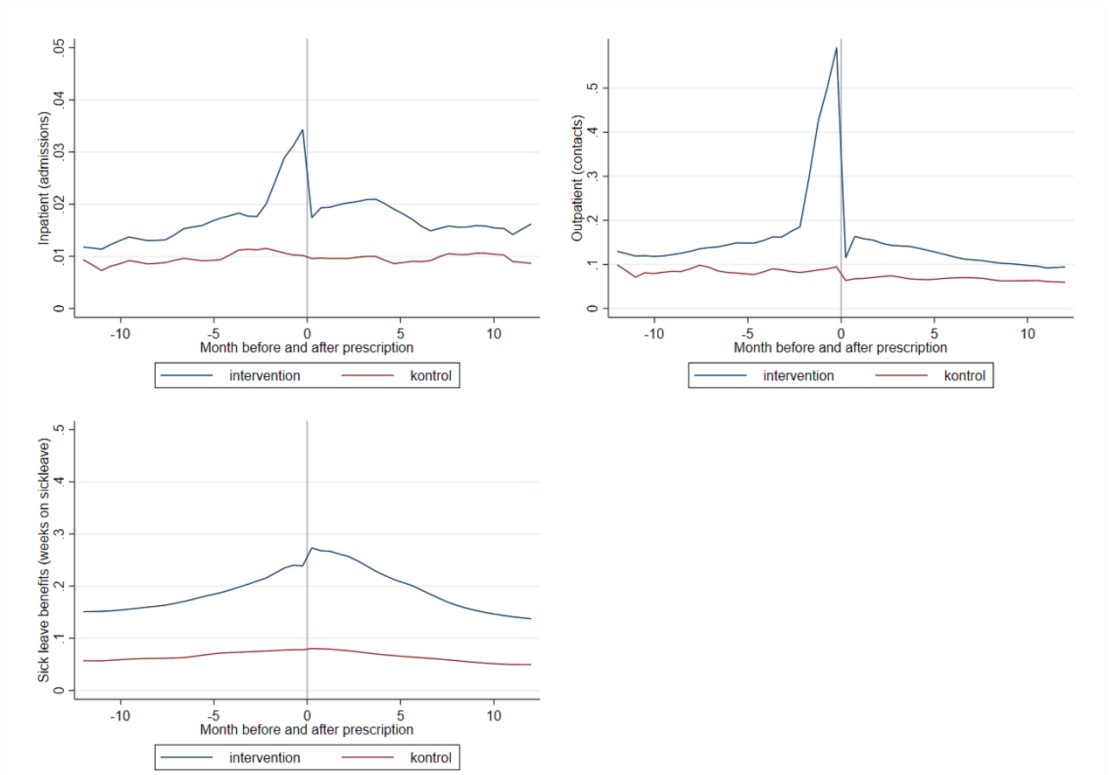


Note: For each figure, the outcomes for the intervention group (blue) and the control group (red) are plotted. The intervention date is set to 0, and positive values along the x-axis show outcomes months before and after ERP prescription. All values are given in averages.

Figure 3.7 is the visualisation of the regression output. Taken at face value, there are no visible changes in primary care contacts during the months before and after ERP prescription other than for visits to the anaesthesiologist where there is a spike for the intervention group, which eventually converges towards the control group as the months pass by. In the ERP prescription vicinity, there appears to be a pattern of non-random spikes, which is another strong indication of unobserved health shocks prior to the intervention date.

3.3.3 Secondary Care Contacts

Figure 3.8 Secondary care contacts and sick leave before and after ERP prescription



Note: For each figure, the outcomes for the intervention group (blue) and control group (red) are plotted. The intervention date is set to 0, and positive values along the x-axis show outcomes months after ERP prescription. All values are given as averages.

After the prescription date, inpatient visits in the intervention group move parallel to the control group, while sick leave benefits and outpatient visits gradually converge as the distance from the prescription date increases. At face value, this implies that, all else being equal, the ERP prescription on average reduces systematic differences between the intervention and control groups in these outcomes. However, given the sudden changes around the intervention date the convergence of outcomes cannot necessarily be ascribed to the ERP prescription.

4 Discussion

4.1 Failure to Identify Causal Effects

Under the leading assumption that pharmacological interventions were considered supplementary, and therefore random conditional on a set of observable characteristics, the regression estimates have a causal interpretation. However, this assumption does not capture the variation in the data, and such a violation introduces endogeneity in the estimation process, which consequentially renders any causal interpretation void. We offer two possible, not necessarily mutually exclusive, sources of endogeneity.

Consider the treatment decision as a weighted decision function:

$$T = \alpha_0 + \alpha_1 NP + \alpha_2 P + \alpha_3 X + \varepsilon$$

where NP and P represents non-pharmacological and pharmacological treatment indicators, respectively, X is a matrix of observable characteristics, and ε is the random variation. In this setup, α_i represents the weights attached to each treatment type and determines the actual treatment that the patient receives. This decision function will serve as the foundation for the following discussion.

Omitted variables

The treatment strategy of chronic pain follows the biopsychosocial model, in which the importance of each aspect varies with morbidity, co-morbidity, pain severity and time. It is likely that non-pharmacological treatment is of much greater importance at the initial treatment stage than expected, and the failure to account for this introduces a confounding variable that is not available, or observable, in the data. In the absence of suitable proxies for non-pharmacological interventions, and assuming that this intervention outweighs the pharmacological intervention, the estimators will be biased.

More formally, it can be argued that for any outcome Y the structural equation of interest is of the form[5]:

$$Y = \beta_0 + \beta_1 T + \beta_2 X + \epsilon$$

where β_i represents coefficients, T is the intervention indicator, and X is a set of observable characteristics. However, as the intervention assignment is a weighted decision function the structural function is of the form:

$$Y = \delta_0 + \delta_1 NP + \delta_2 P + \delta_3 X + \vartheta$$

This implies that unless $\delta_1 = 0$, or in the trivial case $\beta_1 = 0$, the coefficient of interest, δ_2, will be biased. In the non-trivial case, the implication is that non-pharmacological treatments have no effect on the outcome. However, empirical evidence suggests that this is highly unlikely because a recent systematic review of psychological therapies in

[5] For simplicity, and without loss of generality, we use a linear regression without interactions in a cross-sectional setup.

chronic pain management shows that, for example, Cognitive Behavioural Therapy has beneficial, albeit small, effects (Williams, Fisher, Hearn, & Eccleston, 2020).

Selection on observables

The key identifying assumption of the propensity score matching strategy in an observational study is the conditional independence of the intervention assignment of the outcomes (Caliendo & Kopeinig, 2008; King & Nielsen, 2019; Rosenbaum & Rubin, 1983). More formally:

$$Y \perp T|X$$

This assumption is satisfied under the condition that the intervention assignment, T, is determined randomly or the observable characteristics capture all variation in T; which, based on the observed progress in outcome variables prior to ERP prescription, clearly is not the case.

Failure to satisfy this assumption introduces selection bias in the estimates. Even under the assumption that $\alpha_1 = 0$ in the decision function, this assumption rests on the condition that X captures all the variation in the intervention assignment. However, empirical evidence suggests that this is highly unlikely, given the possibility of the importance of non-pharmacological interventions (Breivik et al., 2006; Williams et al., 2020). The data supports the possibility of selection bias, as the pre-intervention trends either diverge, or overlap, in the vicinity of the intervention date, which is a strong indicator that it is not the intervention alone that separates the intervention group from the control group.

Although the case for omitted variables implies a violation of the conditional independence assumption, this relation is not necessarily bidirectional. A violation of the conditional independence assumption does not imply that an observable set of omitted variables exists that could potentially mitigate this violation as this set might not serve as a valid proxy for the unobservable characteristics.

To mitigate such challenges against the identification of causal effects, instrumental variable strategies are often proposed see Angrist et al. (1996) for an introduction to this strategy. Using peer effects among general practitioners, Thingholm (2019) demonstrates the circumstances under which leniency in prescriptions can be considered a valid instrument within this framework. However, this strategy is not possible with the available data.

4.2 Deviations from Protocol

Subsampling

We restricted the time interval in the Sankey diagram to 2015-2017 as the wider interval did not add any information and it complicated the visual interpretation of the diagram.

Omission of point estimates and confidence intervals

As argued in the preceding subsection, the identifying assumptions of the regression analysis are not satisfied. Therefore, the point estimates and confidence intervals are

excluded to avoid unnecessary emphasis on these specific outcomes. These estimates can be obtained upon request, however.

Omitted outcomes

The pill burden, i.e. the number of analgesics patients take on a regular basis, and compliance rate were omitted from the analysis as it was not possible to obtain reliable data on the assigned treatment on a patient level. To estimate these effects we would need to observe the assigned course of treatment, which in the absence of a controlled environment, or a reliable proxy, is not possible as the data only reveal the observed course of treatment for the intervention and control group. Although we acknowledge that each measure can be calculated based on observed data, this approach has negligible added information value at best as primary care prescriptions are not necessarily linked to the chronic pain management in question per se.

4.3 Strengths and Limitations

Using the Danish registries, we can uniquely identify patients within, and across, registries available in Denmark. This implies that we can identify patients and track diagnoses, prescriptions etc. uniquely across all registries and thus exploit all available information. However, the links between registries are not relational as to the specific patients. That is, it is not possible to link, say, the redemption of a given analgesic to a specific diagnosis. Similarly, the Danish health-related registries include only patients who are partially, or fully, reimbursed by the Danish public health insurance, Sygesikring, and therefore exclude OTC analgesics, for example.

The absence of a randomised clinical trial complicates the identification of the effect of the ERP intervention. To mitigate the lack of such a trial, the second best solution could be used, namely to construct, or identify, an intervention that is as good as randomly assigned. This approach, however, even under the assumption that the assignment is statistically independent of observables, and unobservables alike, is sensitive to small deviations in this artificially constructed intervention, and will exclusively apply to the population at hand, or those affected by this specific intervention.

While it is not possible to distinguish between healthcare visits due to acute pain and chronic pain, the employed washout period of two years can partially mitigate the differences arising from this limitation. However, it is not unlikely that this circumstance inflated the estimated effects in absolute value, regardless of the wash-out period.

Another limit of these registries is that they by construction do not include specialised pain clinics. The absence of this specific measure will attenuate the estimated effect in primary care visits.

5 Conclusion

This paper failed to identify any causal effect between ERP use and improved pain management, and therefore it is not possible to provide a meaningful interpretation of the observed behaviour of the patients after they were prescribed ERP.

We ascribe this failure of identification to the implemented strategy as the leading assumption of first-time ERP prescription being as good as randomly assigned does not hold true. While the leading assumption failed and thus rendered any causal inference void, the assumption did reveal the existence of some health shock that differentiated the intervention group from the control group, aside from the ERP prescription alone.

This paper also finds systematic geographical variation in the prescription pattern and use of ERP. Although this cannot readily be ascribed to valid, and tested, factors other than the possibility of variation in pain management practice across regions, the evidence suggests that some regions prefer to use ERP. Patients in, for example, the Zealand Region and The Region of Southern Denmark, relative to The Capital Region of Denmark, are more likely to be prescribed ERP than IRP, while the converse holds true for the Central Denmark and North Denmark Regions. It is not immediately clear, however, whether ERP is used as a replacement for IRPs, NSAIDs or opioids in the pain management.

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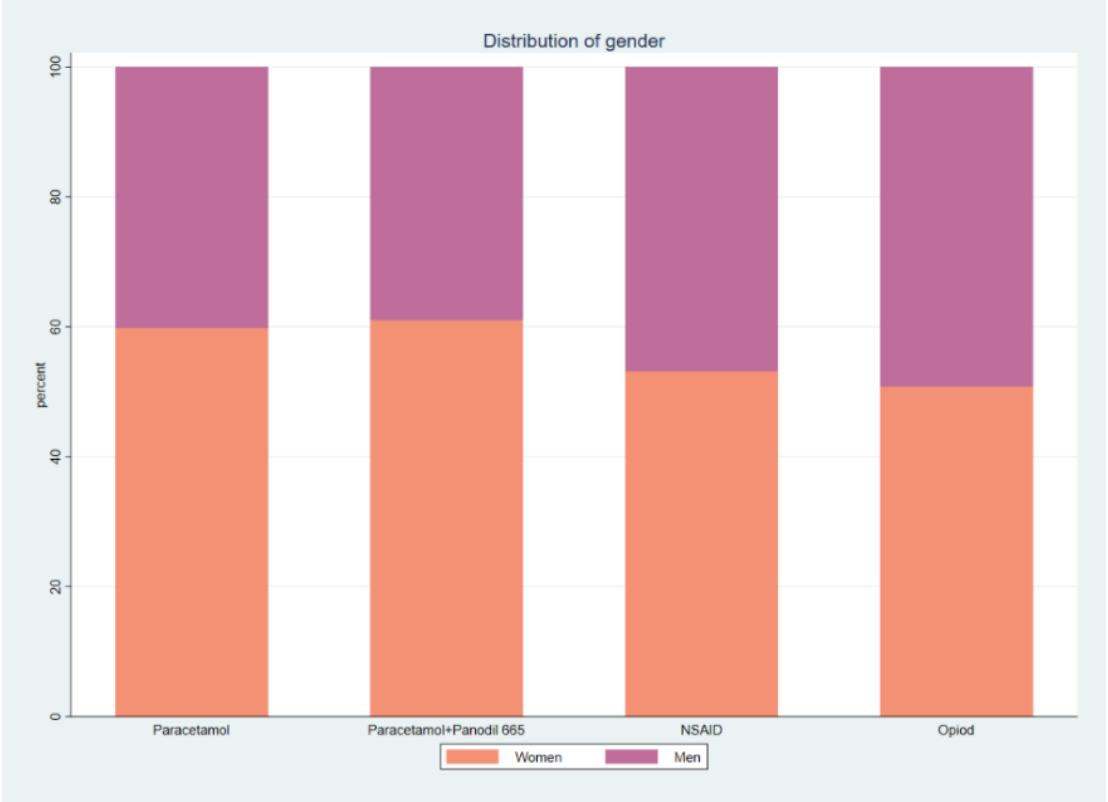
Appendix 1

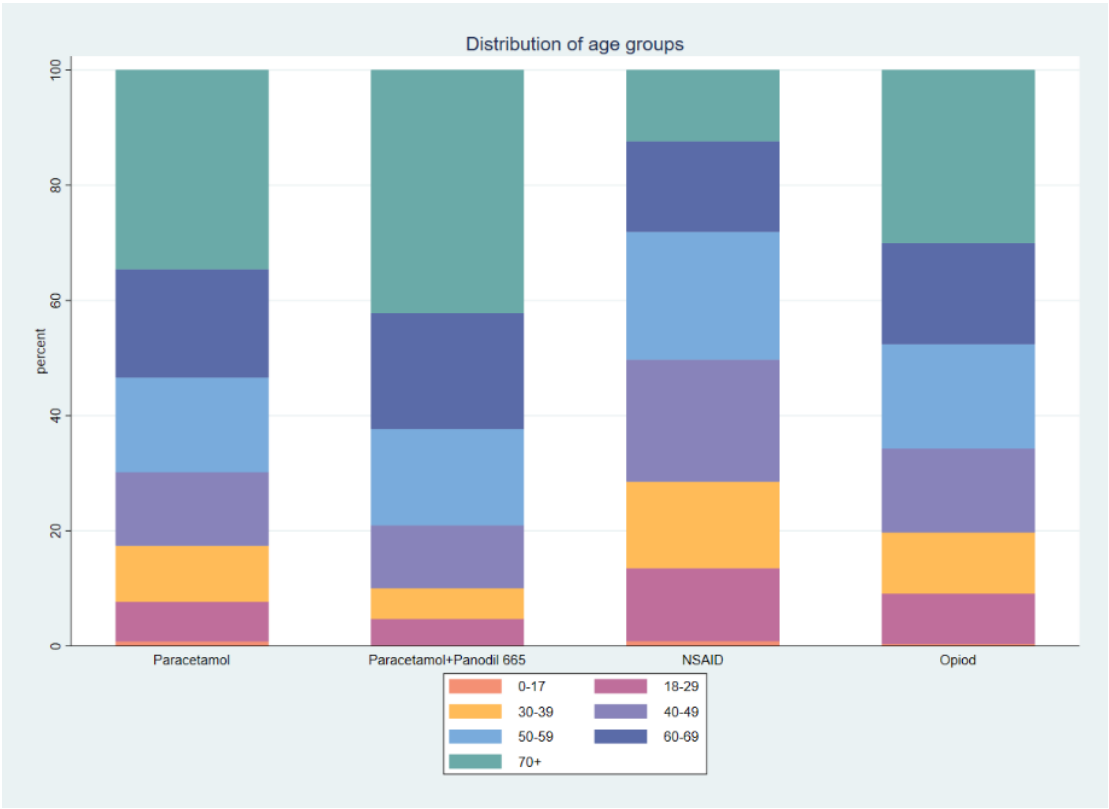
Descriptive Graphs

Appendix figure 1.1 Gender distribution on each step of the analgesic ladder



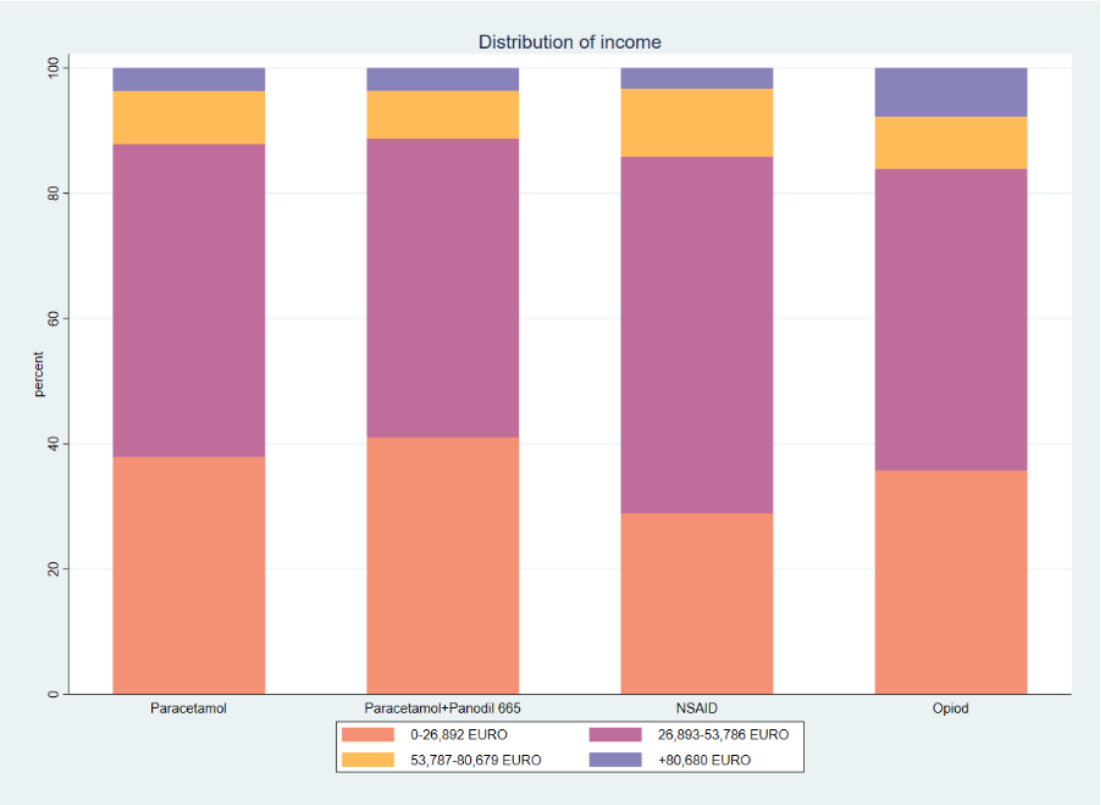
Source: Calculations based on registries provided by Statistics Denmark.

Appendix figure 1.2 Age distribution on each step of the analgesic ladder



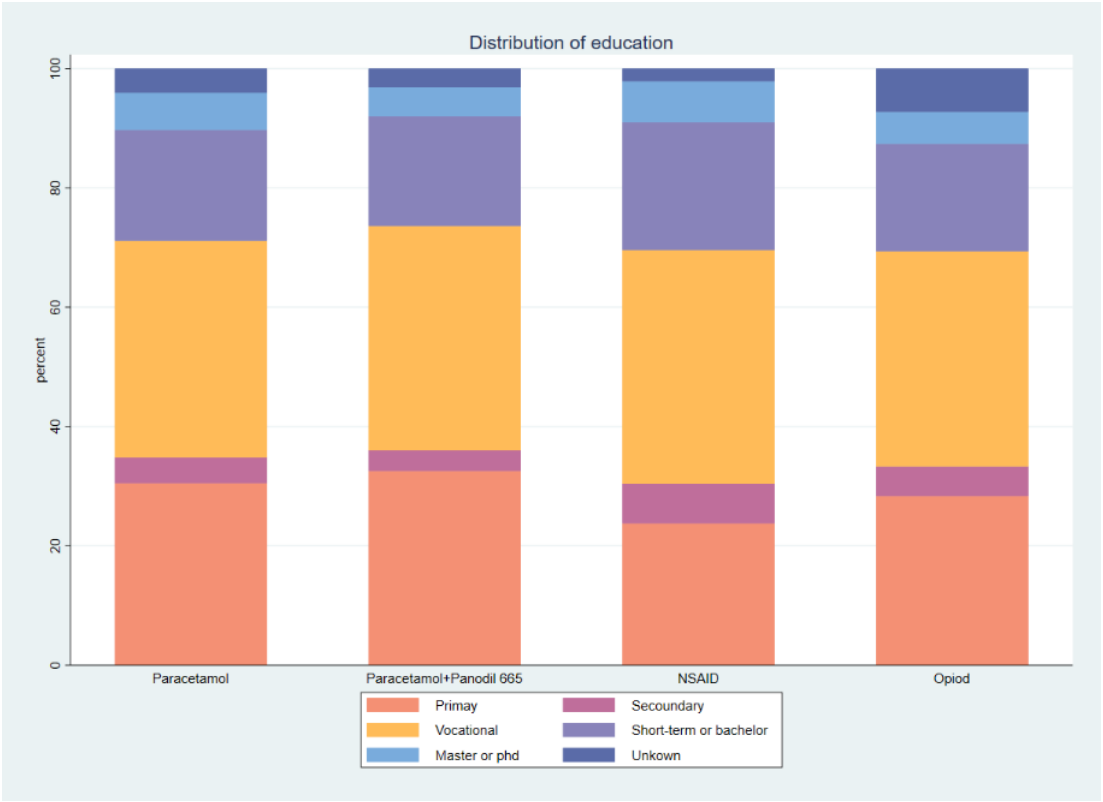
Source: Calculations based on registries provided by Statistics Denmark.

Appendix figure 1.3 Income distribution on each step of the analgesic ladder



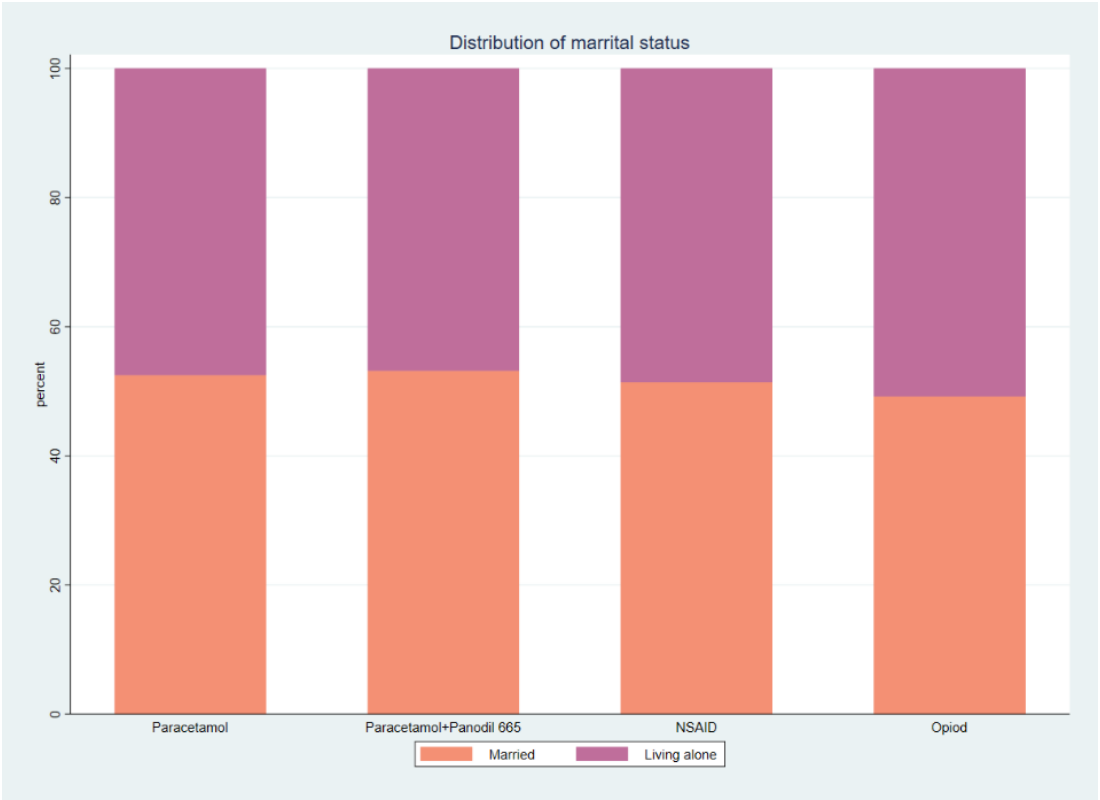
Source: Calculations based on registries provided by Statistics Denmark.

Appendix figure 1.4 Educational distribution in each step on the analgesic ladder



Source: Calculations based on registries provided by Statistics Denmark.

Appendix figure 1.5 Distribution of marital status on each step of the analgesic ladder



Source: Calculations based on registries provided by Statistics Denmark.

Appendix figure 1.6 Distribution of health management region and urbanisation index of municipality on each step of the analgesic ladder

Source: Calculations based on registries provided by Statistics Denmark.

Distribution of the Matched Sample

Appendix table 1.1 Distribution of matching variables

	Control		Intervention	
Gender				
Women	19995	72.8	19760	71.9
Men	7477	27.2	7712	28.1
Age group				
0-17	22	0.1	31	0.1
18-29	366	1.3	423	1.5
30-39	1019	3.7	1176	4.3
40-49	2764	10.1	2953	10.7
50-59	4409	16.0	4538	16.5
60-69	5723	20.8	5817	21.2
70 +	13169	47.9	12534	45.6
Education				
Primary school	219	0.80	237	0.9
Secondary School	13	0.1	17	0.1
Vocational education	204	0.7	241	0.9
short education or bachelor's degree	91	0.3	125	0.4
Master's degree or PhD	23	.08372 16	26	0.1
Unknown	26922	97.997 96	26826	97.6
Income bracket				
0-26892 euros	15456	56.260 92	15248	55.5
26893-53786 euros	10810	39.349 16	10900	39.7
53787-80679 euros	948	3.4507 86	1022	3.7
+80680 euros	258	0.9	302	1.1
Immigrant status				
Native Danish	25978	94.6	25785	93.9
Immigrant	1494	5.4	1687	6.1
Military	9	0.0	16	0.1
Manager	149	0.5	181	0.7
Work requiring bachelor's degree	1284	4.7	1374	5.0
Work requiring master's degree	594	2.2	644	2.3

	Control		Intervention	
Desk job	458	1.7	512	1.9
Service trade	1526	5.6	1676	6.1
Agriculture	47	.2	73	0.3
Construction jobs	317	1.2	398	1.4
Service operators	340	1.2	407	1.5
Other manual jobs	585	2.1	672	2.4
Unknown	22163	80.7	21519	78.3
Marital status				
Married	13449	49.0	13281	48.3
Living alone	14023	51.0	14191	51.7
Health management region				
The Capital Region of Denmark	6896	25.1	6965	25.4
Region Zealand	6633	24.1	6470	23.6
The Region of Southern Denmark	7285	26.5	7285	26.5
Central Denmark Region	4987	18.2	5054	18.41
The North Denmark Region	1671	6.1	1698	6.2
Urbanisation of municipality				
Urban	11449	41.7	11520	41.9
Suburb	5779	21.0	5697	20.7
Rural	8180	29.8	8079	29.4
Remote	2064	7.5	2176	7.9
Co-morbidity				
Charlson index = 0	22611	82.3	22402	81.5
Charlson index = 1	2864	10.4	2971	10.8
Charlson index = 2 or higher	1997	7.3	2099	7.6

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