

Ahammer, Alexander

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## A novel supply-side measure to combat abuse of addictive prescription drugs

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**A novel supply-side measure to combat abuse of  
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by

Alexander AHAMMER

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Johannes Kepler University of Linz  
Department of Economics  
Altenberger Strasse 69  
A-4040 Linz - Auhof, Austria  
[www.econ.jku.at](http://www.econ.jku.at)

[alexander.ahammer@jku.at](mailto:alexander.ahammer@jku.at)

# *A novel supply-side measure to combat abuse of addictive prescription drugs*

Alexander Ahammer<sup>†</sup>

*Department of Economics, Johannes Kepler University, Linz, Austria  
Christian Doppler Laboratory Aging, Health, and the Labor Market, Linz, Austria*

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## ABSTRACT

In the United States, 115 people die each day due to overdose, and a third of overdoses involve the concurrent use of opioids and a class of sedatives called *benzodiazepines*. Facing a similar problem in 2012, Austria responded by installing public health officers (PHOs) as third-party institutions overseeing prescriptions of the most potent and commonly abused benzodiazepine, *flunitrazepam*. Since December 15, 2012, every single flunitrazepam prescription must be authorized and countersigned by a PHO, prescriptions were restricted to a month's supply of the drug, and doses must be dispensed daily, under supervision, in a pharmacy. I identify a sample of opioids addicts in administrative social security data and study their response to this reform. Event studies suggest a persistent decline in flunitrazepam prescriptions but substitution to less potent benzodiazepines following the reform. To examine subsequent health, labor market, and drug abuse-related outcomes, I additionally exploit regional variation in PHO strictness affecting the likelihood that addicts opt to quit the drug due to the reform. I find that addicts who quit after encountering a strict PHO have better health and labor market outcomes, have fewer opioid overdoses, and are less likely to take antidepressants or weak opioids. I discuss how these findings translate to the US setting, and whether a similar policy can help curb its opioid epidemic.

**JEL Classification:** I18, I12, H12

**Keywords:** Opioid epidemic, addictive drugs, supply-control, prescription regulations.

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<sup>†</sup>*Contact information:* Alexander Ahammer, Department of Economics, Johannes Kepler University, Altenberger Straße 69, 4040 Linz, Austria; phone: +43(0)732/2468-7372, e-mail: [alexander.ahammer@jku.at](mailto:alexander.ahammer@jku.at). This paper is the fruit of many insightful discussions with addiction patients, physicians (especially Dr Nina Bödl and Dr Nikolas Gerstgrasser), and public health officers. I am immensely grateful for sharing their expertise and their overall support. I also thank René Böheim, Gordon Dahl, Martin Halla, David Jaeger, Dean Lillard, Jonathan Skinner, and seminar participants at the University of Cape Town and the 3<sup>rd</sup> Applied Economics Workshop at the Free University of Bozen-Bolzano for helpful comments. Christina Natsiou provided invaluable research assistance. Financial support from the Christian Doppler Laboratory Aging, Health, and the Labor Market is gratefully acknowledged. The usual disclaimer applies.

## I. INTRODUCTION

The United States is in the midst of a devastating drug epidemic. Recent numbers from the *Centers of Disease Control and Prevention* suggest that every day 115 people die owing to opioid overdose (CDC 2017b). Overdoses have thereby overtaken homicides, suicides, and vehicle accidents as the leading cause of death among Americans aged below 50 years (CDC 2017a). While the dangers of opioids are well-documented, relatively little is known about a second prescription medication that is fueling the opioid crisis. More than 30% of all opioid-related overdoses involve the concurrent use of *benzodiazepines*, a sedative widely used to treat anxiety and sleep disorders (Sun et al. 2017).<sup>1</sup> Benzodiazepines are popular among opioid addicts because of their own pleasant effects and their ability to potentiate the euphoric effects of opioids (Jones et al. 2012). Hernandez et al. (2018) find that approximately 30% of Medicare opioid users in 2013 and 2014 were also prescribed benzodiazepines, and almost 70% of concurrent users had more than 180 days of overlapping supplies of both medications.<sup>2</sup> However, the combination of the two drugs is extremely dangerous, since both suppress the respiratory system, which is often the cause of overdose fatality. Mortality risk is four to five times higher in patients who are prescribed benzodiazepines together with opioids, compared to those who use opioids alone (Hernandez et al. 2018, Park et al. 2015).<sup>3</sup>

These problems are not limited to the United States. In Austria, a majority of overdose deaths before 2012 involved a combination of opioids and *flunitrazepam*, the most potent benzodiazepine available. The government reacted by installing public health officers (PHOs) as third-party institutions to monitor patients and oversee prescriptions of the drug. Since December 15, 2012, every single flunitrazepam prescription must be preauthorized and countersigned by the district's PHO, prescriptions were restricted to a month's supply of the drug, and doses must be dispensed daily, under supervision, in a pharmacy. Since the reform, patients who opt to take flunitrazepam are not allowed to obtain multiple prescriptions from different physicians at a time and are prohibited from selling their medication and using other benzodiazepines or illicit drugs while being treated. PHOs have access to a nationwide prescription database and perform random urine tests and visual examinations to ensure that patients abide by these rules. If there is evidence of the contrary, it is at the PHO's discretion to refuse authorization or mandate that a lower dose or a different medication be prescribed. I evaluate the efficacy of this reform in a sample of Austrian opioid addicts.

Requiring PHOs to authorize prescriptions has raised the cost of taking flunitrazepam dramatically. Depending on their elasticity of demand, addicts may either continue to take flunitrazepam or

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<sup>1</sup>More generally, benzodiazepines are psychoactive drugs with hypnotic, sedative, and anxiolytic properties. They are clinically indicated for insomnia and anxiety, and are often prescribed off-label for a variety of other conditions as well (such as depression). Benzodiazepine prescriptions saw a sharp rise over recent years: in the United States, the number of adults to whom such drugs were dispensed rose by 67% from 8.1 million to 13.5 million. Overdose deaths involving benzodiazepines increased from 1,135 in 1999 to 8,791 in 2015, although three-quarters of these deaths also involved an opioid (Bachhuber et al. 2016, Lembke et al. 2018).

<sup>2</sup>The lifetime prevalence of benzodiazepine usage in heroin users is over 90% (Yamamoto et al. 2018).

<sup>3</sup>Aside from increased morbidity and mortality, a recent report from the *European Monitoring Centre for Drugs and Drug Addiction* concludes that the concurrent use of drugs from these two classes is associated with a higher risk of acquiring HIV infection, experiencing anxiety and depression, and having poorer treatment outcomes and poorer social functioning (EMCDDA 2018b). In August 2016, the US *Food and Drug Administration* (FDA) issued a black-box warning pointing to the dangers of coprescribing benzodiazepines and opioids (Lembke et al. 2018).

quit the drug, switch to a less potent (and therefore less addictive and harmful prescription drug), or turn to the black market to substitute flunitrazepam with other illicit substances.<sup>4</sup> I analyze whether there is a positive net effect on the average Austrian opioid addict given this set of possible responses. I identify opioid addicts based on a specific set of prescription medications and diagnoses in matched administrative social security and health insurance data.<sup>5</sup> Event study evidence suggests that addicts were significantly less likely to be prescribed flunitrazepam due to the reform and that they began substituting flunitrazepam with less potent benzodiazepines.

To study the net effects on addicts' labor market, health, and drug abuse-related outcomes, I exploit variation in PHO strictness affecting the likelihood that addicts quit flunitrazepam intake after the reform. This is necessary to circumvent selection problems, as the decision to quit or switch medications post-reform is not a random one. Using an instrumental variables (IV) framework, I find generally favorable effects of the reform. Addicts who quit flunitrazepam have better health and labor market outcomes, lower chances of experiencing an opioid overdose (while the likelihood of having a benzodiazepine overdose remains unaffected), and are less likely to be prescribed antidepressants and weak opioids (such as codeine cough syrups). Other outcomes related to illicit opioid or benzodiazepine abuse are unaffected, suggesting that addicts do not turn to the black market to obtain other illicit benzodiazepines or opioids due to the reform. This is corroborated by official statistics suggesting that the black market for flunitrazepam has practically disappeared after the reform. The black market for other benzodiazepines has remained relatively stable but small.

Performing different heterogeneity checks and sensitivity analyses, I find, for example, that younger addicts tend to benefit more than older ones from the reform; that addicts who quit flunitrazepam because they encounter a strict PHO seem to have favorable socioeconomic characteristics, and that both the fear of being scrutinized by the PHO and the decreased flunitrazepam supply itself are important mechanisms in explaining the positive reform effects. Furthermore, it seems that the effects of the reform would have been stronger if patients did not substitute flunitrazepam with less potent prescription benzodiazepines. Finally, I discuss how such a policy could be implemented in the United States to curb its opioid epidemic. I argue that Austria is, in many ways, representative for the United States. It ranks fifth in per capita opioid prescription among OECD member countries, leads the world in per capita morphine prescriptions, and has more fentanyl and hydromorphone prescriptions per capita than that in the States. Moreover, Austrian addicts share similar socioeconomic characteristics with their American counterparts.

I contribute to the growing literature on evaluations of policy measures and regulations in response to the opioid epidemic and illegal drugs in general. The majority of these policies focus on supply side measures, including prescription drug monitoring laws, day supply limits, lock-in

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<sup>4</sup>Note that the probability a patient is able to quit flunitrazepam crucially depends on the time he or she has been using the drug and therefore the level of addiction. As mentioned in section II.3, benzodiazepines are highly addictive, with withdrawal symptoms being even more severe than those of heroin. Substitution to other benzodiazepines is tricky as well, as other preparations are significantly less potent than flunitrazepam. Switching to black market drugs is theoretically possible. Opioid users may use flunitrazepam to enhance the effects of street heroin, which is often of very low quality. In the absence of the potentiator, users may react by increasing their heroin dose.

<sup>5</sup>Note that I have comprehensive data only for Upper Austria, one of the nine Austrian federal states. Upper Austria can be shown to be representative for Austria, its population size is comparable with Philadelphia, PA.

programs, pain clinic laws, and abuse-deterrent drug formulations. Evidence on the effectiveness of these interventions is mixed. Alpert et al. (2018), for example, find that users switched to cheaper substitute drugs, such as heroin, when an abuse-deterrent formulation of oxycodone (a potent opioid) was introduced. Evans et al. (2018) find that each death that could have been prevented due to the reformulation was replaced by one heroin death. Efforts to reduce methamphetamine supply were similarly ineffective, either because the effects were only temporary or because users found other ways to obtain the drug (Dobkin & Nicosia 2009, Dobkin et al. 2014). In contrast, Buchmueller & Carey (2018) show that compulsory prescription drug monitoring significantly reduces opioid misuse in Medicare patients. Enforcing supply barriers may also have positive effects by deterring potential future users, but related outcomes are hardly discussed in the literature.

Demand-side policies, such as naloxone access laws, needle exchange programs, expanding supervised injection sites, and medication-assisted addiction treatment have received less attention in the literature.<sup>6</sup> Effects of these interventions are often ambiguous. Expanding naloxone access, for example, may benefit users but also bears moral hazard risks because users potentially feel safe to consume larger amounts of drugs when an antidote is readily available. Doleac & Mukherjee (2018) document increases in opioid-related emergency room visits and find no effects on opioid-related mortality in states that introduced naloxone access laws. In contrast, Rees et al. (2017) find generally favorable effects of Good Samaritan laws, which decriminalize assisting others who have an overdose. Doleac & Mukherjee (2018) use more granular data and control for a larger number of opioid-related laws invoked simultaneously. Other policies, such as needle exchange programs or supervised injection sites, may indeed benefit users. However, design-based evidence on their impact is not yet available.

This paper is novel in several ways. Overdose figures in the United States continue to increase, suggesting that traditional measures to halt the opioid epidemic have failed. Considering the introduction of third-party authorities charged with overseeing prescriptions is unprecedented in the literature. The measure may be drastic and costly; nevertheless, it serves as an interesting benchmark for the regulation of highly-addictive prescription drugs in general. Moreover, most of the literature so far relies on state-level variation in the introduction of supply-side regulations, while I have access to individual-level information on opioid users over time. Relatedly, I am the first to identify addicts in linked administrative registers, which have a clear advantage over survey or aggregate population data. I have access to individual-level data on all drug prescriptions, drug-related diagnoses (such as hospitalizations following an overdose), and detailed health and labor market histories. Lastly, I am unaware of other papers in the economic literature that tackle the role of benzodiazepines in inciting the opioid epidemic.<sup>7</sup>

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<sup>6</sup>Naloxone is an opioid antagonist which blocks the effects of opioids, especially in overdose.

<sup>7</sup>Recently a number of papers have been published in the medical literature that call attention to the problem, for example Lembke et al. (2018) in the *New England Journal of Medicine* titled 'Our Other Prescription Drug Problem', Bachhuber et al. (2016) in the *American Journal of Public Health*, or Olfson et al. (2015) in *JAMA Psychiatry*.

## II. INSTITUTIONAL SETTING

Austria has a *Bismarckian* social security system that covers sickness, accidents, disability, pension, and unemployment. The system is a pay-as-you-go scheme with compulsory insurance contributions. Virtually every resident receives publicly-funded health care. Enrollment to the system is automatic and linked to employment, but insurance is also guaranteed to coinsured persons (spouses or children), pensioners, individuals with disabilities, and those receiving unemployment benefits. Estimates suggest that 99.9% of the population is covered by health insurance (Hofmarcher & Quentin 2013). The insured have access to a variety of services, including outpatient visits to the general practitioner (GP) and specialists, inpatient care, and prescription drugs. Most healthcare-related costs are covered by the public health insurance with no or only minor copayments. Patients may also visit non-contracted physicians who are not affiliated with a social security institution and can receive care in private hospitals. Payments for these services are only partially refunded. In this paper I focus on Upper Austria, which is one of the nine Austrian federal states and has around 1.5 m residents.

### II.1. How does Austria compare to the United States?

It is important to consider the features of the Austrian social security system discussed above when interpreting the results of this study. Despite the differences in health care access, Austria presents an interesting case for studying the behavior of opioid addicts outside the United States. Due to the recent shift of illicit opioid abuse from urban neighborhoods to more affluent suburban and rural areas with primarily white populations in the United States (Cicero et al. 2014), Austrian addicts now share similar characteristics with their American counterparts. According to the Austrian *Department of the Interior*, those charged with opioid-related offenses in 2015 were most often between 25–39 years old, male, unemployed, poorly educated, and Austrian citizens (and, therefore, primarily white).<sup>8</sup> This is remarkably similar to the population of US heroin users described by Cicero et al. (2014). Although the universal health care access in Austria signifies a marked difference to that in the United States, it has an advantage in that most opioid addicts in Austria appear in administrative data and can be followed over time and along many interesting outcome pathways.

— Figure 1 —

Moreover, in few countries more opioids are prescribed per capita than they are in Austria. Austria ranks fifth in overall per capita opioid prescriptions among OECD countries, surpassed only by the United States, Canada, Germany, and Denmark (see Figure 1). With regard to morphine, Austria leads the world in per capita prescriptions. Figure 2 plots medication-specific prescription data for the top 30 countries worldwide. In Austria, morphine consumption in 2015 was

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<sup>8</sup>Austrians committed 65.9% of drug-related offenses. Non-Austrians drug offenders were most likely—in descending order—to be from Nigeria, Germany, Serbia, Turkey, Algeria, Afghanistan, and Morocco. Source: *Suchtmittel Jahresbericht 2015* (URL: [https://bundeskriminalamt.at/bmi\\_documents/1869.pdf](https://bundeskriminalamt.at/bmi_documents/1869.pdf), accessed December 16, 2018).



213 mg per capita—almost double the rate in Canada, which had the second-highest consumption (18 mg/capita). The United States ranked fourth, with about 61 mg per capita. Oxycodone (Panel B) was, as expected, much more popular in the United States, with 194 mg per capita, while Austria ranked 26<sup>th</sup>, with just over 10 mg per capita. For fentanyl, the most potent of these four drugs, Austria ranked third worldwide (2.6 mg/capita), while the United States ranked twelfth (1.2 mg/capita). Hydromorphone is prescribed most often in Canada (52 mg/capita), followed by Austria (13 mg/capita), and the United States (7 mg/capita).

— Figure 2 —

## II.2. Opioid addiction treatment in Austria

Opioid dependence is a complex health condition that requires long-term treatment and medical care. As the first-line treatment, the *World Health Organization* recommends maintaining patients on opioid agonists such as methadone or buprenorphine (WHO 2009). Austria is one of the few countries worldwide where extended-release morphine is also used in opioid substitution. These medicines mimic the effects of illicit opioids, such as heroin or fentanyl, but are sufficiently long-acting to avoid cycles of intoxication and withdrawal when taken once daily. The primary objective of opioid substitution is harm reduction. Such programs have been shown to be effective in substantially reducing illicit opiate use, HIV risk behaviors, death from overdose, criminal activity, and financial and other stresses on drug users and their families (Lawrinson et al. 2008). Although long-term abstinence can be achieved and is sometimes desired, many patients are in maintenance therapy, receiving a stable dose over an extended period.

Since the early 20<sup>th</sup> century, methadone has been used in Austria to treat opioid addicts; although, at first, it was only prescribed as an *ultima ratio* for long-term addicts who had failed multiple withdrawal attempts. The current form of substitution therapy was established in 1998, when policy makers recognized it as being equally effective as abstinence treatment. Since then, the number of opioid users in substitution treatment has increased steadily. It is difficult to obtain estimates for the proportion of regular users in treatment; official estimates range between 50–70% at any given time (Weigl et al. 2017). The proportion of opioid users treated at least once at *some* point during their drug career is probably much higher.

The barriers for entering the substitution program are minimal; every patient who produces a positive urine test for opioids will, in principle, be admitted. For patients aged below 20 years or those who have taken opioids for less than two years, the prescribing GP is encouraged to obtain a second opinion from a psychiatrist specialized in addiction medicine. Methadone and buprenorphine are the first-choice drugs, whereas extended-release morphine is in principal only permitted if the patient has an intolerance to these two medications. However, patients often prefer morphine because its effects are most similar to those of illicit opioids such as heroin. The morphine preparations used currently in substitution therapy are also the only ones that can be dissolved and injected to increase their euphoric effects. Methadone is only dispensed as a fluid diluted with sugary syrup, which makes it impossible to inject. Buprenorphine is a partial opioid antagonist that does not elicit



euphoria and is therefore hardly abused by addicts.

Substitution treatment is primarily delivered by specifically trained GPs, but specialized outpatient services and hospital ambulances also offer it.<sup>9</sup> Patients are required to sign a contract with their GP at treatment commencement, pledging not to use illicit drugs for the duration of the treatment, nor to distribute or sell the medication to others. Changing GPs should generally be avoided. Similar to long-term pain treatment, opioid substitution requires specific narcotic prescription forms (in German ‘*Suchtgiftrezepte*,’ an example is shown in Figure A.1 in the web appendix) that last for one month.<sup>10</sup> Short-term prescriptions are only allowed in emergencies and for a maximum of three days. Irrespective of the duration, a narcotic prescription is valid only after the physician attaches a vignette containing a unique identification number. This running number is recorded in a nationwide database, which the PHO must access before authorizing the prescription. This ensures that prescriptions cannot be forged and that patients can only obtain one substitution prescription at a time.

District authorities have dedicated departments for the validation of narcotic prescriptions. After patients bring in the scripts, nurses first check whether the formal requirements are met and that the prescribing physician has the necessary qualifications. The prescriptions are then forwarded to the PHO (who is a medical doctor by training) for signature. Substitution patients are subjected to close scrutiny. PHOs require regular urine drug screenings to test the intake of the substitution medication and other illicit substances. If addicts fail tests, they may lose take-home rights (which they can earn after being in the program for some time), be put on a different medication, or be expelled from the program entirely. Additionally, addicts’ arms are regularly inspected for injection marks. Changes in dosage and medication also have to be approved by the PHO. As soon as the prescription is authorized, the patient can bring it to their pharmacy of choice, which will then dispense the medication, under supervision, on a daily basis. The responsible district authority is determined by the addict’s residential address; every district has only one PHO at a given time.

### II.3. Flunitrazepam

Flunitrazepam (marketed under the brand names *Rohypnol*<sup>©</sup> and *Somnubene*<sup>©</sup>) is a powerful benzodiazepine due to its fast-onset action (Simmons & Cupp 1998). Being approximately 10 times as potent as diazepam (*Valium*<sup>©</sup>), it is medically indicated for the treatment of severe insomnia and as a premedication before surgery. Flunitrazepam has not been approved by the FDA and is an illegal drug in the United States. However, it has been available illegally in the country since the early 1990s, especially in the southern states (Forrester 2006). Outside the United States, the

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<sup>9</sup>Before being allowed to treat patients, GPs who want to offer opioid substitution have to acquire an online diploma which covers topics in addiction medicine and narcotic drug law.

<sup>10</sup>If prescribed as pain analgesics, opioids are very similarly regulated. They require special narcotic prescription forms, attached with vignettes that contain a unique running number. Every prescription is thereby documented in an online monitoring system. Pain prescriptions are, however, subject to certain maximum amounts of the drug (e.g., 2 g morphine or 0.2 g oxycodone per patient). If the patient requires successive prescriptions for long-term treatment, PHO approval becomes a necessity, and each prescription has to be countersigned before it can be dispensed at the pharmacy. Weak opioids, such as codeine or tramadol, are not subject to specific provisions if they are prescribed only once. In case of multiple prescriptions, the same regulations apply as for substitution and long-term pain treatment.

drug is marketed in South America, Asia, and Europe. Figure 3 plots monthly benzodiazepine prescriptions between 2010 and 2015 in Upper Austria. Flunitrazepam accounted for roughly 11% of all benzodiazepine prescriptions in 2010. This figure was stable until December 2012, when the new prescription regulation led to a substantial disruption in flunitrazepam supply. By 2015, the proportion of total benzodiazepine prescriptions had decreased to 3.7%. Prescriptions of other benzodiazepines remain remarkably stable over time, despite a clear seasonal pattern (prescriptions are exceptionally high in December and January).

— Figure 3 —

In surveys, opioid users reveal a distinct preference for flunitrazepam over other benzodiazepines (Woods & Winger 1997). The drug not only has the ability to produce a relaxed feeling and intense euphoria when used alone, it is also a powerful potentiator of opioids and can alleviate opioid withdrawal (Simmons & Cupp 1998). Flunitrazepam is usually ingested orally, but is also chewed, dissolved under the tongue, crushed and snorted, or dissolved in a liquid and injected (sometimes together with an opioid) in order to increase its bioavailability. As with all other benzodiazepines, the main side effect of flunitrazepam is the development of physiological and psychological dependence. Patients often continue to use the medication past their original indication, and have trouble quitting the drug due to withdrawal symptoms (Soyka 2017). Doctor shopping, emergency visits, and lost prescriptions are commonly observed among dependent patients. Abrupt flunitrazepam withdrawal can cause uncontrollable and potentially fatal convulsions, symptoms are often described worse than those of withdrawing from heroin.<sup>11</sup> Prolonged use also leads to rapid development of tolerance, which requires dosage increases in order to reamplify the drug's effects. Flunitrazepam was also, by far, the most popular item on forged prescriptions in Austria, which is another indicator of its abuse potential and popularity among addicts (Weigl et al. 2011).

#### **II.4. Reform in flunitrazepam prescription regulations**

Between 2008 and 2012, physicians were allowed to prescribe two-month supplies of flunitrazepam without specific requirements; hence, prescriptions were not monitored or otherwise regulated. However, policy makers soon recognized the abuse potential of flunitrazepam. It became public that a majority of overdose deaths in recent years involved a combination of opioids and flunitrazepam.<sup>12</sup> This is extremely dangerous, even more so than combining opioids with any other benzodiazepine, because of flunitrazepam's high potency. There was also a black market for flunitrazepam. According to *Department of the Interior* reports, in Upper Austria 4,460 illegally sold or stolen pills were seized in 2011, and policed filed 229 charges for illegal possession or selling of flunitrazepam (see Figure A.2 in the web appendix).

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<sup>11</sup>For anecdotal evidence, see, for example, this blog post: <https://www.healthline.com/health/addiction-drug-problem-benzos> (accessed April 17, 2019), titled "My Addiction to Benzos Was Harder to Overcome Than Heroin."

<sup>12</sup>See, for example, this newspaper article: <https://wien.orf.at/news/stories/2566231> (in German, accessed December 14, 2018).

In 2012, the government responded to these problems and substantially restricted outpatient flunitrazepam prescriptions. A decree was drafted by the *Department of Health*, in cooperation with addiction experts and health care officials. It was passed by the *National Council* in late October 2012 and became effective on December 15, 2012.<sup>13</sup> PHOs were introduced as a third-party control organ, and flunitrazepam became the only non-opioid medication that must be prescribed on a special narcotic prescription form. Thus, the same protocol as that discussed in section II.2 was applied also to flunitrazepam. This means that:

- (a) Starting on December 15, 2012, each prescription must be individually authorized and countersigned by the PHO. PHOs may alter or reject prescriptions and mandate that other medications be prescribed if deemed necessary.
- (b) Prescriptions are restricted to a month's supply of flunitrazepam, which is dispensed daily, under supervision, by a pharmacy.<sup>14</sup> All prescriptions are documented in a nationwide database every PHO has access to.
- (c) Patients pay monthly visits to the district authorities where PHOs monitor patients' health status and illicit drug abuse, which includes regular urine screenings and visual body examinations.

Importantly, the change in prescription regulations affects patients differently, depending on whether they were opioid substituted before the reform or not. Substituted patients already committed to a contract that forbids, among other matters, the concurrent use of illicit benzodiazepines and opiates, and abuse of these illicit substances has been monitored by the PHO since the start of their substitution treatment. For these patients, feature (c) has already been in effect. Thus, the reform mainly brought a secured monthly supply of flunitrazepam and a daily dispensing system where flunitrazepam is taken along with the substitution opioid at the patient's pharmacy. Additionally, PHOs gained the right to alter or reject flunitrazepam prescriptions, which was not formally possible before the reform. Thus, it is crucial to distinguish between the effects on substituted and non-substituted patients when evaluating the efficacy of the reform.

Although addicts have a clear incentive to quit or switch medications, only half of the patients in Upper Austria quit flunitrazepam (at least temporarily) after the reform. This may be because flunitrazepam is extremely addictive, and if taken in high doses over an extended period, other benzodiazepines cannot substitute it perfectly. In all likelihood, there is negative selection into continuing taking flunitrazepam post-reform, which also has to be taken into account when evaluating the policy. The black market for flunitrazepam has almost disappeared: the last available statistics are from 2014, when 82 pills were seized in Upper Austria. This is a 98% reduction compared to 2011. The black market for other benzodiazepines (e.g., oxazepam or nitrazepam) has always been

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<sup>13</sup>The relevant legal codes were published online in the Austrian Federal Law Gazette: *BGBI 375/1997* is the original decree that regulates psychotropic substances. The aspects related to prescription modalities and medical care in general have been changed twice: *BGBI 481/2008 §10(2)* introduced the two-month maximum prescriptions and *BGBI 358/2012 §10(3,4)* introduced the regulation of flunitrazepam, which is the central theme of this paper.

<sup>14</sup>As for opioids, however, weekly take-home is possible for employed patients who are at least three months in the program and have passed multiple urine tests.

small. In Upper Austria, 262 non-flunitrazepam pills were seized in 2011 and 267 pills were seized in 2014.

### III. DATA

I combine data from multiple administrative registers. My main source is the *Upper Austrian Health Insurance Fund* (UAHIF) database, which is linked to social security records from the *Austrian Social Security Database* (ASSD). The UAHIF is the main statutory health insurance provider in Upper Austria. It covers around one million members who represent 75% of the Upper Austrian population. Except for workers in the railway and mining industries, all employed individuals in Upper Austria are insured with the UAHIF.<sup>15</sup> Retirees continue to be insured with the UAHIF if they were regular employees or were long-term unemployed prior to their retirement.<sup>16</sup> Unemployed individuals are generally insured with the UAHIF as well, irrespective of their former employment.

The UAHIF database comprises individual-level information on health care service utilization in both the inpatient and outpatient sector for its members. I use these data to identify opioid addicts, to extract benzodiazepine prescriptions, and to compute health-related outcome variables. Additionally, I draw information on employment histories and certain demographics from the ASSD, which is a longitudinal matched employer–employee dataset covering all Austrian workers since the 1970s (Zweimüller et al. 2009). Although the UAHIF provides data starting from 1998, I focus on the window 2010–2015, which is symmetric with respect to the reform in December 2012. All empirical analyses are based on a quarterly panel of opioid addicts (the process of identifying addicts is discussed in the following subsection III.1). The panel is unbalanced as addicts are only included if they were insured with the UAHIF during the quarter in question.

#### III.1. Identifying opioid addicts

The empirical analysis in this paper is based on the population of opioid addicts in Upper Austria. I include every person insured with the UAHIF who was in opioid substitution treatment at least once between 1998 and 2015. As long as the person was insured with the UAHIF in a specific quarter (and still alive), she is included in the data and observed between 2010 and 2015, irrespective of whether she was in substitution treatment during that time, had completed treatment, or had not yet started it. Additionally, I include every person who had a medical condition related to opioid dependence (for example, an overdose) between 1998 and 2015 recorded in the UAHIF data. Again, the person is included for the entire span of 2010–2015, regardless of when the condition was recorded (as long as the person was insured with the UAHIF for the respective quarter). This assumes that whoever was in the substitution program or had an overdose has always been, and will always be, addicted to opioids.

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<sup>15</sup>The remaining 25% are comprised of self-employed individuals, farmers, and civil servants. Those occupational groups are insured with other institutions.

<sup>16</sup>Since drug addiction is considered a chronic illness *de jure*, many addicts in Upper Austria are in disability (or invalidity) retirement. The average age of disability retirees in my sample is 46 years and there are addicts as young as 19 years who are already retired.

This assumption is based on the medical view that opioid addiction is a lifelong chronic illness. Opioid relapse rates are extremely high; it is not uncommon to measure rates of 90% or higher if patients are followed-up long enough (e.g., Smyth et al. 2010). Neurologists have shown that opioid abuse dysregulates brain regions responsible for mediating reward and stress, which is a major reason why addicts chronically relapse (Koob 2008). Even those who use opioids only occasionally at first will often develop a physiological and psychological addiction. In their seminal book on the neurobiological mechanisms behind addiction, Koob, Arends & Le Moal (2014) note that

*The natural history of opioid addiction reflects a disorder that is remarkably stable over time. Although repeated cycles of remission and resumption of use occur, these patterns extend over long periods of time. Longitudinal studies have shown that heroin addiction, at least for some individuals, is a lifelong condition.* (p.145)

This repeated cycle of remission and relapse is another reason why I include patients even *before* they were substituted or diagnosed with an opioid-related disease. Substitution normally supersedes regular opioid abuse; therefore, the entry into the program merely signifies the switch from illicit opioids to the substitute drug. The same argument can be made for opioid-related conditions, which are likely to be a result of prior opioid abuse. In any case, including individuals who are not currently abusing opioids should lead to a downward bias in the estimated reform efficacy, because they are less likely to be affected by the change in flunitrazepam regulations. Below I also show that results are practically unchanged when addicts only enter the sample upon their first substitution treatment or diagnosis.

Substitution treatment can be identified in the UAHIF data because a specific group of long-acting opioids (ATC code N07BC, ‘*Drugs used in opioid dependence*’)—including methadone, buprenorphine, and also (in Austria) certain extended-release morphine preparations—are only approved for substitution purposes.<sup>17</sup> Drugs in this class are specifically designed for opioid substitution (also indicated by their names, e.g., *Substitol*, *Suboxone*, or *Compensan*), they come only in dosages that would be far too high for most regular pain patients. As discussed in section II.2, these drugs require specific narcotic prescription forms which must be countersigned by the regional PHO before a pharmacy can dispense them. Table A.1 (web appendix) summarizes the number of identified substitution patients per year. Official statistics before 2011 are unreliable, but a comparison with figures from later years indicates that, in this study, I observe at least 94% of all substituted patients in Upper Austria. This is reasonable, as most addicts will either be in regular employment or unemployed, and both groups are covered by the UAHIF. Since the current form of substitution treatment was initiated in 1998, I observe the complete treatment history of most patients in the data.

In addition to substitution patients, I include every patient who was diagnosed with an addiction-related disorder between 1998 and 2015. I consider the ICD-10 categories F11 (*opioid-related disorders*), T40.0–T40.4 (*poisoning by opium, heroin, methadone, and other opioids*), and R78.1

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<sup>17</sup>ATC is an abbreviation for the *Anatomical Therapeutic Chemical Classification System*, a system of codes developed by the WHO for the classification of medical drugs. Note that there are also methadone, buprenorphine, and morphine preparations classified as N02A, the usual pain medication category.

(*finding of opiate drug in blood*). These amount to 9,780; 360, and 20 cases, respectively. Note that the UAHIF records diagnoses only for inpatient stays and sick leaves, whereas ambulance visits are not included in the data. In total, I have a sample of 3,805 addicts who are observed on a quarterly basis between 2010 and 2015. Disregarding quarters during which addicts were not insured with the UAHIF or had already died, this amounts to a total of 80,769 observations. This sample may be negatively selected because I do not observe opioid users who have never been substituted, and have never been to a hospital or taken sick leave where an opioid-related diagnosis was recorded. This largely applies to users whose drug career started towards the end of the observation window or those who used opioids only occasionally — which is a rare phenomenon due to the immense addictive potential of opioids (Koob 2008). Most regular users, in contrast, are included in the data. As argued in section II.2, I already observe up to 70% of regular users currently in substitution treatment at any point in time. The proportion of users who had been treated at least once in an 18-year time span, or had some kind of opioid-related diagnosis, is probably much higher. For the sake of simplicity, I refer to individuals in the panel as *addicts* henceforth.

— Table 1 —

Summary statistics for the addict sample are provided in Table 1, column (1). Females account for 29% of the sample, 82% have Austrian citizenship. The average age is 35 years. Approximately half the addicts live in a city, and a majority have no university degree. In a given quarter, two-thirds are in opioid substitution. Columns (2) and (3) provide statistics for the pre- and post-reform periods, respectively. Means remain largely similar, although addicts observed post-reform are naturally older and slightly more likely to live in a city. The proportion of addicts substituted in a quarter increases by 3 percentage points (pps) between the two periods. Panel B provides different indicators of benzodiazepine usage. Approximately 58% of addicts were prescribed a benzodiazepine at some point; 22% had at least one flunitrazepam prescription; and every second addict had a clonazepam, diazepam, nitrazepam, or oxazepam prescription. Out of those patients who are prescribed a benzodiazepine in a given quarter, 17% are prescribed flunitrazepam, whereas 81% are prescribed any of the other short-acting benzodiazepines. These figures change dramatically between the two periods; the share of flunitrazepam decreases by 14 pps, and that of other benzodiazepines increases by 11 pps. Similarly, the likelihood that an addict is prescribed flunitrazepam in any given quarter decreases from 5% to 2%, while the likelihood another benzodiazepine is prescribed increases from 14% to 18%. The number of observations also indicate sample attrition. Approximately 4% of the sample is lost, either because they had died or were not insured with the UAHIF in some quarter.

### III.2. Key variables

My main variable of interest is flunitrazepam usage. I construct a binary variable equal to unity if at least one flunitrazepam prescription had been issued to the addict in a given quarter, and zero otherwise. This measures the extensive margin of flunitrazepam use. I also have information on the



number of packages and the total amount, in mg, prescribed per quarter. Since these two measures yield similar conclusions, for the sake of brevity, I report only the results based on the dichotomous measure. Figure 4 plots the percentage of addicts prescribed flunitrazepam and other short-acting benzodiazepines by opioid substitution status in each quarter. Substituted patients are generally more likely to be prescribed benzodiazepines. By the end of 2011, almost 10% of substituted patients concurrently use flunitrazepam; after the reform, this figure drops to around 3%. Patients not substituted in a given quarter are already less likely to be prescribed flunitrazepam before the reform; post-reform, the figure drops to under 2%. Prescriptions of other benzodiazepines increase slightly over time, both in substituted and non-substituted patients.

— Figure 4 —

Moreover, I consider a battery of health, labor market, and addiction-related outcomes. To measure health status, I extract information on the probability that the addict dies within one year of the examined quarter,<sup>18</sup> quarterly physician visits (adding up both GP and specialist visits), outpatient expenses (all expenses a physician bills to the insurance provider), medication expenses (the total cost of prescription drugs; over-the-counter drugs are not observed), and inpatient hospital days. Continuous health measures, such as outpatient or prescription drug expenses, are highly skewed due to the inclusion of quarters with zero expenses. As it has recently been popularized in the economics literature, I use the inverse hyperbolic sine function (asinh) to transform these variables.<sup>19</sup> Unlike the natural logarithm this function is well-defined at 0 and it parallels the natural logarithm for values of or greater than 2. Under this specification, regression coefficients can be interpreted as approximate log point effects.

As labor market outcomes, I consider binary variables indicating whether the addict is employed, unemployed, and on disability pension in a given quarter. The latter is particularly interesting because it marks an addict’s exit from the labor market, which often happens through disability pension in Austria. Opioid addiction is considered a chronic illness, which provides the legal basis for allowing addicts to retire even at a very young age (see footnote 16). Since labor market status may change during a quarter, I pick the one with the longest spell duration in case multiple spells are present within a quarter. Descriptive statistics can be found in Table 1, Panel C1. Roughly the same percentage of addicts are either employed or unemployed, while 12% are in disability retirement.

I also consider certain diagnoses and medications which are proxies for illicit benzodiazepine and opioid abuse, and indicators of addiction-related problems. These measures should reveal whether the reform drives addicts to the black market or to use illicit opioids. Most importantly, I consider opioid overdoses (ICD-10 codes T40.0–T40.3 and F11.0) and benzodiazepine overdoses

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<sup>18</sup>In the ASSD I can follow addicts’ survival until December 31, 2016. The one-year window I use to analyze mortality, albeit short, guarantees that I observe the entire panel for exactly one year after the quarter of observation.

<sup>19</sup>The inverse hyperbolic sine function is defined as  $\text{asinh}(y) = \ln(y + \sqrt{y^2 + 1})$ , with  $\text{asinh}(y) \approx \ln(y) + \ln(2)$  for  $y \geq 2$  and  $\text{asinh}(0) = 0$ . In Figure A.3 (web appendix) I plot the distributions of the four health outcomes transformed by the asinh function and the  $\ln(1 + y)$  function, where the constant 1 is added to the outcome before the logarithmic transformation, for comparison. The distributions look highly similar, but the asinh transformations are shifted to the right for  $y \geq 2$ .



(T41.4 and F13.0). Both are measured with error, because I only observe overdoses if they are followed by an inpatient stay or a period of sick leave, and as long as the doctor uses the correct diagnosis code. The likelihood an addict experiences an opioid overdose is 3% per quarter; for a benzodiazepine overdose it is 1% (see Table 1, Panel C2). If taken in excessive amounts, benzodiazepines can also greatly impair vision and cognitive functioning, and a large portion of the existing literature explores the relationship between benzodiazepine misuse and road traffic and motor vehicle accidents (e.g., Smink et al. 2010). I therefore consider external causes of injury (ICD-10 category S) as an additional outcome variable. This also serves as a proxy for black market benzodiazepine misuse, otherwise not captured in the data. The typical infections associated with opioid misuse are HIV and Hepatitis C (Zibbell et al. 2017). Both are relatively rare in Austria (EMCDDA 2018a), and I observe only new diagnoses made during the observation window (and as long as they are followed by an inpatient stay or a period of sick leave). Therefore, the incidences for both conditions are close to zero in Table 1. Finally, I consider prescriptions of antidepressants (addicts often have comorbid psychological problems), weak opioids such as codeine and tramadol (which can be prescribed without special narcotic prescription forms), and antivirals (which are used as a proxy for preexisting HIV and Hepatitis C infections). According to Table 1, approximately 20% of addicts are prescribed antidepressants, 14% are prescribed weak opioids, and 2% are prescribed antivirals in a given quarter. The latter would mean that 76 addicts are infected with HIV or Hepatitis C, which is in accordance with the official statistics (EMCDDA 2018a).

#### IV. EMPIRICAL STRATEGY

Conceptually, I think of addicts as agents who continuously face the decision of whether to take flunitrazepam. The new regulations introduced with the 2012 reform effectively increased the cost of taking flunitrazepam. Given a relatively inelastic demand and the absence of perfect substitutes for the drug, this is a supply shock that likely leads to fewer prescriptions overall. To test this conjecture, I use a flexible semi-parametric event study specification. Let  $i = 1, \dots, n$  denote an Upper Austrian addict and let  $\mathfrak{F}_{it}$  be a dummy variable equal to unity if  $i$  is prescribed flunitrazepam in quarter  $t = 1, \dots, T_i$ . The total number of observations in the panel is  $N = \sum_{i=1}^n T_i$ . Furthermore, I denote relative time by  $\tau_t = t - t_0$ , where  $t_0$  is the final pre-treatment quarter. The probability of flunitrazepam prescription is explained by the fixed effects model

$$\mathfrak{F}_{it} = \sum_{s=-8 | s \neq 0}^8 \beta_s \cdot \mathbf{1}\{\tau_t = s\} + \mathbf{x}'_{it} \boldsymbol{\Gamma} + \boldsymbol{\theta}_i + \varepsilon_{it}, \quad (1)$$

where  $\mathbf{1}\{\tau_t = s\}$  is a binary variable indicating quarter  $s = -8, \dots, -1, 1, \dots, 8$  relative to  $t_0$  with  $\mathbf{1}\{\tau_t = 0\}$  being left out as the reference quarter,  $\mathbf{x}_{it}$  is a vector of time-varying control variables (most notably patient age in 5-year bins),  $\boldsymbol{\theta}$  is an addict fixed effect capturing time-invariant addict heterogeneity, and  $\varepsilon_{it}$  is a random error term. Standard errors are robust and clustered at the addict level.

The main coefficients of interest are the series of post-reform estimates  $\{\hat{\beta}_s\}_{s \geq 1} = (\hat{\beta}_1, \dots, \hat{\beta}_8)$ ,

which represent within-addict changes in flunitrazepam prescriptions induced by the reform, conditional on  $\mathbf{x}_{it}$ . In order to identify the causal effect of the reform, I need to assume that prescription probabilities would have continued along the same trend absent the reform. This assumption fails in the presence of time-varying unobservables that are correlated with both the reform and the probability of flunitrazepam prescription. Those who were on the drug had a clear incentive against changing medications prior to the reform, as other benzodiazepines are only imperfect substitutes to flunitrazepam due to their lower potency. Physicians, on the other hand, may have anticipated the reform, already cracking down on flunitrazepam prescriptions before December 2012.

However, anticipatory behavior is largely ruled out by the timing of the reform. Although it was passed by the *National Council* on October 30, the earliest newspaper articles covering the reform were released on December 13, two days before it came into force.<sup>20</sup> This will be confirmed by the inspection of pre-trends  $\{\hat{\beta}_s\}_{s<0} = (\hat{\beta}_{-8}, \dots, \hat{\beta}_{-1})$  in equation (1), which should reveal anticipatory effects if present.

#### IV.1. Instrumental variables model

Apart from benzodiazepine usage itself, the 2012 reform may have also affected the health and labor market status of addicts. To analyze these outcomes, I require a different type of model, namely one in which the change in flunitrazepam usage due to the reform enters as a treatment variable. However, addicts who opt to continue taking flunitrazepam are likely negatively selected. That is, if the level physiological and psychological addiction is low, addicts will either quit or switch to a less potent benzodiazepine (for example, if the drug had been used only for a short period, in low doses, or not at all). Ignoring this selection would yield biased estimates of the effect of quitting flunitrazepam, given that the level of addiction is also correlated with the outcome variables. To take this source of endogeneity into account, I exploit variation in PHO strictness across districts to identify whether addicts choose to quit taking flunitrazepam. For every district  $d$ ,

$$\begin{aligned}\mathfrak{F}_{idt}^0 &= \alpha \cdot (strict_{dt} \times post_t) + \mathbf{x}'_{idt}\mathbf{\Lambda} + \theta_i + f(t) + v_{idt} \\ y_{idt} &= \varphi \cdot \mathfrak{F}_{idt}^0 + \mathbf{x}'_{idt}\mathbf{\Lambda} + \theta_i + f(t) + u_{idt},\end{aligned}\tag{2}$$

with  $\mathfrak{F}_{idt}^0 = 1 - \mathfrak{F}_{idt}$  being a binary variable indicating whether *no* flunitrazepam was taken in  $t$ . This variable is instrumented by the district-specific strictness measure  $strict_{dt}$ , as explained below, which is multiplied by a post-reform dummy variable,  $post_t = \mathbf{1}\{t \geq t_0\}$ , accounting for the fact that PHOs had no influence on flunitrazepam prescriptions before the reform. Additionally, the model allows for a set of time-varying control variables  $\mathbf{x}_{idt}$ , including age in 5-year bins, patient fixed effects  $\theta_i$ , and a non-parametric time trend  $f(t)$  (i.e., dummies for every quarter). Standard errors are two-way clustered at the district and addict level; the former is the main source of variation in the instrumental variable. Note that this framework is similar to a *fuzzy* or instrumented difference-in-difference design in the spirit of Abdulkadiroğlu et al. (2016) and de Chaisemartin & D'Haultfœuille

<sup>20</sup>This is also consistent with anecdotal evidence from the substitution doctors I interviewed. Most reported that they were rather surprised by the government's sudden action and did not know about the reform until a directive was issued by the *Department of Health* in early December.

(2018).<sup>21</sup>

PHO leniency is defined as the fraction of addicts substituted on extended-release morphine, relative to the total number of opioid substituted addicts in a quarter. Most patients have a strong preference for morphine, because it is the closest drug to illicit opioids such as heroin and it can produce a much more intense feeling of euphoria than does methadone or buprenorphine (Weigl & Busch 2013). However, the efficacy of morphine in addiction treatment has long been disputed among policy makers and addiction experts. It is the only preparation that can be dissolved and injected to increase its potency, which is frequently observed among users. There is a thriving black market for morphine, which grew almost to the size of the market for heroin.<sup>22</sup> Morphine is responsible for a majority of opioid overdose cases in Austria (Weigl & Busch 2013). Proponents, in contrast, argue that the availability of morphine in Austria is one of the main reasons for the comparably high rate of addicts in substitution treatment, because patients who strongly dislike ordinary substitutes are retained in treatment. Indeed, empirical evidence suggests that extended-release morphine can lead to better treatment retention, self-reported quality of life, fewer withdrawal symptoms, craving, and complementary drug consumption (Jegu et al. 2011).

This dissent is the reason for considerable local variation in morphine prescriptions (Weigl & Busch 2013), and much of this variation is due to differential preferences of incumbent PHOs. Official substitution guidelines stress that methadone and buprenorphine ought to be used as first-line drugs, while morphine is indicated only if the other two drugs are poorly tolerated. However, poor tolerance is not restricted to adverse symptoms, such as nausea or allergic reactions, and addicts may simply lament over persisting withdrawal symptoms to become eligible for morphine. PHOs can influence prescriptions in two ways; either directly, through their veto right, or indirectly, by restricting take-home and holiday rights. The latter is executed frequently, using the argument that take-home doses may be sold on the black market (as argued above, buprenorphine and methadone are hardly abused and their black market is virtually non-existent in Austria). Assuming that the proportion of patients *not* substituted with morphine is a good proxy for PHO strictness, the local average treatment effect (LATE)  $\hat{\phi}$  from (2) identifies the effect of quitting flunitrazepam in response to encountering a strict PHO following the reform. From an addict's perspective, the reform increases the cost of taking flunitrazepam. I expect addicts to continue taking the medication only if the cost of PHO scrutiny is lower than that of withdrawing or switching to another benzodiazepine.

Identification requires that PHO strictness influence health and labor market outcomes only through its effect on patient substitution. At first this appears viable, since PHOs can only influence substitution prescriptions and not the regular health care usage or even labor market status of the addict directly. However, I also have to assume that patients do not systematically move to districts where PHOs are more lenient, and this decision is related to their health and labor market status. Such a bias, however, is likely negligible. Addicts are a highly immobile part of the population,

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<sup>21</sup>See also the Hudson et al. (2017) on interpreting models which combine difference-in-difference and instrumental variable estimation.

<sup>22</sup>In 2015, for example, there were 1,666 criminal charges related to heroin and 1,213 related to illicitly dealt morphine. The latter is popular because information asymmetry reduces substantially when buying a prescription drug (which cannot be spiked with cutting agents).

because moving is expensive. Suggestive evidence for this conjecture is that 75% of the addicts in the present sample did not move districts between 2010 and 2015, and 90% did not move or only moved once. More importantly, 95% continue to live in the same district for at least two years after the last pre-reform quarter, and only 4% of the remaining 5% do not have an employer in the new district they move to.

— Figure 5 —

Another implicit assumption is that the potential growth paths of both flunitrazepam usage and the outcomes are orthogonal to the instrumental variable. This is tantamount to a parallel-trends assumption in the standard difference-in-differences model. In Figure 5, I therefore compare pre-reform trends in districts with strict PHOs to those with comparably lenient PHOs. I split the sample according to values above and below the median of  $strict_{dt}$ , with the former characterizing strict PHOs and vice versa. I find no significant differences in pre-reform trends for flunitrazepam usage (panel A) and all outcomes except for physician visits and outpatient expenses (panels C and D). Those two variables appear to be systematically higher in districts with stricter PHOs, although the difference is small in magnitude (less than 0.2 log points for physician visits and less than 0.4 for outpatient expenses). Nevertheless, estimates for these two outcomes should be taken with a grain of salt.

Another concern is that the variation in morphine prescriptions may simply reflect differences in patient characteristics across districts. High-risk patients may be more likely to receive morphine, and a higher density of morphine patients in a district could be the result of harsh local conditions, which may also be related to health and labor market outcomes of the individual (for example, a high unemployment rate). However, in this case, there should also be significant differences in the pre-trends in Figure 5. This is not what I observe. Most health and labor market indicators are statistically equivalent before the reform, which would not be the case if there were unobservable differences in underlying conditions between the districts.

One caveat of the model is that it remains agnostic about the role of substitution to other benzodiazepines in explaining the observed effects. The estimated LATE is a composite effect, capturing multiple mediating factors that occur between the stop of flunitrazepam usage and the observed change in outcomes in the causal chain. This also includes the consumption of other benzodiazepines, as long as addicts initiate this substitution as a result of the treatment. A suggestive test is to control for the usage of other benzodiazepines in (2) and observing the behavior of  $\hat{\varphi}$ . Depending on whether taking other benzodiazepines improves or hinders the treatment success, the LATE will be bigger or smaller in magnitude, respectively. Unfortunately, it is impossible to separately identify the effects of substitution without additional assumptions in the above framework. Substitution to the black market for benzodiazepines is highly unlikely; as discussed above, the black market has practically disappeared in 2012.

## V. RESULTS

The newly-introduced supply-side regulation has a substantial effect on flunitrazepam prescriptions among Upper Austrian opioid addicts. In Figure 6 I plot estimates for the probability that an addict takes flunitrazepam over time, conditional on flexible age controls and individual-level fixed effects. I consider a time span of two years before and after the reform, and the coefficient of the last pre-reform quarter is normalized to zero. Most importantly, prescriptions do not appear to follow a significant trend in the pre-reform period. For example, if prescriptions already have a downward trend before the reform, anticipatory effects may be present. Although the estimate for  $\hat{\beta}_{-4}$  is statistically significant at the 5% level, the whole series of pre-reform coefficients  $\{\hat{\beta}_{s \leq 0}\}$  is jointly insignificant with  $F = 1.31$  ( $p = 0.225$ ).

— Figure 6 —

Immediately after the reform, flunitrazepam prescriptions drop significantly. In the first post-reform quarter, the probability that an addict is prescribed flunitrazepam decreases by 1.54 pps ( $p < 0.001$ ). The decrease is fairly stable over time; two years after the reform, the probability still decreases by 2 pps ( $p < 0.001$ ). Before the reform, the unconditional probability that an addict was taking flunitrazepam is 5% (see Table 1) — this decreases by up to 41% due to the reform. In Figure 7, I perform an equivalent exercise on the conditional probability that an addict is prescribed another short-acting benzodiazepine (in particular, clonazepam, diazepam, nitrazepam, or oxazepam). Again, pre-reform trends are close to zero in magnitude and statistically insignificant, suggesting that the main identification assumption holds also for this outcome. It turns out that the reform leads addicts to be more likely to consume weaker benzodiazepines, as the probability of taking the latter increases by up to 4.45 pps ( $p < 0.001$ ) during the post-reform period. This may indicate a substitution effect, where addicts switch from a more to a less potent benzodiazepine. However, the effect appears to be slightly delayed. In the first two post-reform quarters, the increase in other benzodiazepines is small in magnitude and insignificant at the 5% level (a similar trend was observed in the unconditional means shown in Figure 4). Beginning with the second half-year, the effect increases substantially, but it flattens after year 3. This increase amounts to roughly 30% of the unconditional pre-reform probability of taking other benzodiazepines.

— Figure 7 —

### V.1. Health and labor market outcomes

Next, I consider whether changes in flunitrazepam usage induced by the 2012 reform affect the health and labor market status of addicts. *A priori* it is unclear whether these effects are positive or negative. The literature clearly suggests that the long-term use of flunitrazepam, especially in combination with opioids, is detrimental. In this case, quitting the drug is expected to have positive effects on health and labor market status. However, if patients are forced into physical withdrawal,

outcomes (especially in the short-term) may also become worse. I employ the IV model in equation (2), where flunitrazepam usage — or rather, the absence of flunitrazepam usage — is instrumented by PHO strictness, multiplied by a post-reform dummy. The resulting LATE identifies the effect of switching from taking flunitrazepam to *not* taking flunitrazepam because a strict PHO is encountered due the reform. Results are reported in Table 2, Panel A. The first stage  $F$ -test indicates sufficient power of the IV with  $F = 22.3$ .

— Table 2 —

The estimates suggest that the reform has generally favorable effects in terms of health and labor market status when flunitrazepam intake is discontinued. While there are no measurable effects on the probability of death within one year, I find that physician visits, outpatient and prescription drug expenditures, and days spent in a hospital decrease significantly. Physician visits decrease by approximately 0.5 log points ( $p < 0.001$ ) and medication expenses decrease by 1 log point ( $p < 0.001$ ). Both reductions amount to roughly one-fourth of the variables' sample means. Outpatient expenses decrease by about 0.7 log points ( $p < 0.001$ ) or 17% of the sample mean, hospital days decrease by 0.1 log points ( $p < 0.001$ ). This is the largest effect in the health dimension, equivalent to a 31% reduction with respect to mean hospital days. In terms of labor market status, I find that addicts are 0.6 pps ( $p < 0.001$ ) more likely to become employed and 0.4 pps ( $p < 0.1$ ) less likely to become unemployed due to the reform. Additionally, it appears that addicts are 0.4 pps ( $p < 0.001$ ) less likely to go into disability pension.

In Panels B1 and B2 of Table 2, I stratify the addict population according to age and gender. Effects seem to be driven by younger addicts, as coefficients for those under 30 years old are generally larger in magnitude than for those who are older. The decreased probability of going into disability pension and the decrease in hospital days, in contrast, are only significant for older addicts. For younger addicts, there appears to be a reduction in the probability of dying within one year, which is significant at the 10% level. However, in economic terms, this effect is rather small. Splitting by gender also provides some interesting insights. The effects on physician visits and outpatient expenses are similar for both genders. The reform benefits female addicts slightly more in terms of employment, while males experience a much larger reduction in the amount of drugs prescribed and the probability of going into disability pension. Effects on unemployment are almost identical in magnitude, but the coefficients become insignificant due to the sample stratification. Surprisingly, for women, I find a 2.7% increase in the probability of dying within one year due to the reform. This is in stark contrast to other effects estimated from this model, and it should not be overinterpreted before we know more about the nature of this effect.

## V.2. Drug abuse and addiction-related outcomes

In Table 3, I report effects of the 2012 reform on addiction-related outcomes and indicators of illicit opioid and benzodiazepine usage. The reform may have led addicts to purchase benzodiazepines on the black market or to substitute with illicit opioids. The results generally tell a different story.



Apart from better health and labor market outcomes, I also find evidence that opioid overdoses, in fact, decrease by 2.1 pps due to the reform, although this effect is only significant at the 10% level. This could either indicate that flunitrazepam and opioids are complements, or that the PHO scrutiny has a deterrent effect on opioid abuse. I find no effects on benzodiazepine overdoses, accidents, HIV, Hepatitis C diagnoses, or antiviral prescriptions. Illicit opioid use therefore does not seem to have increased; if anything, it has decreased. However, the reform decreased the probability of antidepressant prescription by 8.2 pps ( $p < 0.001$ ), which amounts to a 40% reduction with regard to the sample mean. This is consistent with the evidence cited above, evidencing an increased susceptibility to depression when benzodiazepines and opioids are used concurrently. Additionally, I find a 14 pp ( $p < 0.001$ ) decrease in the probability of prescription of weak opioids (in particular codeine cough medication, which is often abused), which corresponds to an almost 100% reduction in terms of the sample mean. Consuming these medications violates the treatment contract signed by addicts, and can provoke sanctions by the PHO if detected in a urine screening. Since addiction-related problems seem, if anything, to decrease, it appears that addicts do not simply switch to the black market for flunitrazepam or substitute with heroin in response to the reform.

— Table 3 —

In Panels B1 and B2 of Table 3, I again report differential LATEs for samples split according to age and gender. Similar to the health and labor market outcomes above, the effects of the reform are largely similar across the socioeconomic spectrum. However, it seems that the reduction in opioid overdoses seems to be driven by younger and female addicts, while the reduction in antidepressant prescriptions is only found in older and male addicts. The latter are also less likely to be diagnosed with Hepatitis C due to the reform. The zero effects on benzodiazepine overdoses, accidents, HIV, and antiviral medication prescriptions are similar across age and gender. For younger addicts, the effect on HIV diagnoses is significant at the 10% level, but it is practically zero. Although there is evidence for effect heterogeneity in certain outcomes, overall it seems that the reform benefits addicts across the demographic spectrum.

### V.3. Complier analysis

So far, the results clearly suggest that the 2012 reform had positive effects on a variety of outcomes and across different demographic groups. Importantly, these positive effects are driven by a specific part of the addict population, the so-called *compliers*. Those are addicts who decide to quit flunitrazepam because they encounter a strict PHO due to the reform, and they may be systematically different from the average addict. The reason is that compliers are likely people on the margin of taking flunitrazepam, for whom the cost of quitting are relatively low. To learn more about compliers, I employ an analysis in the spirit of Angrist & Fernández-Val (2013) that allows to identify their expected socioeconomic characteristics based on observable variables. Table 4 summarizes complier ratios for several socioeconomic observables that are available in the data. A complier ratio is the relative likelihood a complier has the given characteristic. It is the first stage in model (2),



estimated only for the subset of addicts with the given characteristic, relative to the overall first stage for the full sample.

— Table 4 —

The results indicate that compliers are 9.7% more likely to be Austria citizens, 16.1% less likely to be younger than 30 years of age, 20.2% more likely to have post-compulsory education, and 18.8% more likely to live in urban areas. For females the complier ratio is insignificantly different to 1. Additionally, I check the complier ratio with respect to the duration an addict has taken benzodiazepines in the data. The shorter the duration, the lower I expect the cost of quitting flunitrazepam to be. Indeed, I observe that addicts whose first benzodiazepine prescription was issued less than 2 years ago are 46.7% more likely to comply. Thus, addicts who are subject to favorable socio-economic conditions tend to be more likely to quit flunitrazepam intake when encountering a strict PHO. This is consistent with the idea that addicts will only opt to continue taking flunitrazepam if the cost of PHO scrutiny are lower than that of withdrawing the drug, under the premise that the conditions analyzed here decrease the cost of withdrawing.

#### **V.4. Pathways— PHO scrutiny vs. restricted drug supply**

To derive policy recommendations, it is important to understand the mechanisms governing the improvement in health and labor market outcomes apparent from the above results. It is especially important to differentiate two channels. Addicts may quit flunitrazepam due to the reform (1) because they want to avoid being scrutinized by the PHO (addicts may, for example, prefer to continue using illicit drugs, which is difficult when they have to undergo regular urine testing), or (2) because of the restricted but secure supply and the daily dispensing of the drug itself.<sup>23</sup> I can distinguish these two channels by estimating the model in equation (2) separately for opioid substituted and non-substituted addicts, because the former had been exposed to PHO scrutiny already before the reform. If estimates remain significant when considering only those substituted, it is reasonable to assume that the second channel, i.e., the restricted supply and the daily dispensing of the drug, is driving the results. If, in contrast, positive effects are found only for non-substituted addicts, PHO scrutiny is more likely to explain the results.

In Panel C of Table 2 and Table 3 I report LATE estimates based on two subsamples containing only substituted and only non-substituted addicts. Although addicts do not benefit equally across all outcomes, quitting flunitrazepam due to the reform has generally positive effects, regardless of substitution status. Nevertheless, I find that specific LATEs are only significant in either of the two subsamples, which suggests that there are indeed different mechanisms governing the positive reform effects. The reductions in mortality, hospital days, disability pension, opioid overdoses, and antidepressant prescriptions are only significant for substituted addicts (who had already been exposed to PHO scrutiny), but insignificant for non-substituted addicts (who were introduced to PHO

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<sup>23</sup>There is also a third channel: if addicts in the sample were forging flunitrazepam prescriptions, the reform can also have positive effects by introducing the compulsory monitoring system and making prescriptions forgery-proof. However, this will likely affect only few people in the sample.

scrutiny after the reform). This leaves only the restriction in drug supply and the daily dispensing as a driving factor. Another implication is that flunitrazepam and opioids are complements, because overdoses would likely increase if the two were substitutes. This makes sense, since one potentiates the other’s euphoric effects. By the same argument, it follows that the negative effects on unemployment, Hepatitis C diagnoses, and antiviral prescriptions can only be explained by the exposure to PHO scrutiny introduced by the reform, because these outcomes are only significant for non-substituted addicts. Coefficients on all other outcomes are similar in magnitude and significance, suggesting that the restriction in drug supply and exposure to PHO scrutiny are both important mechanisms.

## V.5. Sensitivity analyses

One caveat of the IV model is that it remains agnostic about the role of substitution to other benzodiazepines in explaining the positive effects of the reform. Figure 7 clearly shows that the reform induced a significant increase in the usage of other short-acting benzodiazepines after six months. This substitution may affect reform outcomes in different ways. It is possible that it would be even better for the addicts if they quit benzodiazepine intake completely, yet substituting may also offset negative effects that arise when addicts have to withdraw from flunitrazepam “cold turkey.” If substitution is caused by the cessation of flunitrazepam intake after the reform, it is captured by the IV estimates in model (2). However, the actual extent to which it mediates the estimated reform effects is unclear and cannot be isolated in my empirical framework.

A suggestive test is to control for the intake of other benzodiazepines in model (2). If the LATE estimate changes significantly, the mediating effect is likely to be present. Depending on whether substituting to weaker benzodiazepines is related to better or worse addict outcomes, the estimated LATE will either decrease or increase. Note that this is an imperfect test, as it is only informative about the presence of a mediator, but without additional assumptions I cannot estimate its actual effect on the outcome variables.

— Figure 8 —

Figure 8 plots the change in estimated LATEs when I augment model (2) with a variable indicating whether other short-acting benzodiazepines (specifically, clonazepam, diazepam, nitrazepam, and oxazepam) were prescribed to the addict. The dark gray bars indicate the estimated LATEs conditional on the mediator, along with their 95% confidence intervals. For comparison, the light gray bars represent the baseline LATEs from Table 2. The estimated LATEs are uniformly larger when the mediating variable is controlled for. This indicates that reform effects could be even stronger if patients avoided substituting flunitrazepam with other benzodiazepines. However, the absolute difference in coefficients is rather small (and their confidence intervals largely overlap), suggesting that the reform has favorable effects regardless of whether addicts substitute to other benzodiazepines. The same exercise can also be applied to the addiction-related outcomes from Table 3, which leads to similar conclusions (see Figure A.4 in the web appendix).

Another potential concern is that these estimates are based on a sample that includes addicts even before their first substitution spell or opioid-related diagnosis was recorded. Both these events likely follow a period where addicts were using opioids illicitly. The inclusion of this period allows me to capture addicts' behavior already before they are institutionalized. However, this is potentially problematic, as estimates may be biased towards zero if they include individuals who are not exposed to flunitrazepam. In Figure A.5, I therefore provide a robustness check where the main results from Figures 6 and 7 are repeated based on a sample where addicts only enter upon the start of their first substitution spell or when an opioid-related diagnosis is recorded for the first time. It turns out that the estimates for this restricted sample largely coincide with the baseline estimates. Thus, estimates are robust regardless of whether addicts are included prior to their first recorded treatment.

## VI. CONCLUSION AND IMPLICATIONS FOR THE UNITED STATES

A devastating drug epidemic has manifested in the United States and it may soon spread to Europe. Every day, 115 people die from opioid overdose, which has become the leading cause of death for Americans aged below 50 years. This signifies a substantial shock to the economy, as welfare of more than half a trillion dollars is lost. Relatively little is known about the role of benzodiazepines in fueling the opioid epidemic. These antianxiety and sleeping medications are popular among opioid users due to their own pleasant effects and their ability to potentiate the euphoric effects of opioids. Estimates suggest that 30% of all opioid overdoses involve the concurrent use of benzodiazepines. The reason is that both drugs suppress the respiratory system, which is often the cause of overdose fatality. Concurrent use of opioids and benzodiazepines is associated with a fivefold increase in the overdose risk compared to that related to the use of opioids alone.

In this paper, I use Austrian data to analyze benzodiazepine misuse in opioid addicts. In 2012, the Austrian government enacted new prescription regulations on flunitrazepam, one of the most potent benzodiazepines available. Since December 15, 2012, flunitrazepam must be prescribed on a special narcotic prescription form, which is also used for long-term opioid prescriptions. This mandated that every single prescription be authorized and countersigned by the regional PHO, and that the drug be dispensed daily at a pharmacy. Patients who opted to continue taking flunitrazepam are under close scrutiny. They are prohibited from taking illicit opioids or other benzodiazepines, which is regularly monitored through urine screenings and visual examinations.

I identify opioid addicts in administrative registers and study their behavior along different dimensions. In the first step, I show that the probability that an addict takes flunitrazepam decreases by up to 40% after the reform. With half a year delay, addicts become more likely to take other benzodiazepines due to the reform, which may point towards a substitution effect. In a second step, I use an IV framework exploiting variation in PHO strictness across districts to identify the probability that addicts will continue to take flunitrazepam after the reform. I find the effects of the reform to be generally favorable. Addicts who quit flunitrazepam intake because they encounter a strict PHO following the reform have better health and labor market outcomes, have fewer opioid overdoses,

and are less likely to take antidepressants and weak opioids (such as cough syrups). Other outcomes related to illicit opioid or benzodiazepine abuse are unaffected, suggesting that addicts do not switch to the black market for illicit benzodiazepines or opioids in response to the reform. Although effects differ slightly when the population is stratified by age and gender, positive effects of the reform are found across the entire socioeconomic spectrum.

This analysis shows that restricting access to a highly addictive drug can improve addict outcomes, even if they switch to substitute drugs with lower potency. For many outcomes there is also evidence that patients have equally better outcomes regardless of whether they were substituted before or after the reform, which indicates that restricting access to the drug is more likely to explain the positive effects than is monitoring illicit drug abuse. In the context of the US opioid epidemic, an obvious candidate for such a supply-side restriction would be oxycodone, which is nowadays the main gateway drug to opioid addiction. However, is the implementation of such a policy feasible in the United States?

To answer this question, some caveats of this study need to be discussed. Although I argue that Austria is representative for the United States in terms of addict characteristics and preferences for prescription opioids, there are still major differences between the two countries. It is unclear whether the reform would be as effective in terms of health care outcomes under a different institutional setting (particularly with regard to health care access). Moreover, the opioid epidemic in the United States is still much larger in scope than it is in Austria — this is evident, for example, in the (relatively) much lower number of opioid overdoses. It cannot be ruled out that this is due to unobservable differences in preferences or attitudes, though most would argue that the regulatory environment in Europe is decelerating the epidemic (e.g., EMCDDA 2017). Opioid addicts behave very similarly, regardless of the setting they are in, the neurological cycles of intoxication, withdrawal, and craving are universal (Koob et al. 2014).

Even if we believe that Austria is representative for the United States, there may still be institutional hurdles that impede the implementation of a similar policy in the States. As opposed to prescription drug monitoring programs (which have low marginal cost and require marginal effort only from the prescribing physician), it may not be feasible to have PHOs countersign every opioid prescription in every US district or municipality. This is due mainly to the sheer volume of prescriptions and number of addicts in certain regions. However, one may think of similar control mechanisms that are less costly. Instead of PHOs, for example, it may also be viable to establish a third-party institution where nurses, social workers, or civil servants, instead of medical doctors, are employed to monitor prescriptions. Instead of monthly prescriptions, addicts could get bi- or tri-monthly scripts to reduce the bureaucratic overhead. Urine screenings are already performed by prescribing physicians. Here, cost may even be saved if the process is centralized in regional institutions due to economies of scale. A careful cost-benefit analysis will ultimately be necessary to determine the viability of such measures.

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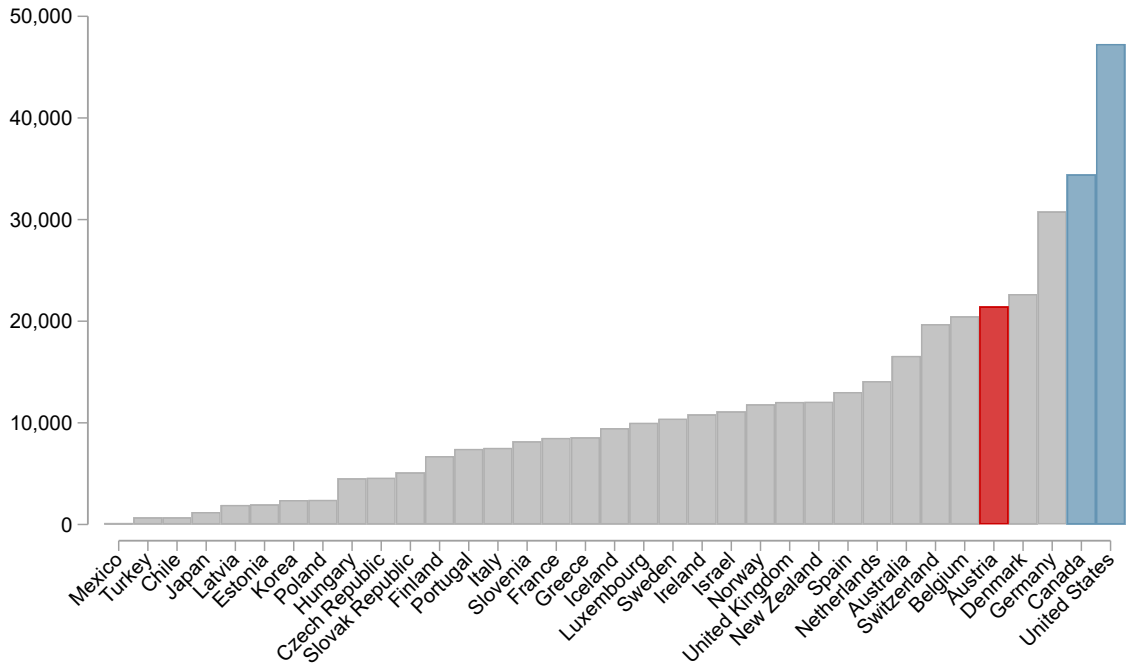
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## A. FIGURES AND TABLES

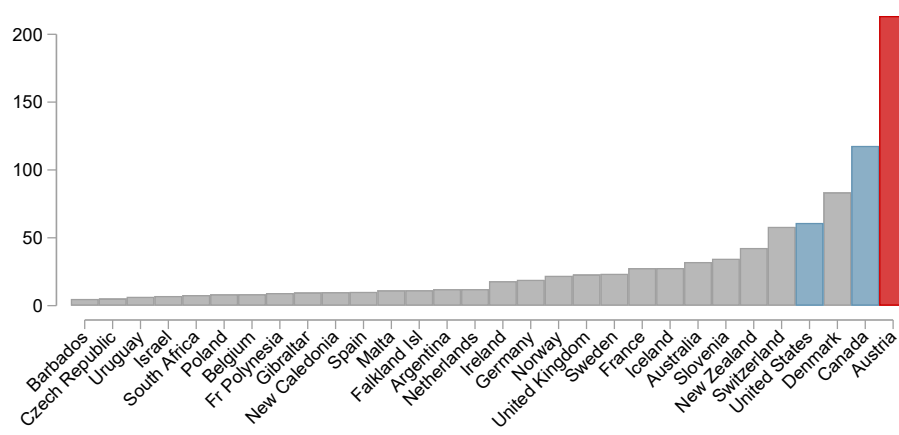
FIGURE 1 — Per million capita opioid prescriptions 2018 across OECD countries.



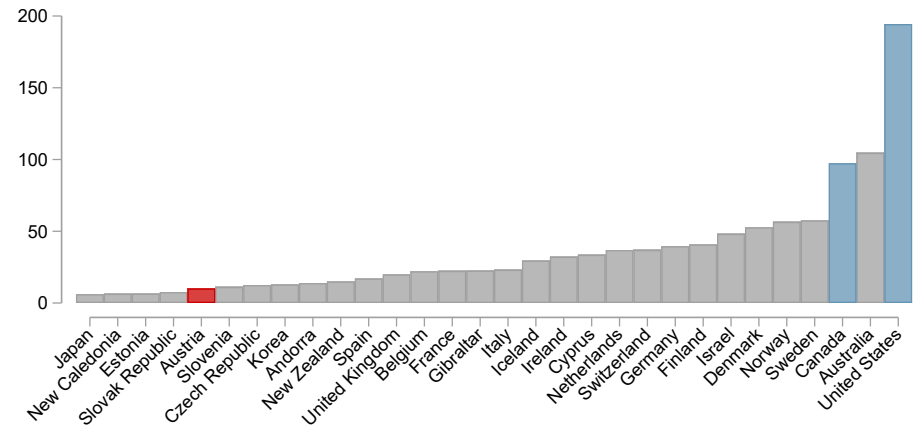
*Notes:* This graph shows per million capita opioid prescriptions in 2018 across OECD countries. The red bar ■ represents Austria and the blue bar ■ Canada and the United States. The data are drawn from the *OECD Economic Surveys: United States 2018*, OECD publishing (see also [www.oecd.org/els/health-systems/opioids.htm](http://www.oecd.org/els/health-systems/opioids.htm), last accessed November 29, 2018).

FIGURE 2 — Per capita prescriptions of popular opioid medications 2015, top 30 countries worldwide.

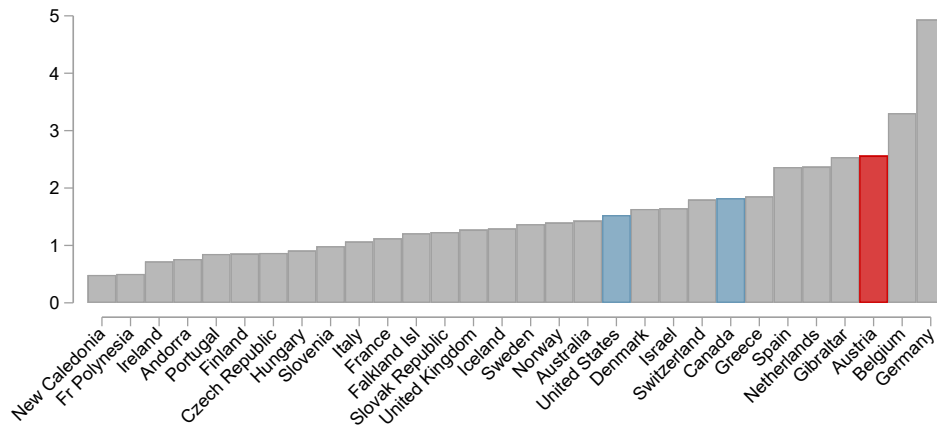
Panel A. **Morphine**



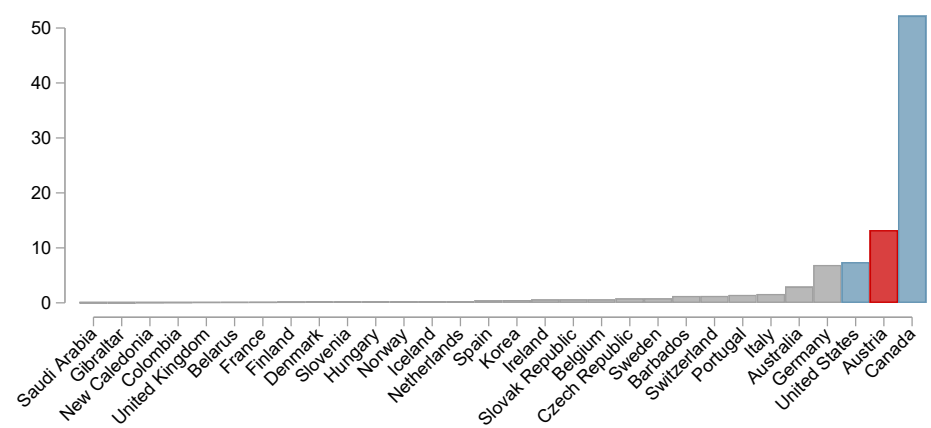
Panel B. **Oxycodone**



Panel C. **Fentanyl**

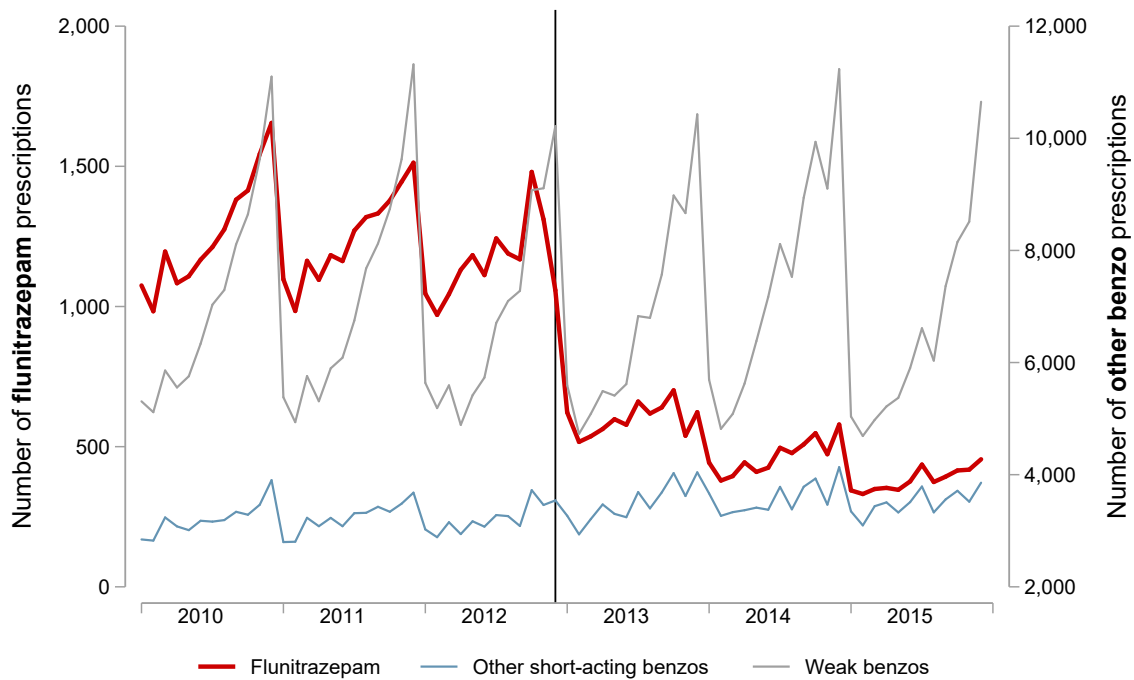


Panel D. **Hydromorphone**



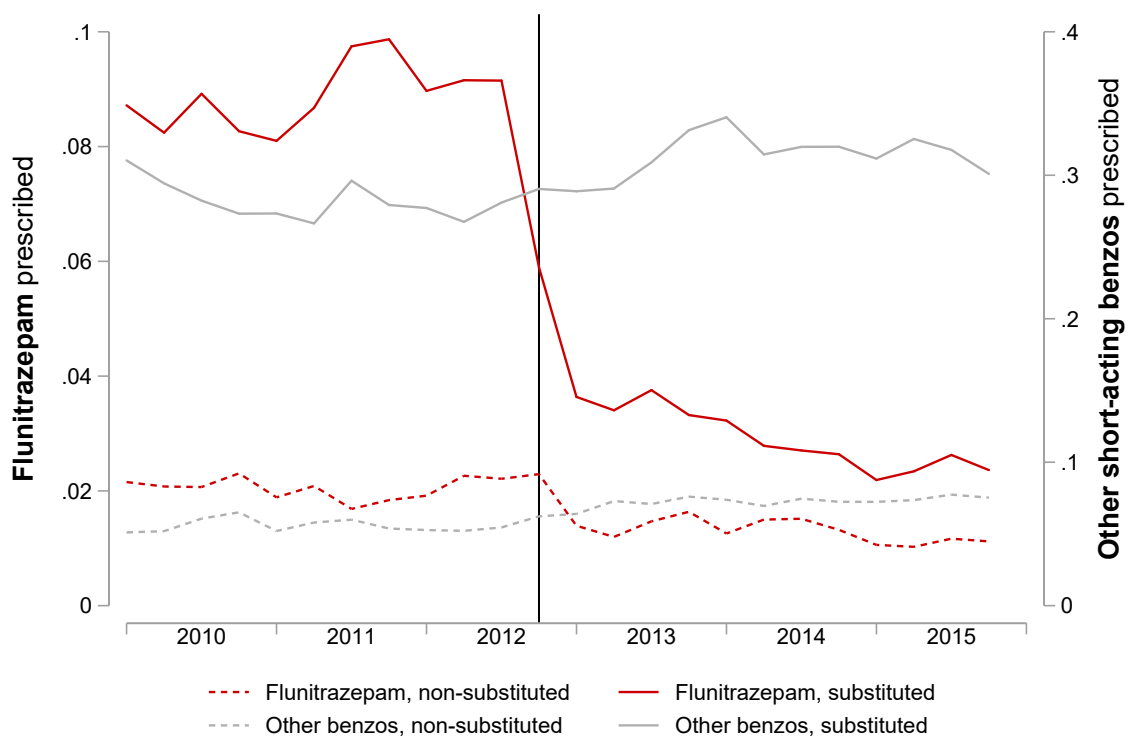
Notes: These graphs show the per capita consumption in mg of the respective medication in 2015 for the 30 countries worldwide with the highest consumption. The red bars represent Austria and the blue bars Canada and the United States. The data are compiled by the *Pain & Policy Studies Group* at the University of Wisconsin (URL: <http://www.painpolicy.wisc.edu/global>, accessed December 16, 2018). Originally, consumption data were taken from the *International Narcotics Control Board (INCB) 2015 Estimated World Requirements* report, while population data are from the *World Health Organization*.

FIGURE 3 — Monthly benzodiazepine prescriptions, 2010–2015.



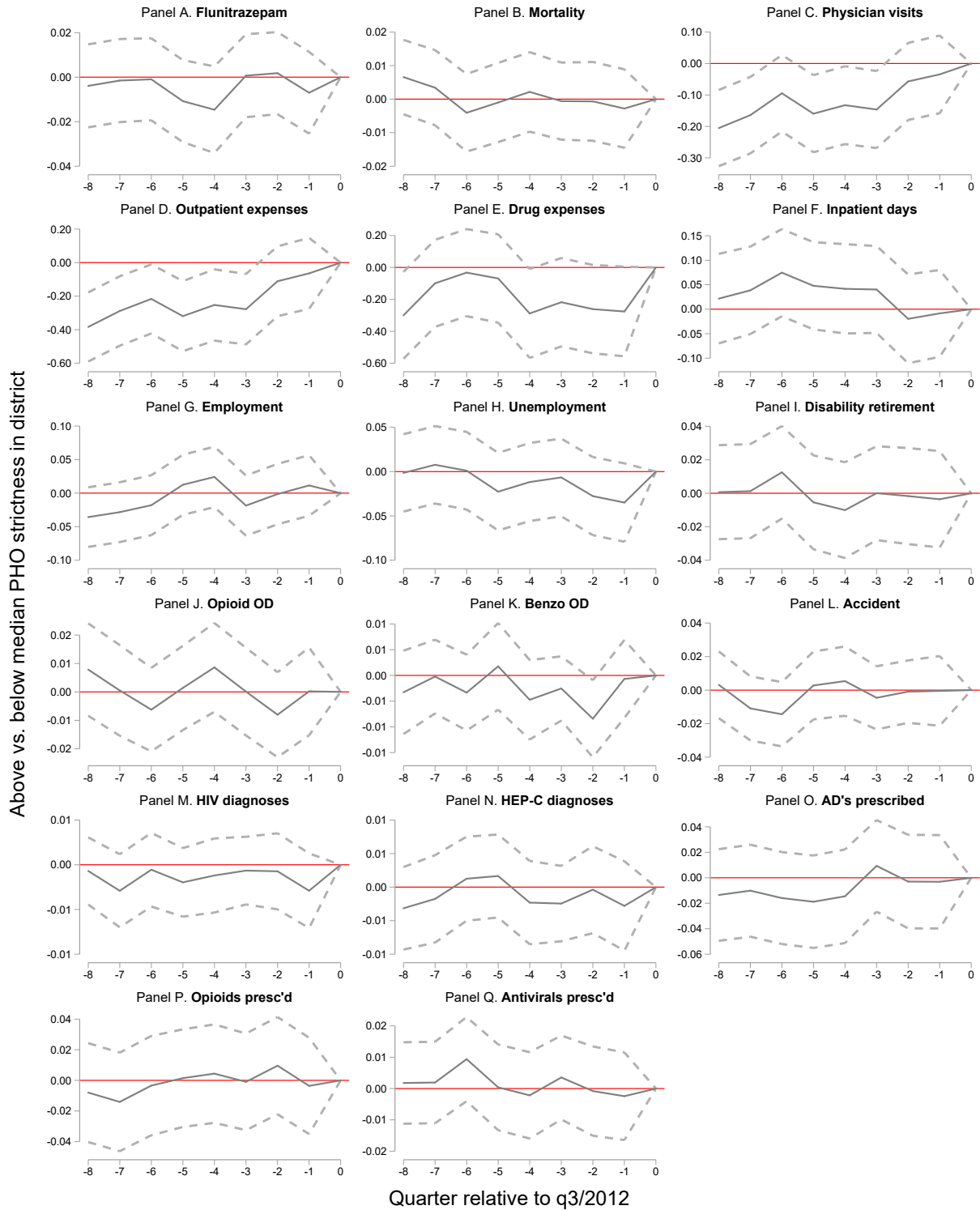
*Notes:* This graph depicts time series for different types of benzodiazepines prescribed to UAHIF insurees in Upper Austria between 2010–2015 (note that these data are based on all UAHIF insurees, not just the ones in the addict sample). Flunitrazepam prescriptions are on the left axis, while the other two categories (other short-acting and weak benzodiazepines) are on the right axis. Short-acting benzodiazepines are clonazepam, diazepam, nitrazepam, and oxazepam. Weak benzos are all other (typically long-acting) benzodiazepines, most commonly alprazolam (the main active agent in medications such as *Xanax*®) and triazolam (*Halcion*®). One prescription equals one package of the medication (for flunitrazepam, in 98% of cases this is a package of *Somnubene*® or *Rohypnol*® containing 10 pills à 1 mg). The black vertical line indicates the introduction of the regulations for flunitrazepam prescriptions on December 15, 2012.

FIGURE 4 — Share of benzodiazepine prescriptions by opioid substitution status, 2010–2015.



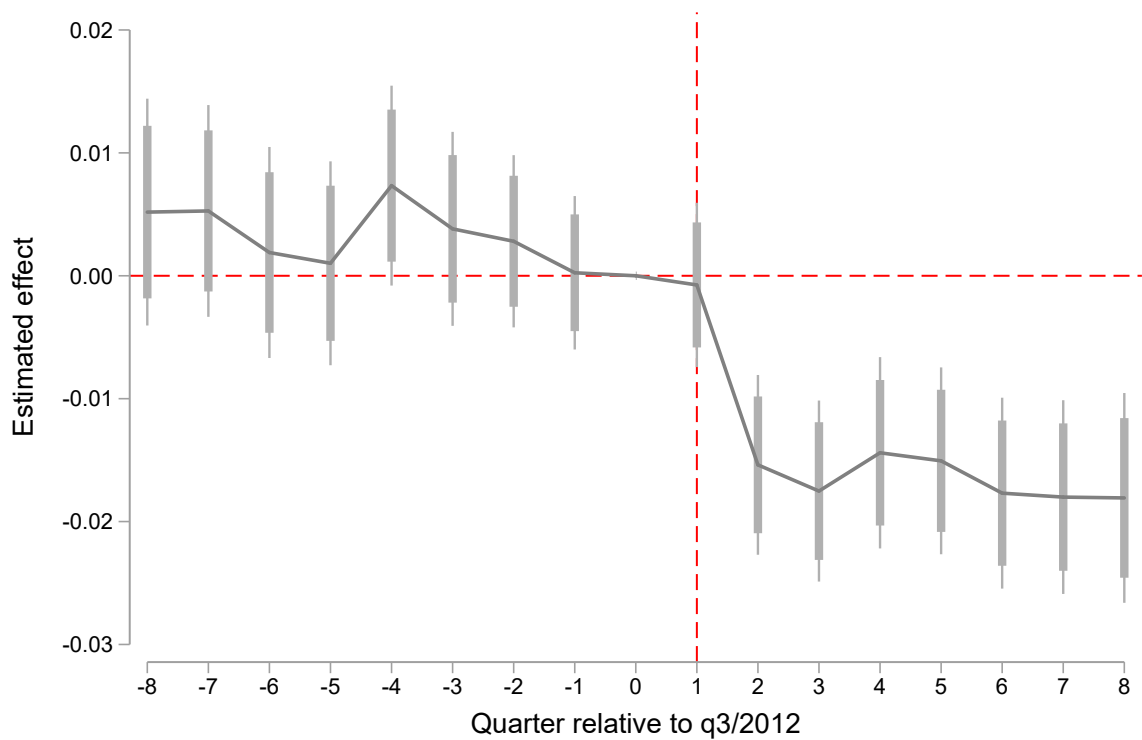
*Notes:* This graph plots the quarterly share of addicts who are prescribed flunitrazepam and other short-acting benzodiazepines (clonazepam, diazepam, nitrazepam, and oxazepam) by opioid substitution status in the current quarter. The flunitrazepam share is plotted on the left axis, the share of other benzodiazepines on the right axis. Computations are based on the UAHIF addict sample ( $N = 80,769$ ).

FIGURE 5 — Testing for differences in pre-reform trends between addicts living in districts with strict and lenient PHOs.



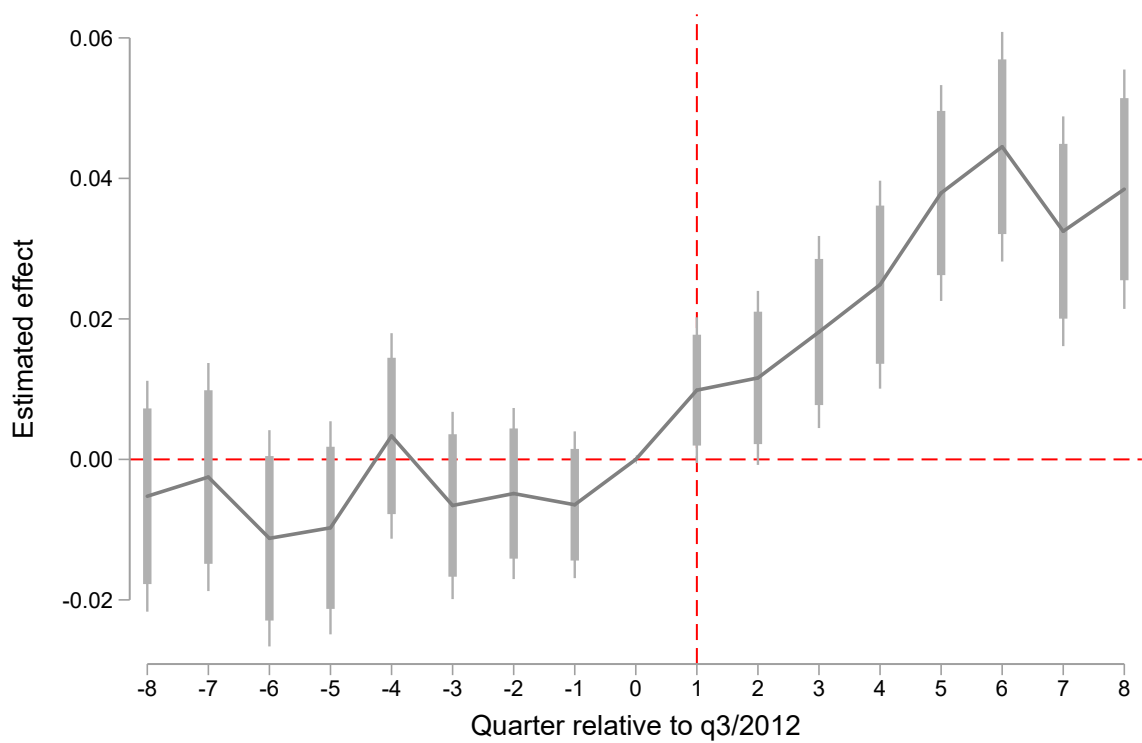
*Notes:* These event studies are based on a linear model where flunitrazepam usage (panel A) and the outcome variables (panels B–Q) are each regressed on a dummy variable indicating whether the PHO strictness measure in an addict’s district is above the median (or zero if it is below), interacted with a series of dummy variables indicating the eight pre-reform periods, and controlled for addict age in 5 year bins. The graph plots the coefficients of the interaction terms, along with their 95% confidence intervals. All coefficients are in reference to the last pre-reform quarter q3/2012, not the entire post-reform period. Computations are based on the UAHIF addict sample ( $N = 80,769$ ).

FIGURE 6 — Event study on the conditional probability of taking flunitrazepam around the 2012 reform.



*Notes:* This event study depicts the series of estimated coefficients  $\{\hat{\beta}_s\} = (\hat{\beta}_{-8}, \dots, \hat{\beta}_{-1}, \hat{\beta}_1, \dots, \hat{\beta}_8)$  from equation (1), which can be interpreted as the changes in the conditional probability an addict takes flunitrazepam eight quarters before and after the introduction of the new regulations in flunitrazepam prescriptions on December 15, 2012. The model also allows for addict fixed effects and flexible age controls. All coefficients are normalized to the last pre-reform quarter (q3/2012), vertical lines depict 95% and 99% confidence intervals based on addict-level clustered standard errors. Computations are based on the UAHIF addict sample ( $N = 80,769$ ).

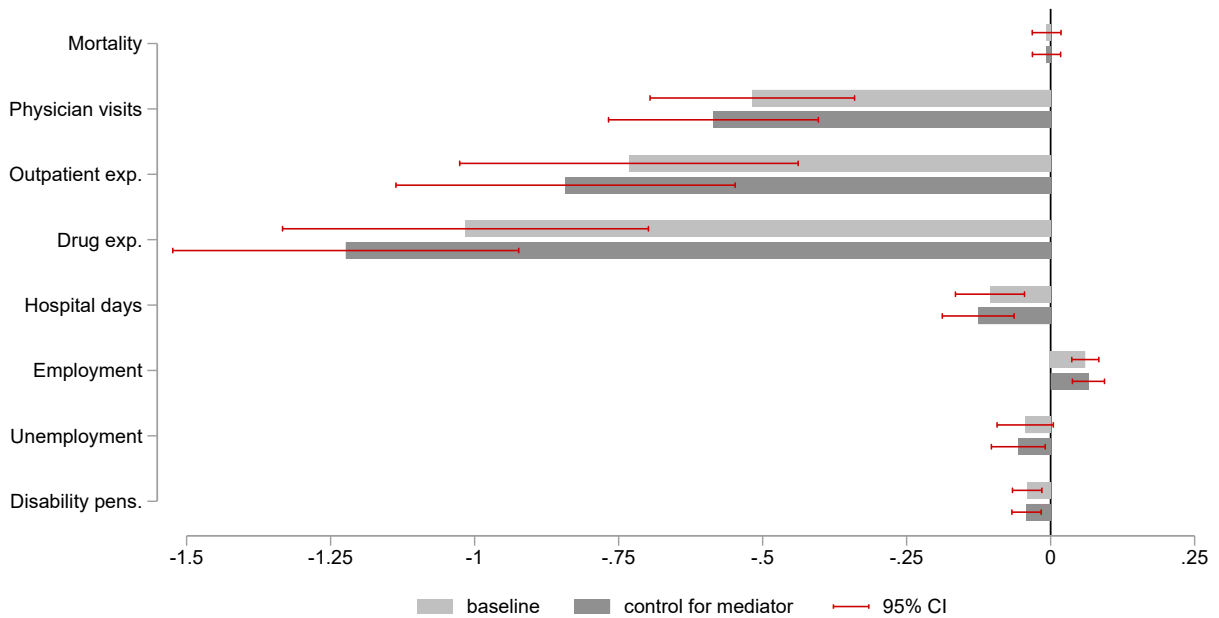
FIGURE 7 — Event study on the conditional probability of taking other short acting benzodiazepines around the 2012 reform.



*Notes:* This graph replicates the event study from Figure 6 based on the model in (1), but considering changes in other short-acting benzodiazepines (in particular, clonazepam, diazepam, nitrazepam, and oxazepam) instead of flunitrazepam. As before, the model also allows for addict fixed effects and flexible age controls. All coefficients are normalized to the last pre-reform quarter (q3/2012), vertical lines depict 95% and 99% confidence intervals based on addict-level clustered standard errors. Computations are based on the UAHIF addict sample ( $N = 80,769$ ).



FIGURE 8 — Change in estimated LATEs when the usage of other short-acting benzodiazepines is controlled for.



*Notes:* This graph summarizes the change in LATEs from model (2) when a mediator variable indicating whether other short-acting benzodiazepines (clonazepam, diazepam, nitrazepam, and oxazepam) were prescribed to the addict is controlled for. The LATEs conditional on the mediator variable are depicted as dark gray bars. For comparison, the baseline LATEs from Table 2, Panel A, are given as light gray bars. The graph also displays 95% confidence intervals. Figure A.4 in the web appendix summarizes the change in addiction-related outcomes from Table 3.

TABLE 1 — Descriptive statistics of the UAHIF addict sample.

	Full sample		Difference b/w pre- and post-reform				
			pre-period		post-period		<i>p</i> -value
	(1)		(2)		(3)		(4)
<i>Panel A. Addict characteristics</i>							
Female	0.29	(0.45)	0.29	(0.45)	0.29	(0.45)	0.571
Austrian citizenship	0.82	(0.38)	0.82	(0.38)	0.82	(0.39)	0.043
Age in years	34.85	(14.63)	33.67	(14.93)	36.11	(14.19)	0.000
Urban region	0.46	(0.50)	0.45	(0.50)	0.47	(0.50)	0.000
Education							
Compulsory education	0.12	(0.32)	0.12	(0.32)	0.12	(0.32)	0.436
Apprenticeship training	0.39	(0.49)	0.39	(0.49)	0.39	(0.49)	0.854
High school	0.45	(0.50)	0.45	(0.50)	0.45	(0.50)	0.798
University	0.04	(0.20)	0.04	(0.20)	0.04	(0.20)	0.864
Currently in opioid substitution	0.66	(0.47)	0.64	(0.48)	0.67	(0.47)	0.000
<i>Panel B. Medication status</i>							
Ever prescribed a benzodiazepine <sup>†</sup>	0.58	(0.49)					
Ever prescribed flunitrazepam <sup>†</sup>	0.22	(0.41)					
Ever prescribed other short-acting benzo <sup>†</sup>	0.50	(0.50)					
Share of flunitrazepam in prescr. benzos <sup>‡</sup>	0.17	(0.37)	0.24	(0.43)	0.10	(0.29)	0.000
Share of other short-acting benzos <sup>‡</sup>	0.81	(0.39)	0.75	(0.43)	0.86	(0.35)	0.000
Flunitrazepam prescribed in quarter	0.03	(0.18)	0.05	(0.21)	0.02	(0.14)	0.000
Other benzo prescribed in quarter	0.16	(0.37)	0.14	(0.35)	0.18	(0.39)	0.000
<i>Panel C1. Health and labor market outcomes</i>							
One year mortality	0.02	(0.12)	0.01	(0.12)	0.02	(0.12)	0.492
asinh(physician visits)	2.15	(1.33)	2.05	(1.34)	2.26	(1.31)	0.000
asinh(outpatient expenses)	4.20	(2.22)	4.03	(2.23)	4.37	(2.19)	0.000
asinh(medication expenses)	4.50	(3.03)	4.28	(3.07)	4.73	(2.97)	0.000
asinh(hospital days)	0.33	(0.96)	0.35	(0.98)	0.32	(0.95)	0.000
Employed	0.41	(0.49)	0.43	(0.50)	0.40	(0.49)	0.000
Unemployed	0.41	(0.49)	0.40	(0.49)	0.41	(0.49)	0.123
Disability retirement	0.12	(0.32)	0.12	(0.33)	0.12	(0.32)	0.276
<i>Panel C2. Addiction-related outcomes</i>							
Opioid overdoses	0.03	(0.16)	0.03	(0.17)	0.03	(0.16)	0.074
Benzodiazepine overdoses	0.01	(0.08)	0.01	(0.08)	0.01	(0.09)	0.219
Accidents and injuries diagnosed	0.04	(0.20)	0.04	(0.20)	0.04	(0.20)	0.022
HIV diagnosed	0.00	(0.03)	0.00	(0.04)	0.00	(0.03)	0.130
Hepatitis C diagnosed	0.00	(0.05)	0.00	(0.06)	0.00	(0.05)	0.126
Antidepressants prescribed	0.20	(0.40)	0.20	(0.40)	0.20	(0.40)	0.186
Weak opioids prescribed	0.14	(0.35)	0.15	(0.36)	0.13	(0.34)	0.000
Antivirals prescribed	0.02	(0.14)	0.02	(0.14)	0.02	(0.14)	0.305
Number of observations ( <i>N</i> )	80,769		41,464		39,305		
Number of addicts ( <i>n</i> )	3,805		3,698		3,529		

*Notes:* This table presents descriptive statistics of addict characteristics, medication indicators, and outcome variables for the sample of addicts in the UAHIF data. Section III.1 provides a detailed explanation on how the sample is composed. Column (1) reports statistics based on all available observations in the data, means are averaged over the period 2010–2015. Columns (2) and (3) report means separately for the pre- and post-reform period. The *p*-values in column (4) are for two-sample *t*-tests on the differences in means of columns (2) and (3).

<sup>†</sup> These variables are constant across time periods.

<sup>‡</sup> These shares are computed as the fraction of addicts taking the respective medication out of all addicts taking *any* benzodiazepine (also counting weak benzos such as alprazolam or triazolam). Thus, the shares may not necessarily sum to one.

TABLE 2 — Instrumental variable estimates on general health and labor market outcomes.

	Health outcomes					Labor market outcomes		
	One year mortality (1)	Physician visits <sup>†</sup> (2)	Outpatient expenses <sup>†</sup> (3)	Medication expenses <sup>†</sup> (4)	Hospital days <sup>†</sup> (5)	Employed (6)	Unemployed (7)	Disability pension (8)
<i>Panel A. Baseline LATE estimates</i>								
No flunitrazepam taken	-0.007 (0.013)	-0.518*** (0.091)	-0.732*** (0.150)	-1.016*** (0.162)	-0.105*** (0.031)	0.060*** (0.012)	-0.044* (0.025)	-0.041*** (0.013)
Mean of outcome	0.015	2.151	4.197	4.502	0.334	0.414	0.406	0.119
Std. dev. of outcome	0.123	1.329	2.219	3.029	0.962	0.493	0.491	0.324
<i>Panel B1. Heterogeneous effects by age</i>								
Age ≤ 30 ( <i>n</i> = 2,238)	-0.004* (0.002)	-0.655*** (0.248)	-0.870*** (0.248)	-1.385*** (0.403)	-0.312 (0.286)	0.088* (0.053)	-0.098*** (0.034)	-0.046 (0.035)
Age > 30 ( <i>n</i> = 2,360)	-0.008 (0.015)	-0.476*** (0.085)	-0.697*** (0.147)	-0.924*** (0.172)	-0.117* (0.071)	0.053*** (0.014)	-0.051* (0.027)	-0.028** (0.013)
<i>Panel B2. Heterogeneous effects by gender</i>								
Females ( <i>n</i> = 1,106)	0.027*** (0.010)	-0.586*** (0.095)	-0.729*** (0.157)	-0.430*** (0.158)	-0.225*** (0.085)	0.086** (0.037)	-0.050 (0.039)	-0.005 (0.015)
Males ( <i>n</i> = 2,699)	-0.016 (0.017)	-0.502*** (0.123)	-0.735*** (0.199)	-1.204*** (0.236)	-0.068 (0.050)	0.055*** (0.009)	-0.048 (0.033)	-0.048*** (0.015)
<i>Panel C. Heterogeneous effects by substitution status</i>								
Substituted ( <i>n</i> = 2,768)	-0.028*** (0.007)	-0.467*** (0.092)	-0.746*** (0.146)	-0.970*** (0.144)	-0.115** (0.049)	0.062*** (0.015)	-0.031 (0.030)	-0.058*** (0.018)
Non-substituted ( <i>n</i> = 1,792)	0.006 (0.021)	-0.548*** (0.129)	-0.736*** (0.145)	-1.194*** (0.242)	-0.049 (0.099)	0.051* (0.027)	-0.069* (0.041)	-0.007 (0.018)

*Notes:* This table reports estimated LATEs of stopping flunitrazepam in response to encountering a strict PHO due to the 2012 reform on general health and labor market outcomes. Each column in Panel A represents a separate panel IV regression where the endogenous variable is an indicator for whether flunitrazepam was taken by the addict, and the IV is PHO strictness in the district the addict lives in, multiplied with a post-reform indicator. Each regression additionally controls for age in 5 year bins, a non-parametric time trend, and addict fixed effects. The panel comprises *n* = 3,805 addicts, the total number of observations in each regression is *N* = 80,769. The first stage Kleibergen-Paap *F*-statistic is 22.3 in all regressions. Panels B1, B2, and B3 report differences in estimated LATEs when the sample is split according to age (panel B1), gender (B2), and substitutions status (B3). Standard errors in parentheses are two-way clustered on the district and individual level, stars indicate statistical significance: \* *p* < 0.10, \*\* *p* < 0.05, \*\*\* *p* < 0.01.

<sup>†</sup> Continuous and count outcomes are transformed using the inverse hyperbolic sine function (arcsinh).

TABLE 3 — Instrumental variable estimates on addiction-related outcomes.

	Overdoses		Diagnoses			Prescription drugs		
	Opioid overdoses (1)	Benzo overdoses (2)	Accidents & injuries (3)	HIV diagnoses (4)	Hepatitis C diagnoses (5)	Antidepressants prescribed (6)	Opioids prescribed (7)	Antivirals prescribed (8)
<i>Panel A. Baseline LATE estimates</i>								
No flunitrazepam taken	-0.021* (0.012)	-0.000 (0.005)	-0.002 (0.006)	-0.009 (0.006)	-0.003 (0.003)	-0.082*** (0.024)	-0.140** (0.059)	-0.004 (0.011)
Mean of outcome	0.028	0.007	0.042	0.001	0.003	0.198	0.141	0.019
Std. dev. of outcome	0.165	0.084	0.201	0.034	0.054	0.399	0.348	0.138
Number of observations	80,769	80,769	80,769	80,769	80,769	80,769	80,769	80,769
Number of addicts	3,805	3,805	3,805	3,805	3,805	3,805	3,805	3,805
<i>Panel B1. Heterogeneous effects by age</i>								
Age ≤ 30 (n = 2,238)	-0.103* (0.062)	-0.007 (0.034)	0.024 (0.020)	0.000* (0.000)	-0.009 (0.025)	-0.019 (0.037)	-0.032 (0.046)	-0.015 (0.020)
Age > 30 (n = 2,360)	-0.007 (0.007)	-0.004 (0.003)	-0.003 (0.006)	-0.011 (0.007)	-0.003* (0.002)	-0.084*** (0.027)	-0.172*** (0.062)	-0.004 (0.012)
<i>Panel B2. Heterogeneous effects by gender</i>								
Females (n = 1,106)	-0.055** (0.026)	-0.004 (0.015)	-0.005 (0.023)	-0.004 (0.004)	0.005 (0.006)	-0.039 (0.051)	-0.214*** (0.046)	-0.021 (0.021)
Males (n = 2,699)	-0.013 (0.013)	0.000 (0.004)	-0.001 (0.004)	-0.011 (0.007)	-0.005* (0.003)	-0.097*** (0.028)	-0.119* (0.063)	0.001 (0.013)
<i>Panel C. Heterogeneous effects by substitution status</i>								
Substituted (n = 2,768)	-0.031** (0.015)	0.002 (0.007)	-0.002 (0.008)	-0.012 (0.010)	-0.002 (0.004)	-0.079*** (0.030)	-0.110** (0.045)	0.005 (0.013)
Non-substituted (n = 1,792)	-0.002 (0.010)	-0.001 (0.008)	0.009 (0.010)	-0.004 (0.007)	-0.008*** (0.003)	-0.072 (0.060)	-0.167*** (0.062)	-0.044*** (0.013)

Notes: This table reports estimated LATEs of stopping flunitrazepam in response to encountering a strict PHO due to the 2012 reform on addiction-related outcomes. Each column in Panel A represents a separate panel IV regression where the endogenous variable is an indicator for whether flunitrazepam was taken by the addict, and the IV is PHO strictness in the district the addict lives in, multiplied with a post-reform indicator. Each regression additionally controls for age in 5 year bins, a non-parametric time trend, and addict fixed effects. The panel comprises  $n = 3,805$  addicts, the total number of observations in each regression is  $N = 80,769$ . The first stage Kleibergen-Paap  $F$ -statistic is 22.3 in all regressions. Panels B1, B2, and B3 report differences in estimated LATEs when the sample is split according to age (panel B1), gender (B2), and substitutions status (B3). Standard errors in parentheses are two-way clustered on the district and individual level, stars indicate statistical significance: \*  $p < 0.10$ , \*\*  $p < 0.05$ , \*\*\*  $p < 0.01$ .

TABLE 4 — Complier characteristics.

Variable	Sample mean	Complier ratio	95% CI
Female	0.29	1.087	(0.887,1.286)
Austrian citizenship	0.82	1.097	(1.051,1.142)
Age $\leq 30$	0.50	0.839	(0.719,0.959)
More than compulsory education	0.43	1.202	(1.050,1.355)
Urban area	0.46	1.188	(1.013,1.363)
First benzo prescription less than 2 years ago <sup>†</sup>	0.20	1.467	(1.189,1.745)

*Notes:* This table presents observed complier characteristics based on calculations proposed by Angrist & Fernández-Val (2013). The complier ratio is the relative likelihood that a complier has the given characteristic. It is derived as the ratio of the first stage for addicts with the given characteristic to the overall first stage as in equation (2). A ratio larger than 1 indicates that compliers are more likely to have the given characteristic. Standard errors used to calculate confidence intervals are bootstrapped with 99 repetitions.

<sup>†</sup> Indicator which is equal to one if the first package of flunitrazepam or any of the other short-acting benzodiazepines (clonazepam, diazepam, nitrazepam, and oxazepam) *in the data* was prescribed less than 2 years before the quarter of observation.

## A. WEB APPENDIX

This web appendix contains additional tables and figures for the paper “Behavioral responses to supply-control of highly addictive drugs—Evidence from a population of opioid addicts” by Alexander Ahammer.

FIGURE A.1 — Special narcotic prescription form.

**Nö.** SG1200601163

GKK  Substitutions-EINZEL-verschreibung  Substitutions-DALER-verschreibung  *Die Einzelverschreibung ist gültig 3-5 Tage bei Auszubildenden.*

Betr.-KK  VAEB  BVA (öf. Bod.)  .. gew. Wirtsch.  Bauern

Erwerbstätig  **ERW** Pensionist(in)  Kriegshinterbliebene(r)

Aussteller – Bitte zutreffendes Feld ankreuzen!

Familienname(n) \_\_\_\_\_ Vorname(n) \_\_\_\_\_ Versicherungsnummer \_\_\_\_\_

Patient  \_\_\_\_\_ Tag \_\_\_\_\_ Monat \_\_\_\_\_ Jahr \_\_\_\_\_

Ans \_\_\_\_\_

Versicherter (Nur auszufüllen, wenn Patient ein Angehöriger ist) \_\_\_\_\_ Tag \_\_\_\_\_ Monat \_\_\_\_\_ Jahr \_\_\_\_\_

Ausstellungsdatum 17.01.2013

Compensan ret. 300 (dreihundert)

OP II (zwei) Nr. XXX (dreissig)

S.: 1 x täglich 600mg.

Zur Substitutionstherapie,

Wegen Kurs wöchentlich zu beziehen, Bestätigung liegt vor.

Pat. scheint stabil

Tägliche Dosierung und Abgabemodus

Taxsumme \_\_\_\_\_

Rezept-Nr. \_\_\_\_\_

Anzahl d. Rp.-Geb. \_\_\_\_\_

Hinweise siehe Rückseite!

968424 995389

### SUBSTITUTIONSVerschreibung

Gültig nach Vidierung durch den Amtsarzt für einen Monat  
(Siehe Rückseite, Hinweise Punkt A.3.)

insgesamt entspricht  
von 21.01.2013 bis 19.02.2013 30mal 2 OP/Monat  
Tag Monat Jahr Tag Monat Jahr

Vidierung durch den Amtsarzt

[Redacted Signature and Stamp]

18. Jan. 2013

Stempel der Apotheke

Tag	Mon.	Abgabebestätigung (Signum)
14.		
15.		
16.		
17.		
18.		
19.		
20.		
21.		
22.		
23.		
24.		
25.		
26.		
27.		
28.		
29.		
30.		
31.		

Notes: This is an example for a typical special narcotic prescription form for 300 mg of the extended-release morphine preparation *Compensan*. The narcotic vignette with its unique running number can be seen on top, the PHO stamp and signature is in the field ‘Vidierung durch den Amtsarzt.’ Source: *Apothekerkammer Niederösterreich, Neuerungen in der Psychotropenverordnung* (Elisabeth Schober-Oswald, January 22, 2013)



TABLE A.1 — Identified opioid-substituted patients in Upper Austria based on UAHIF data, 1998–2015.

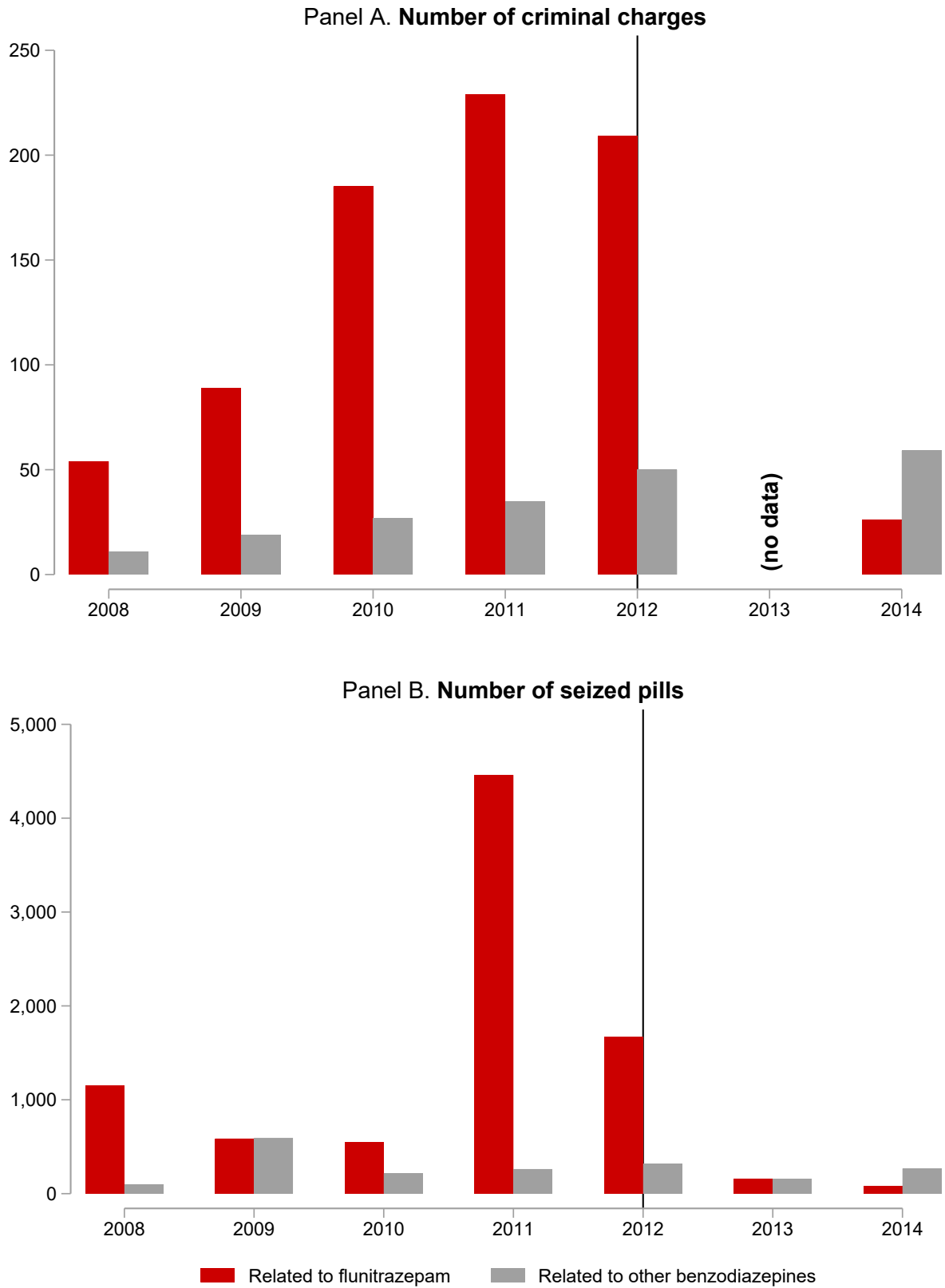
Year	Medication						Substituted		
	<i>Buprenorphine</i>		<i>Methadone</i>		<i>Morphine</i>		<i>UAHIF</i>	<i>official</i> <sup>†</sup>	<i>% observed</i>
	Patients	%	Patients	%	Patients	%			
1998	0	0.0%	192	89.7%	22	10.3%	214	204	104.9% <sup>‡</sup>
1999	5	1.9%	196	73.7%	65	24.4%	266	—	—
2000	46	12.8%	192	53.5%	121	33.7%	359	331	108.5% <sup>‡</sup>
2001	53	14.2%	155	41.7%	164	44.1%	372	351	106.0% <sup>‡</sup>
2002	85	19.0%	136	30.4%	227	50.7%	448	395	113.4% <sup>‡</sup>
2003	90	15.9%	131	23.2%	344	60.9%	565	455	124.2% <sup>‡</sup>
2004	124	17.5%	134	18.9%	451	63.6%	709	516	137.4% <sup>‡</sup>
2005	149	17.8%	201	24.0%	486	58.1%	836	576	145.1% <sup>‡</sup>
2006	201	21.3%	222	23.5%	522	55.2%	945	585	161.5% <sup>‡</sup>
2007	277	27.0%	270	26.3%	479	46.7%	1,026	782	131.2% <sup>‡</sup>
2008	366	30.6%	311	26.0%	518	43.3%	1,195	977	122.3% <sup>‡</sup>
2009	409	30.7%	394	29.6%	530	39.8%	1,333	1,221	109.2% <sup>‡</sup>
2010	474	30.2%	485	30.9%	609	38.8%	1,568	1,363	115.0% <sup>‡</sup>
2011	472	29.3%	445	27.7%	692	43.0%	1,609	1,633	98.5%
2012	486	29.4%	457	27.6%	710	43.0%	1,653	1,732	95.4%
2013	514	30.3%	451	26.5%	734	43.2%	1,699	1,794	94.7%
2014	539	30.6%	463	26.3%	759	43.1%	1,761	1,872	94.1%
2015	582	31.6%	462	25.1%	798	43.3%	1,842	1,948	94.6%

*Notes:* Comparison of identified opioid-substituted patients between the UAHIF data and official statistics for Upper Austria. If patients took multiple medications within a year (e.g., because they switched medications), I count only the medication they took for the majority of the year. Percentages are computed with regard to the UAHIF column.

<sup>†</sup> Official statistics are taken from yearly *Gesundheit Österreich* reports on the drug situation in Austria, which publish numbers of persons registered at the Austrian *Department of Health*. The reports can be accessed here: [https://www.sozialministerium.at/site/Gesundheit/Gesundheitsfoerderung/Drogen\\_Sucht/Drogen/Berichte\\_zur\\_Drogensituation\\_in\\_Oesterreich](https://www.sozialministerium.at/site/Gesundheit/Gesundheitsfoerderung/Drogen_Sucht/Drogen/Berichte_zur_Drogensituation_in_Oesterreich), some are available in English as well.

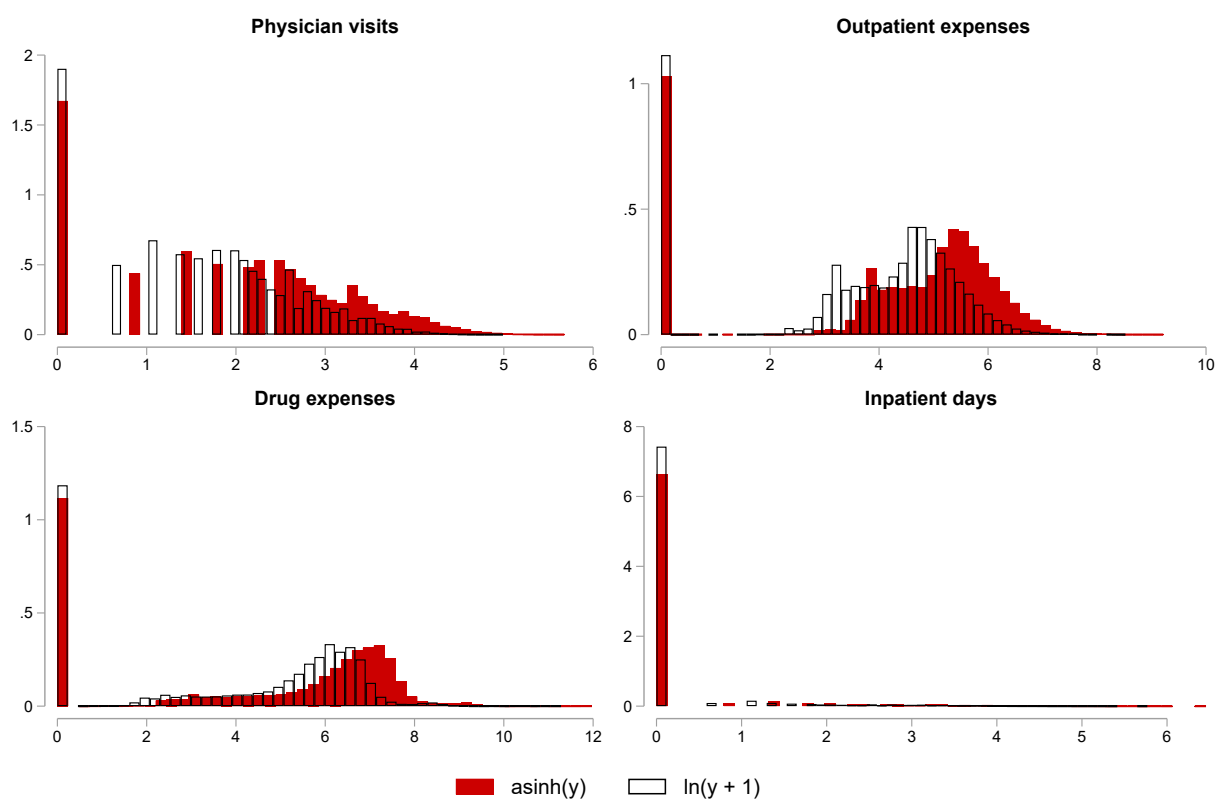
<sup>‡</sup> Before 2011 the number of patients reported to the *Department of Health* by the federal states is lower than the actual number of patients, apparently because for a subset of patients the state identifier was missing in the official data (see Weigl et al. 2011, notes below Table A22). This is the reason why I observe more patients than in the official statistics.

FIGURE A.2 — Number of pressed charges related to flunitrazepam and other benzodiazepines and number of seized pills for both groups, Upper Austria 2008–2014.



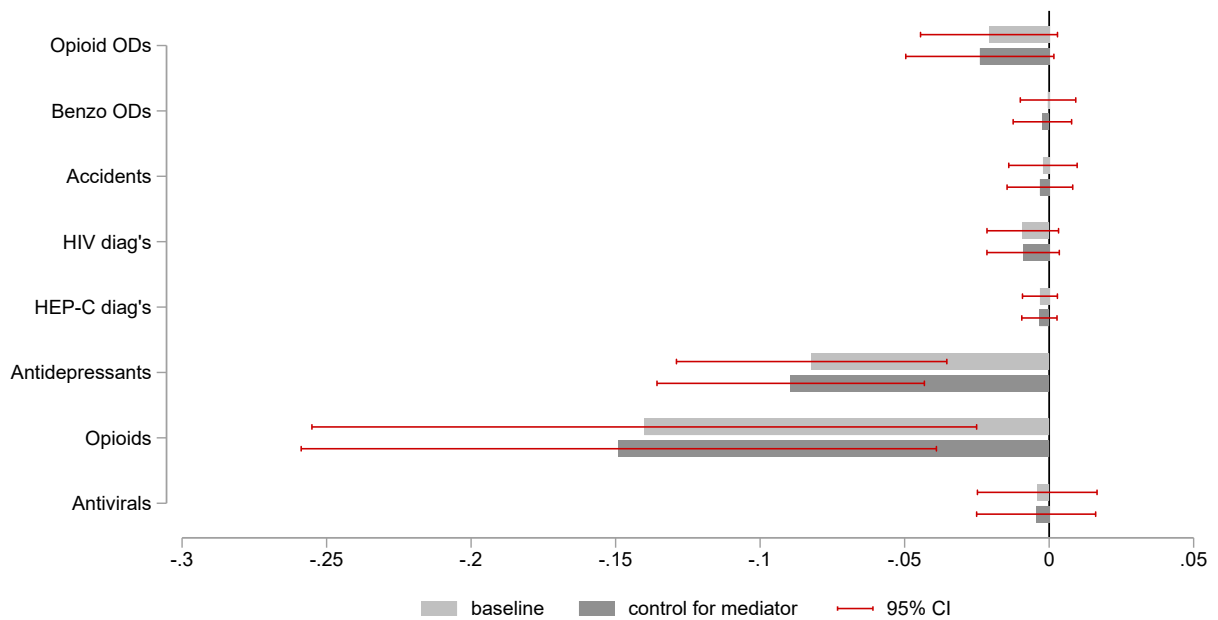
Notes: Criminal charges may be related to illegal possession or sale of either flunitrazepam or other benzodiazepines. In 2013 no data was collected. Source: *Annual Reports of Drug-Related Crime*, Austrian Department of the Interior, available at <https://bundeskriminalamt.at/302/start.aspx> (last accessed April 21, 2019).

FIGURE A.3 — Asinh transformation of continuous and count outcomes.



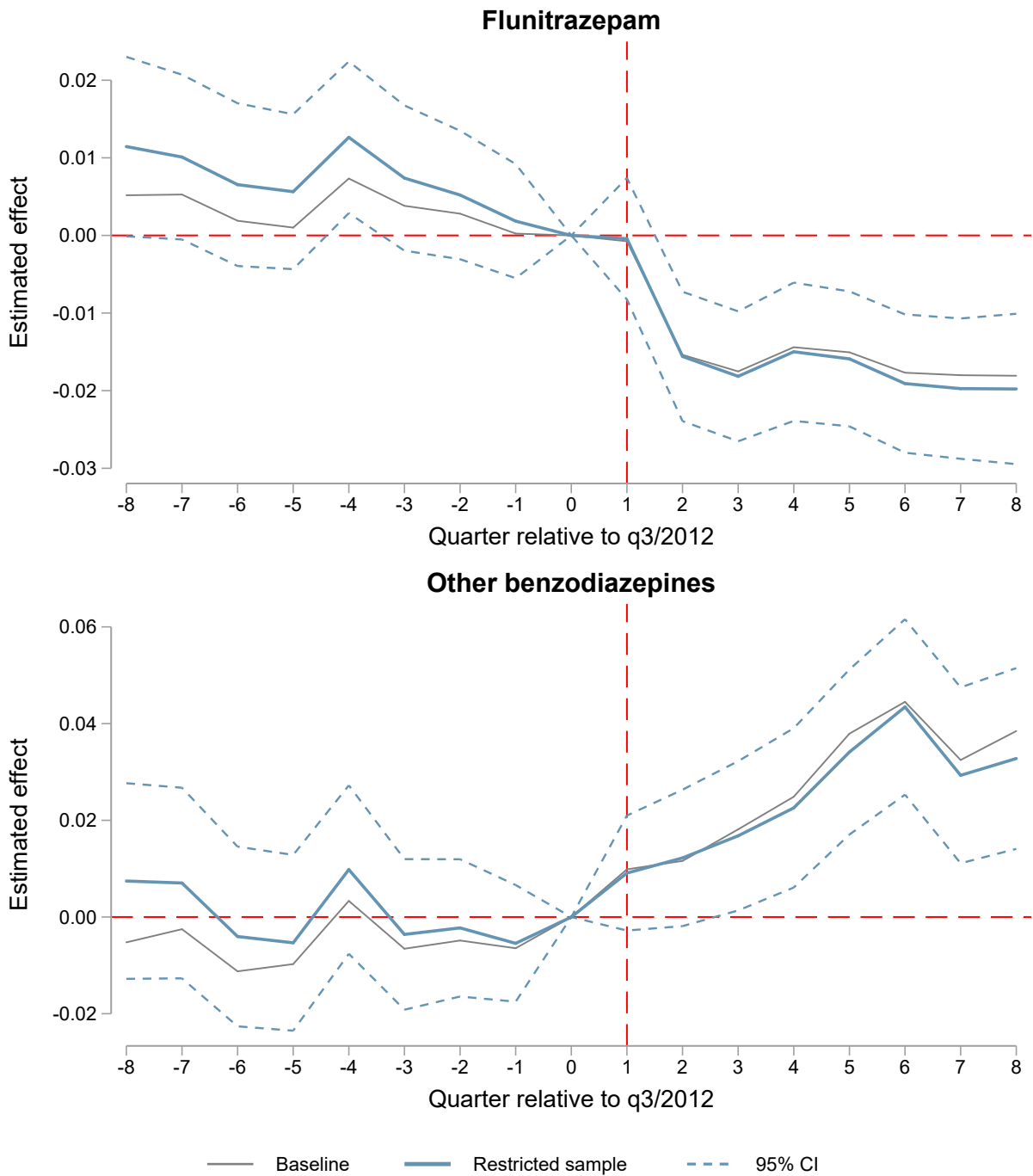
*Notes:* These histograms depict the distributions of continuous and count outcomes transformed by the inverse hyperbolic sine function. For comparison, the graphs also show transformations by the natural logarithmic function, where the constant 1 is added before the transformation is applied.

FIGURE A.4 — Change in LATEs when mediation through the usage of other benzodiazepines is controlled for, addiction-related outcomes.



Notes: This graph resembles Figure 8 in the main paper, but shows the change in LATEs for addiction-related outcomes. The gray line represents the LATE when a variable is controlled for that indicates whether other short-acting benzodiazepines (clonazepam, diazepam, nitrazepam, and oxazepam) were prescribed to the addict. The LATEs where mediators are controlled for are given as dark gray bars. For comparison, the baseline LATEs from Table 2, Panel A, are given as light gray bars. The graph also displays 95% confidence intervals.

FIGURE A.5 — Change in prescriptions when addicts do not enter the sample prior to their first opioid-related treatment.



Notes: This figure plots the change in prescriptions when addicts do not enter the sample prior to their first substitution treatment or opioid-related diagnosis in the data. The baseline estimates are taken from Figures 6 and 7. The lines depict estimated coefficients for the conditional probability an addict takes the respective medication eight quarters before and after the introduction of the new regulations in flunitrazepam prescriptions on December 15, 2012. The models also allow for addict fixed effects and flexible age controls. All coefficients are normalized to the last pre-reform quarter (q3/2012). The 95% confidence interval plotted as a dashed blue line corresponds to the estimates based on the restricted sample, it is based on addict-level clustered standard errors. All computations are based on the UAHIF addict sample ( $N = 80,769$ ).