Pharmaceutical Drug Regulation and Mortality: The Peculiar Case of E-cigarettes

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The Food and Drug Administration (FDA) is tasked with regulating pharmaceutical drugs in the U.S. and approving new drugs.

FDA drug regulation involves a lengthy, costly, and high-uncertain drug approval process; expensive post-market surveillance; and high regulatory barriers for making even small changes after initial approval is received,

- Average time to bring new pharmaceutical compound to market is 15 years, 7 of which is spent on preparing original application
- Firm spending on approved compound averages $2.9 billion, including post-approval monitoring (DeMasi et al., 2016)

Only 11.8% of new compounds approved for human subjects are approved for marketing.
FDA drug regulation represents a trade-off between safety/efficacy and speed.

Social welfare could accrue earlier with fast approval, but at the risk of welfare losses from unsafe/ineffective compounds.

Studies have found that decreasing drug review times:
- has no effect on adverse events (Grabowski & Wang, 2008)
- increases firm R&D expenditures (Vernon et al., 2006),
- increases drugs in development (Chorniy et al., 2021)
- increases market entry (Jia et al., 2023)

The 1992 Prescription Drug User Fee Act, which reduced FDA review times, increased social surplus by $14–$31 billion per year (Philipson et al., 2008).

Upper bound of life-years lost is 56,000, suggesting that faster decisions outweighed costs.
Most research estimates effect of FDA drug review times, just one aspect of FDA drug regulation, on social welfare, adverse events, innovation, etc.

**Big Picture Question:** How does FDA drug regulation *writ-large* impact consumer welfare and mortality?

In this paper, we evaluate a single “drug”, *e-cigarettes*, that unexpectedly “escaped” FDA drug regulation in 2009 due to change in federal law.

**Research Question** How did e-cigarettes impact mortality and social welfare, compared to nicotine replacement therapy (NRT)?

Studying the effect of e-cigarettes on mortality, and comparing these effects to NRT, provides a ‘glimpse’ into a modern-day world without FDA drug regulation.
In 8/2006, the Ruyan v8 e-cigarette began being imported into the U.S.

In 3/2009, the FDA declared e-cigarettes to be unapproved drug and began seizing them at ports of entry

Two e-cigarette companies subsequently took the FDA to court challenging their declaration that e-cigarettes were a drug and seeking an injunction against seizures

The FDA’s policy at the time was that they could declare any tobacco product as a “drug”, unless the federal gov’t indirectly declared the product as a “tobacco product” through legislation
In 6/2009, the Family Smoking Prevention and Tobacco Act (TCA) was signed into law.

The TCA gave the FDA new authority to regulate existing tobacco products, like cigarettes, and a pathway to regulate new products if the FDA “deemed” them as tobacco products through the federal rule-making process.

An unintended effect of the TCA, however, was that it diminished the FDA’s legal argument that e-cigarettes were a drug, since Congress now legislated that even new tobacco products can be regulated as tobacco products.

In 1/2010, a district court judge sided with industry, ruling that the FDA must regulate e-cigarettes as a tobacco product, not a “drug”.
The FDA began the process of deeming e-cigarettes as tobacco products, which was finalized in 8/2016.

As a consequence e-cigarettes were entirely unregulated federally for 7 years after TCA (10 years after importation in 2006), but were still subject to product liability law.

E-cigarette companies avoided drug approval process, could innovate without regulator approval, could enter without regulatory barriers, and avoided potential product safety recalls.

In this unregulated marketplace, e-cigarette sales exploded: Gen 1: Disposables; Gen 2: “Vape pens” with refillable cartridges, tanks, and rechargeable batteries; Gen 3: “Tanks” and “mods” with more customization; Gen 4: “Pods”, nicotine salts, more flavors
Nicotine Drug Searches

![Graph showing Google Trends search intensity for Electronic Cigarette Searches, NRT Searches, and Prescription Pill Searches from 2004 to 2018.](image)

- **Electronic Cigarette Searches**
- **NRT Searches**
- **Prescription Pill Searches**
In contrast to e-cigarettes, consider slow evolution of other smoking cessation medications:

- In 1984, 2mg NRT gum first marketed.
- 4 mg gum in 1993; Over-the-Counter (OTC) gum in 1996; mint and orange flavored gum in 1999 and 2000.
- It took 9 years before nicotine gum could be sold with a higher nicotine strength, 12 years before it could be sold OTC, and 15 years before nicotine gum could be sold with a flavor
- Cyctisine, a highly effective smoking cessation drug available elsewhere, not approved as a drug in the U.S.
**Big Picture Question:** What are the public health benefits, or harms, from FDA drug deregulation?

**Research Question:** How do e-cigarettes and over-the-counter NRT impact mortality for high-smoking demographics relative to low-smoking demographics?

**Data:** NVSS restricted-use mortality data, BRFSS

**Identifying Variation:** Cross-sectional variation in smoking prevalence prior to drug introduction

**Estimation Strategy:** Bite-style differences-in-differences

**Results:** E-cigarettes saved roughly 1.7 million life-years from 2007-2019, or $13.3 billion in annual consumer surplus.

E-cigarettes reduced smoking. No detected effect from NRT on mortality or smoking.
We use data from BRFSS from 1989-2020 to construct smoking bite


Mean daily smoking rate prior to e-cigarettes is 12.0% (16.7% for NRT). Avg. of 1,220 (575) respondents used to construct e-cigarette bite (NRT bite).

- Highest daily smoking rate (ENDS intro) is 33.6%: 40-44 years old, American Indian, female, rural, South
- Lowest daily smoking rate (ENDS intro) is 0.16%: 70-74 years old, Asian/Pacific Islander, female, rural, West

Require at least 100 respondents to calculate prevalence. Daily smoking prevalence is preferred bite.
Restricted-use death records from NVSS from 1989-2020. Contains detailed information from death certificates in U.S.

Create panel of all-cause and cause-specific mortality rates by demographic group from 1989-2019

Smoking-attributable ICD codes from Lariscy (2019). Include prostate and breast cancer due to causal evidence linking smoking to these causes (Lariscy, 2019).

Panel consists of annual mortality rates for 960 groups from 1989-2019. 28,800 group-year observations
We also examine current and daily smoking prevalence as outcomes at the yearly level.

Calculate same as before with bite variable: estimate mean smoking prevalence by group using BRFSS sampling weights.

Drop census region as a demographic dimension to increase cell sizes.

Merge current and daily smoking prevalence onto our mortality panel.
Reduced-Form Estimation

- We estimate a bite-style DID model given below (Bartik, 1991; Allcott & Rafkin, 2022)

\[
y_{it} = \alpha + \beta \cdot \theta_i + \gamma_i + \phi_t + \epsilon_{it}.
\]

- \(y_{it}\): mortality per 100,000 for group \(i\) in year \(t\)
- \(\theta_i\): daily smoking prevalence of group \(i\) in 2 years prior to drug introduction
- \(\gamma_i\): county fixed effects
- \(\phi_t\): year fixed effects
- \(\epsilon\): error term, cluster at demographic group level
- Note: Estimate through OLS, weight by population.
Pre-Trend Correction Procedure

- **Identifying Assumption**: Prior to drug introduction, mortality among high-smoking groups trends parallel to that of low-smoking groups.

- Challenge is that parallel trend assumption rarely holds
  - i.e. mortality for higher-smoking groups tends to increase relative to lower smoking groups, prior to drug introduction.

- To ensure parallel trends, use Andrew Goodman-Bacon (2021) pre-trend correction:
  1. For each demographic group, regress $y_{it}$ on linear trend using pre-period years
  2. Take residuals from regression above, call 'adjusted' outcome
  3. Use adjusted outcome in Equation (1) and event studies

- This procedure effectively transforms mortality from levels to deviations in mortality from the pre-period linear trend, extrapolated into the post period.
Mortality Event Studies

**Figure:** All-Cause Mortality Event Studies

(a) NRT Introduction

\[ \beta (SE) = -2.60 (1.46), \bar{y}_{pre} = 1,311 \]

Implied % Change = $-0.20\%$

(b) E-cigarette Introduction

\[ \beta (SE) = -15.47 (1.98), \bar{y}_{pre} = 1,352 \]

Implied % Change = $-1.07\%$
Takeaways: Mortality rates after 2007 fell by 1.07% (relative to pre-2007 trend) for every 1pp difference in daily smoking from 2005-2006. No significant effects from OTC NRT.

Now let’s look at how drug introduction impacted smoking prevalence...
Smoking Event Studies

**Figure**: OTC NRT Introduction and Smoking Prevalence

(a) Current Smoking

\[ \beta (SE) = 0.0006 (0.0008), \bar{y}_{pre} = 0.43 \]

Implied % Change = 0.14%

(b) Heavy Smoking

\[ \beta (SE) = 0.0002 (0.0006), \bar{y}_{pre} = 0.21 \]

Implied % Change = 0.11%
Smoking Event Studies

**Figure:** E-cigarette Introduction and Smoking Prevalence

(a) Current Smoking

\[ \beta (SE) = -0.0023 (0.0009), \bar{y}_{pre} = 0.19 \]

Implied % Change = $-1.21\%$

(b) Heavy Smoking

\[ \beta (SE) = -0.0014 (0.0007), \bar{y}_{pre} = 0.15 \]

Implied % Change = $-0.93\%$
Smoking Event Studies

- **Takeaways** Current smoking rates fell by 1.21% (relative to pre-2007 trend in smoking) for every 1pp difference in daily smoking pre-e-cigarette introduction.

- Daily smoking rates fell by 0.93% (relative to pre-2007 trend) for every 1pp difference in daily smoking pre-e-cigarette introduction.

- No significant effects from OTC NRT introduction.
Summary of Results

Social Welfare

Introduction

Background

Data

Estimation

Results

Summary of Results

Mortality Results by Age

**Figure:** Summary of Main Estimates and Age-Heterogeneity Estimates

(a) E-cigarette Introduction

![Graph showing mortality results by age](image-url)
Mortality Results by Specification

Figure: Summary of Main Estimates and Robustness Estimates

(a) E-cigarette Introduction
Results by Cause of Death

**Figure:** Summary of Main Estimates by Cause of Death

(a) E-cigarette Introduction
Consumer Surplus

- We calculate consumer surplus as follows:


2. We’ve now converted our estimates into implied changes in mortality evaluated at the mean daily smoking rate. Multiply by population to convert from mortality rate to mortality reductions.

3. Smoking cessation should increase life expectancy by 9, 6, 4, and 2.85 years for those 35-44, 45-54, 55-64, and 65+, respectively (Philipson & Jena, 2006; Taylor et al., 2002). Multiply deaths averted from step 2. by expected gain in life-years.
4. Discount gain in life-years from step 3. by 50% to account for mix of smoking reduction and smoking cessation from our results. Discount by 50% again to account for Darden (2018) finding that life years lost from smoking are roughly half of CDC estimates.

5. We now have a total of roughly 165k life-years gained annually from e-cigarettes, or 2.2 million from 2007-2019.

6. Multiply life-years gained by VSLY ($100,000 per life-year), discount to 2007 using 3% market interest rate, convert to 2019 dollars.

**Takeaways** Total of $173 billion in consumer surplus from 2007-2019, or $13.3 annually.
FDA drug regulation can unintentionally reduce innovation and diminish social welfare

This study examines how e-cigarettes, a drug which unexpectedly managed to “escape” FDA drug regulation, impacted mortality, compared to NRT.

Our results indicate that e-cigarettes saved 1.66 million life years and generated $173 billion in consumer surplus from 2007-2019.

This suggests that FDA drug regulation may be too restrictive, and deregulation could lead to public health gains.

Our study also suggests if the FDA Center for Tobacco Products is successful in clearing the e-cigarette marketplace of all but 23 authorized e-cigarette products, this is likely to offset mortality reduction gains that e-cigarettes are otherwise providing.