Happy pills? Cause and consequences of the upsurge in antidepressant use

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Depression

- Increase in the prevalence of depression symptoms in most OECD countries. Estimates range: 12–25%.
- The burden of depression and other mental health conditions is on the rise globally. → WHO’s mental health Gap Action Programme (mhGAP).
- Switzerland (SHS): mild 22%, moderate 4.6%, severe 1.9%.  
  - Higher among the young (34%) and women (30 %). Lower among the elderly (below 20%).
  - Inversely related to income.
Antidepressant drugs consumption
2000 and 2013 (or nearest year)

*DDD = Defined Daily Dose as defined by the WHO
Data sources: OECD Health Statistics 2015, IMS Health Switzerland
The dramatic increase in Antidepressant use

- Dramatic increase in antidepressant (AD) use with the introduction of the Selective Serotonin Reuptake Inhibitors (SSRI)
  - **USA**: 13% of people reported to take ADs within the last month
    ADs are (3rd most prescribed drug)
  - **OECD**: AD use has more than doubled in the last 15 years
  - **Switzerland**: pharma industry represents almost 5% of Swiss GDP
- Massive **economic burden of depression** but...
  - non-psychiatric prescriptions in primary care, often without depression diagnoses (off-label prescription)
  - there are rising concerns about their use...
Rising concerns

- Efficacy of antidepressants is mostly grounded on RCT but several meta-studies questioned the results:
  - **Short** duration of RCT, **small** samples, under-reporting of **adverse** events and questionable **clinical** significance (e.g., Fournier et al, JAMA 2010, Jakobsen et al. BMC-Ps. 2017)
  - **Selective** Publication of Antidepressant Trials (Turner et al. NEJM 2008)
  - **Placebo** effects account for up to 80% of the total measured effect (Currie and Macload ECMA 2020)
  - **FDA** issued a black box warning in 2004: increasing suicide risk among adolescent
  - **Withdrawal** symptoms (Davies et al. 2019)
- Unknown consequences of **off-label** prescriptions “**expose patients to unknown health risks if their clinical characteristics differ from the patient population studied in clinical trials**” (Wong et al. 2017).
Some recent newspapers coverage

'We are a sedated society': the rise in antidepressants during lockdown

One in six of the population is on antidepressants, and the numbers are rising. Are GPs being too 'trigger-happy' with prescriptions?

Opinion

It's Not Just a Chemical Imbalance

Thinking of my mental illness as preordained missed many of the causes of — and solutions to — my emotional suffering.

By Kelli Maria Korducki

Ms. Korducki is a writer.

July 27, 2019

The hard truths your psychiatrist may not be telling you about antidepressants

The Rise of All-Purpose Antidepressants

Doctors are increasingly prescribing SSRIs to treat more than just depression.
Happy pills? Mental health effects of the dramatic increase in antidepressant use

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\textsuperscript{2}Department of Management, Information and Production Engineering (DIGIP), University of Bergamo, Italy
\textsuperscript{3}Department of Agricultural and Resource Economics, University of Connecticut, United States.
This study

- Granular data on AD sales at product level, hospitalization and suicides from 106 small Swiss regions over the period 2003–2014
- To identify the causal effect of AD sales on health, we exploit product innovation and pharmaceutical companies market power:
  - we assign pharmaceutical company national sales of AD to Swiss regions using their market power for non-AD drugs
- We find that an increase in AD sales of one defined daily dose (DDD) per 1,000 inhabitants (roughly 3% of 2003 sales):
  - increases emergency hospitalization by almost 1%, mainly driven by admission for depression (+6%)
  - noisy estimates for suicides
  - we do not find any economically relevant effects on labor market outcomes
- We find similar results when we exploit prescription practice spillovers from neighboring countries
AD and health

- Extensive literature on the spatial correlation between AD consumption and suicides to evaluate the population health effects in the “real world”
- Ludwig and Marcotte (JHE 2009) provides plausible causal evidence at population level
  - they find that an increase of SSRI sales by one pill per capita reduces suicides by 5%
  - AD consumption in the US has increased by more than 400% by the early 1990's
  - suicide is a very low probability event
- Currie and Macload (2020) on physician decision making skills in AD treatment
- Cuddy and Currie (2020): inappropriate mental health treatment with antidepressants in children increases emergency hospitalizations and health care costs
Conceptual framework for antidepressant benefits and prescription thresholds

![Graph showing benefits of antidepressant treatment across different depression severities and prescription thresholds. The graph compares SSRIs and TCAs, with shaded areas indicating different guideline prescription thresholds.](image)
Drug advertising

- **Direct to consumer advertising**: causal link between pharmaceutical marketing and prescription drug utilization (e.g., Shapiro, JPE 2018; Sinkinson and Starc, RES 2019; Shapiro, AEJ:Micro 2020)

- The Swiss government **sets prices** for prescription drugs and direct-to-consumer advertising is **forbidden**

- Pharma companies can influence their sales only through **physician detailing** → We provide evidence for this channel

- We use **voluntary disclosure** information on detailing and marketing activities to health care professionals of 11 big pharma companies in Switzerland.

- We show that the regional expenditure in detailing activities by pharmaceutical companies is strongly correlated with **revenues** and **market shares**.
Data

- **AD sales** from IMS Health Switzerland (now IQVIA):
  - Sales data at the product level by pharmaceutical sales region (237 regions) from 2002 to 2014 → consumption of each AD product in defined daily doses (DDD) per 1,000 inhabitants per year
- **Hospital discharge data** by cause from the Federal Statistical Office (FSO)
- **Suicides**, socio-demographic information, and physician concentration are available at municipal level (FSO)
- **Labour market** data from the Swiss Labour force survey (SLFS)
- Data are then aggregated at spatial mobility data (SMR), 106 small local labor markets
Defined daily doses per 1,000 population


Generic

Original/Branded

Defined daily doses per 1,000 population


Generic

Original/Branded
Determinants of AD sales (Masiero, Mazzonna, Verbeek, 2018)
Mental health outcomes in Switzerland by small areas

(a) AD sales in 2003

(b) AD sales in 2014

(a) Depression admissions 2003

(b) Depression admissions 2014
The effect of AD use on hospital admission and suicides (Empirical model)

We rely on the following empirical model:

\[ y_{rt} = \beta_1 AD_{rt} + X_{rt}\beta_2 + \vartheta_r + \lambda_t + \epsilon_{rt} \] (1)

- \( y_{rt} \) is the log of the mental health outcome (number of hospital admissions for mental health problems, depression or number of suicides) in region \( r \) at time \( t \)
- \( AD_{rt} \) represents AD sales (DDD per 1'000 inhabitants)
- \( X_{rt} \) includes demographics (age distribution, share of females, share of German speakers, and share of foreigners) and the density of AD prescribing physicians
- \( \vartheta_r \) are region fixed effects, \( \lambda_t \) are time fixed effects, and \( \epsilon_{rt} \) is the idiosyncratic error term
Research design: exploiting pharmaceutical industry market power

National AD sales at company level are assigned to regions using 2002 market “shares”:

- the introduction of several new products provides substantial variation in the national growth rate across companies (supply-driven)

- Exogeneity of our shares:
  1. we use regional market shares rather than regional sales relative to national sales
  2. the market shares are computed using non-AD drugs sales
Estimates of the effect of AD sales on mental health outcomes

<table>
<thead>
<tr>
<th>Outcomes (ln):</th>
<th>Mental disorder</th>
<th>Depression</th>
<th>Suicide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model (1)</td>
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<td>(.002)</td>
<td>(.004)</td>
<td>(.002)</td>
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<td>.065***</td>
<td>.011</td>
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<td>(.023)</td>
<td>(.008)</td>
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<td>.065***</td>
<td>.010</td>
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<td>(.010)</td>
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<td>(.008)</td>
</tr>
</tbody>
</table>

1st stage

- FE: .112*** (.031)
- 2SLS: .108*** (.033)

Reduced form

- FE: .002** (.001)
- 2SLS: .002** (.001)

Year FE: Yes
Region FE: Yes
Demographics: Yes
Physician density: No
Unemployment rate: No
Observations: 1,272

Standard errors are robust and two-way clustered (Cameron et al. 2011) at region and year level.
Validity of our research design

- We calculate the so-called ‘Rotemberg weights’ (Goldsmith-Pinkam et al. 2020) showing which pharmaceutical companies are driving our results and whether results are different across different pharma/products.
- We show that our results are largely driven by Mepha-Theva that introduced several new generics since 2004.
- Alternative hospitalizations as placebo
- Alternative instrument based on prescribing practice spillovers from neighboring countries
Trends in hospital admission for depression (Mepha-Teva)

![Graph showing trends in hospital admission for depression (Mepha-Teva). The graph displays the log admission for depression from 1999 to 2014, with two lines representing low and high shares. The low share line is represented by a dotted line, and the high share line is represented by a solid line. The y-axis represents the log admission for depression, ranging from 3.5 to 6.0, while the x-axis represents the years from 1999 to 2014.]
Additional results

- Labor market outcomes
- Physician detailing per capita and pharmaceutical companies market shares and revenues
Conclusions

- We find that AD sales increase emergency hospitalizations mainly driven by admission for depression related problems (+6.5%).
- Our findings should be interpreted in the light of the actual prescription threshold and off-label use.
- Official guidelines support psychotherapy for mild and moderate depression but yet few patients use it.
- Our research sheds light on one of the causes of over-treatment with pharmacotherapy → the influence of pharmaceutical company over doctor prescription practice.
- Other potential causes:
  - undercapacity of psychotherapists
  - psychotherapy is a time-consuming treatment
  - patients bias and beliefs (Cronin et al. 2020)
Happy pills? (Red Hook, NY)
Appendix
## Alternative hospitalization outcomes

<table>
<thead>
<tr>
<th>Outcomes (ln):</th>
<th>Emergency Hospitalization excl. mental health</th>
<th>Elective Hospitalization excl. mental health</th>
<th>Infectious diseases</th>
<th>Bone fractures</th>
<th>Pregnancy and childbirth</th>
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<tbody>
<tr>
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<td>12.69</td>
<td>12.69</td>
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<td>103.11</td>
<td>6.97</td>
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Alternative IV: Prescribing practice spillovers

- This instrument is meant to take into account that around \(30\%\) of doctors practicing in Switzerland have foreign qualifications and almost all of them (25%) studied in one of the four big neighboring countries, namely Germany, Austria, France and Italy.

- Based on this observation, we build our instrument using spatially weighted averages of AD sales in neighboring countries and assign them to local areas as follows:

\[
\tilde{AD}_{rt} = \frac{\sum_c w_{cr} AD_{ct}}{\sum_c w_{cr}},
\]

- \(\tilde{AD}_{rt}\) is a measure of AD sales in region \(r\) at time \(t\) based on spillovers effects generated by exogenous prescribing practices.

- \(AD_{ct}\) is AD sales in country \(c\) and year \(t\).

- \(w_{cr}\) is the squared inverse of geographical distance between country \(c\) and the centroid of region \(r\).

- Main assumption: AD consumption in neighboring countries affects the mental health of the neighboring Swiss regions only through spatial spillover in prescription practice.
Practice spillover instrument and changes in AD use over time

Defined daily doses per 1,000 population

- AU
- CH
- DE
- FR
- CH-IV
- IT

IV2: Estimates of the effect of AD sales on mental health outcomes using the practice spillovers instrument

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<th>Outcomes (ln):</th>
<th>Mental disorder</th>
<th>Depression</th>
<th>Suicide</th>
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<td>.357*** (.062)</td>
<td>.354*** (.062)</td>
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<td>.007*** (.002)</td>
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<td>Physician density</td>
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<td>Unemployment rate</td>
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Physician detailing per capita and pharmaceutical companies market shares and revenues

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Off-label use

➤ **Common off-label use:**

➤ **Investigational use:**
   - Arthritis, Deficits caused by stroke, Diabetic neuropathy, Hot flashes, Irritable bowel syndrome, Migraine, Neurocardiogenic syncope (fainting), Panic disorder, Post-traumatic stress disorder, Premature ejaculation.