





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

*DDD = Definied 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



By Julia Calderone on November 1, 20



Happy pills? Mental health effects of the dramatic increase in antidepressant use

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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



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 \rightarrow 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



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Determinants of AD sales (Masiero, Mazzonna, Verbeek, 2018)



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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

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The effect of AD use on hospital admission and suicides (Empirical model)

We relies on the following empirical model:

$$y_{rt} = \beta_1 A D_{rt} + X_{rt} \beta_2 + \vartheta_r + \lambda_t + \epsilon_{rt}$$
(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
- ▶ ϑ_r are region fixed effects, λ_t are time fixed effects, and ϵ_{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

Introduction of new AD drugs in Switzerland (2002–2014)



Estimates of the effect of AD sales on mental health outcomes

Outcomes (In):	Mental disorder		Depre	Depression		Suicide	
Model	(1)	(2)	(1)	(2)	(1)	(2)	
FE	.002 (.002)	.002 (.002)	.012** (.005)	.011** (.004)	001 (.004)	001 (.002)	
2SLS	.021**	.022**	.065***	.065***	.011	.010	
	(.009)	(.010)	(.023)	(.024)	(.008)	(.008)	
1st stage	.112*** (.031)	.108*** (.033)	.112*** (.031)	.108*** (.033)	.112*** (.031)	.108*** (.033)	
Reduced form	.002** (.001)	.002** (.001)	.007*** (.002)	.007*** (.002)	.001 (.001)	.001 (.001)	
Year FE Region FE Demographics Physician density Unemployment rate	Yes Yes Yes No No	Yes Yes Yes Yes Yes	Yes Yes No No	Yes Yes Yes Yes Yes	Yes Yes No No	Yes Yes Yes Yes Yes	
Observations	1,272	1,272	1,272	1,272	1,272	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 link
- Alternative instrument based on prescribing practice spillovers from neighboring countries https://www.initeduction.com

Trends in hospital admission for depression (Mepha-Teva)



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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 interpret 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 \rightarrow 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

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Alternative hospitalization outcomes

Outcomes (In):	Emergency Hospitalization excl. mental health	Elective Hospitalization excl. mental health	Infectious diseases	Bone fractures	Pregnancy and childbirth
2SLS	.009	003	008	006	.003
	(.006)	(.011)	(800.)	(.008)	(.005)
Year FE	Yes	Yes	Yes	Yes	Yes
Region FE	Yes	Yes	Yes	Yes	Yes
Demographics	Yes	Yes	Yes	Yes	Yes
Physician Density	Yes	Yes	Yes	Yes	Yes
Observations	1,272	1,272	1,272	1,272	1,272
Kleijbergen-Paap F	12.69	12.69	12.69	12.69	12.69
Mean	924.76	637.96	35.55	150.97	111.36
Within SD	69.48	72.78	9.41	23.34	11.28
Between SD	100.50	103.11	6.97	27.91	13.07

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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:

$$\widetilde{AD}_{rt} = \frac{\sum_{c} w_{cr} AD_{ct}}{\sum_{c} w_{cr}},$$

- ► 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



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

Outcomes	Menta	l disorder	Depre	ession	Sui	cide
(In): Model	(1)	(2)	(1)	(2)	(1)	(2)
2SLS	.021***	.021***	.067***	.066***	.003	.001
	(.008)	(.008)	(.020)	(.020)	(.006)	(.006)
1st stage	.357***	.354***	.357***	.354***	.357***	.354***
	(.062)	(.062)	(.062)	(.062)	(.062)	(.062)
Reduced form	.007***	.008***	.024***	.023***	.001	.000
	(.002)	(.002)	(.005)	(.005)	(.002)	(.002)
Year FE Region FE Demographics Physician density Unemployment rate	Yes Yes Yes No No	Yes Yes Yes Yes Yes	Yes Yes No No	Yes Yes Yes Yes Yes	Yes Yes No No	Yes Yes Yes Yes Yes
Observations	1,272	1,272	1,272	1,272	1,272	1,272
Kleijbergen-Paap F	33.603	32.625	33.603	32.625	33.603	32.625

Labor market outcomes

Outcomes	Unemployment	Labor force	Ln(mean income)	Ln(mean hours)
FE	0001	.0010***	0024***	0014***
	(.0001)	(.0003)	(.0007)	(.0003)
2SLS (IV1)	0004	.0007	.0061**	0015
	(.0007)	(.0010)	(.0025)	(.0012)
2SLS (IV2)	0001	.0006	.0003	0018
	(.0002)	(.0007)	(.0013)	(.0011)
Year FE	Yes	Yes	Yes	Yes
Region FE	Yes	Yes	Yes	Yes
Demographics	Yes	Yes	Yes	Yes
Mean of dep. var.	.016	.878	11.04	3.63**
Observations	1,085	1,085	1,085	1,085
Kleijbergen-Paap F	11.238	11.238	11.238	11.238

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Physician detailing per capita and pharmaceutical companies market shares and revenues

Model:	(1)	(2)	(3)	(4)
Market charge	004***	005***	005***	002*
Warket shares	(.001)	(.001)	(.002)	(.001)
Revenues	.142***	.111***	.054***	.064***
	(.029)	(.025)	(.016)	(.022)
Year FE	Yes	Yes	Yes	Yes
Demographics	Yes	Yes	Yes	Yes
Canton FE	No	Yes	No	Yes
Region FE	No	No	Yes	No
Company FE	No	No	No	Yes
Observations	3,123	3,123	3,123	3,123



Off-label use

Common off-label use:

Abuse and dependence, ADHD (in children and adolescents), Anxiety disorders, Autism (in children), Bipolar disorder, Eating disorders, Fibromyalgia, Neuropathic pain, Obsessive-compulsive disorder, Premenstrual dysphoric disorder.

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.

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