research

Antidepressant treatment in fathers during conception appears to be safe for offspring
p 395

The unintended consequences of opioid prescribing in the US following 2014 regulatory changes
p 396

Use of a nicotine patch before quitting unlikely to increase longer term cessation
p 398

ORIGINAL RESEARCH Nationwide prospective cohort study

Paternal use of antidepressants and offspring outcomes in Sweden

Viktorin A, Levine SZ, Altemus M, Reichenberg A, Sandin S

Cite this as: *BMJ* 2018;361:k2233
Find this at: http://dx.doi.org/10.1136/bmj.k2233

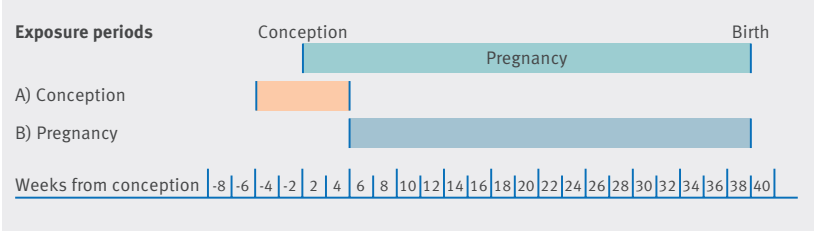
Study question Does antidepressant treatment of fathers around the time of conception increase the risk of adverse outcomes in offspring through negative effects on sperm?

Methods Of 170 508 Swedish children born in 2006-07 and followed up to age 8-9 years, 3983 children born to fathers receiving antidepressant treatment during the conception period (from four weeks before estimated conception date to four weeks after) were compared with 164 492 children born to fathers not receiving antidepressant treatment. The group of 3983 children exposed during conception were then compared with 2033 children born to fathers who initiated antidepressant treatment later during the pregnancy period (from four weeks after estimated conception date to childbirth). Exposure groups were compared for risk of preterm birth, malformations, autism, and intellectual disability.

Study answer and limitations Paternal antidepressant use during the conception period was not associated with preterm birth (adjusted odds ratio 0.91 (95% confidence interval 0.79 to 1.04)) or malformations (1.06 (0.90 to 1.26)) using logistic regression, compared with no paternal use during the conception period or pregnancy period. No association was seen between antidepressant use during the conception period and autism (adjusted hazard ratio 1.13 (0.84 to 1.53)) or intellectual disability (0.82 (0.51 to 1.31)) using Cox regression. In children whose fathers initiated antidepressant treatment during the pregnancy period, results were similar for all outcomes apart from intellectual disability, which had an increased adjusted hazard ratio (1.66 (1.06 to 2.59)). With limited previous research on this topic, replication of these findings and investigation of other outcomes are warranted.

What this study adds Antidepressant treatment in fathers around the time of conception appears to be safe for offspring. Instead, underlying characteristics in fathers could be associated with autism or intellectual disability in offspring.

Funding, competing interests, data sharing Supported by the National Institutes of Health, Beatrice and Samuel A Seaver Foundation, Fredrik and Ingrid Thuring Foundation, and Swedish Society of Medicine. All authors declare no competing interests. No additional data are available.



Three mutually exclusive exposure groups were created in the study: children born to fathers receiving antidepressant treatment during the conception period; children born to fathers receiving no antidepressant treatment during the conception period (A) but who started treatment during the pregnancy period only (B); and children born to fathers not receiving antidepressant treatment during the conception period or pregnancy period

Tighter prescribing regulations drive illicit opioid sales

ORIGINAL RESEARCH Interrupted time series analysis

Effect of restricting the legal supply of prescription opioids on buying through online illicit marketplaces

Martin J, Cunliffe J, Décary-Hétu D, Aldridge J
Cite this as: *BMJ* 2018;361:k2270
Find this at: http://dx.doi.org/10.1136/bmj.k2270

Study question What was the effect of the supply side intervention of rescheduling of hydrocodone combination products by the US Drug Enforcement Administration in October 2014 on illicit sales through online markets (cryptomarkets)?

Methods Using web crawling software the authors collected data from 31 of the world's largest cryptomarkets operating from October 2013 to July 2016. The main outcome measures were the illicit sales and availability of prescription opioids (eg, oxycodone, hydrocodone, fentanyl, tramadol), prescription sedatives, prescription steroids, prescription stimulants, and illicit opioids (heroin, kratom, and opium). The study included descriptive analysis and an interrupted time series analysis comparing sales within and outside the USA.

Study answer and limitations The trade in prescription opioids through US cryptomarkets increased immediately after the schedule change, with no statistically significant changes in other drug categories. In July 2016 sales of opioids through US cryptomarkets represented 13.7% of all drug sales (95% confidence interval 11.5% to 16.0%) compared with a modelled estimate of 6.7% of all sales (3.7% to 9.6%) had the new schedule not been introduced. This corresponds to a 4 percentage point yearly increase in the amount of trade that prescription opioids represent in the US market, set against no corresponding changes for comparable products or for prescription opioids sold outside the US. The study also found substantial increases in the illicit trade of fentanyl through cryptomarkets between 2014 and 2016, from 2.5% of prescription opioid sales to 21.6% by the end of the study period. The authors cannot, however, rule out contemporaneous factors that might have accounted for the observed increases in sales of illicit opioids.

COMMENTARY The predictable consequence of cutting supply without tackling demand

Overdoses claimed 63 632 lives in the US in 2016, and two thirds of deaths involved opioids.[1] During the first decade of the US crisis, prescription opioids contributed to most fatalities. As opioid prescribing rates fell after 2010, deaths involving heroin—and more recently, fentanyl—have skyrocketed. Even as opioid prescribing has reached its lowest level in a decade, these less expensive, more available, and highly potent illicit market alternatives continue to drive the surge in fatal poisonings,[2 3] with prescription opioids now contributing to only one in four overdose deaths.[1 4]

Policies that suppress access to prescription opioids without reducing demand are known to fail. In a linked paper, Martin and colleagues[5] consider the unintended consequences of one such supply side intervention, the 2014 rescheduling of hydrocodone combination products from schedule III to schedule II by the US Drug Enforcement Administration.[6] This seemingly obscure regulatory shift has far reaching consequences. Patients can only obtain refills for a schedule II drug through a visit in person to their provider and pharmacist, creating barriers to medication access that disproportionately affects individuals with limited mobility and those in rural areas. Schedule II prescribing and distribution practices also receive closer scrutiny by state and federal regulators, chilling access across the board.[7]

> Attempts to disrupt darknet sales are likely to cause an endless game of "whack-a-mole"

Spike in darknet sales

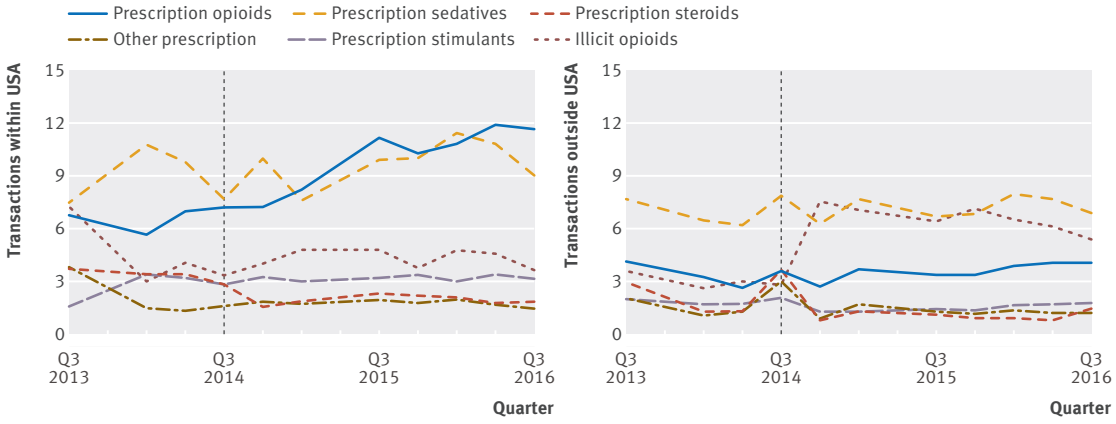
Predictably, prescriptions for hydrocodone combination products decreased markedly after the 2014 rescheduling.[8] Martin and colleagues found, however, that darknet sales of prescription opioids spiked.

The darknet, an encrypted network built on top of the existing internet accessible only through specially configured software that allows users to remain anonymous, is host to numerous illicit online marketplaces ("cryptomarkets") that match buyers and sellers of illicit goods, including scheduled substances.[9] This analysis illustrates the unintended but foreseeable consequences of supply side interventions concerning drugs.

Given the historical over-reliance on law enforcement to solve American addiction crises,[12] the current federal response to rising cryptomarket opioid sales is unsurprising; the US Department of Justice recently announced it is doubling resources allocated to combating drug sales through the darknet. This approach is unlikely to succeed. When large cryptomarkets are shut down, the number of online sellers drops temporarily but then rapidly recovers and marketplaces fragment.[13] Attempts to disrupt darknet sales are therefore likely to cause an endless game of "whack-a-mole" in which new cryptomarkets surface to replace old ones, and sellers and buyers simply migrate from one site to another.

Demand for opioids in the US will decrease sustainably only when high quality, evidence based prevention and treatment programmes are broadly implemented, robustly funded, and universally accessible. Several youth prevention programmes have been shown to reduce the incidence of substance use problems and deserve widespread investment (see http://samhsa.gov/nrepp). Standard-of-care addiction treatment that

Scott E Hadland
scott.hadland@bmc.org
Leo Beletsky
See bmj.com for author details



Percentage of all illicit drug transactions via cryptomarkets from within the United States and elsewhere by drug category, for third quarter 2013 to third quarter 2016

What this study adds The scheduling change coincided with a statistically significant, sustained increase in illicit trading of prescription opioids on cryptomarkets in the US. Such changes were not observed for other drug groups or in other countries. A move was observed towards the purchase of more potent forms of prescription opioids, particularly oxycodone and fentanyl.

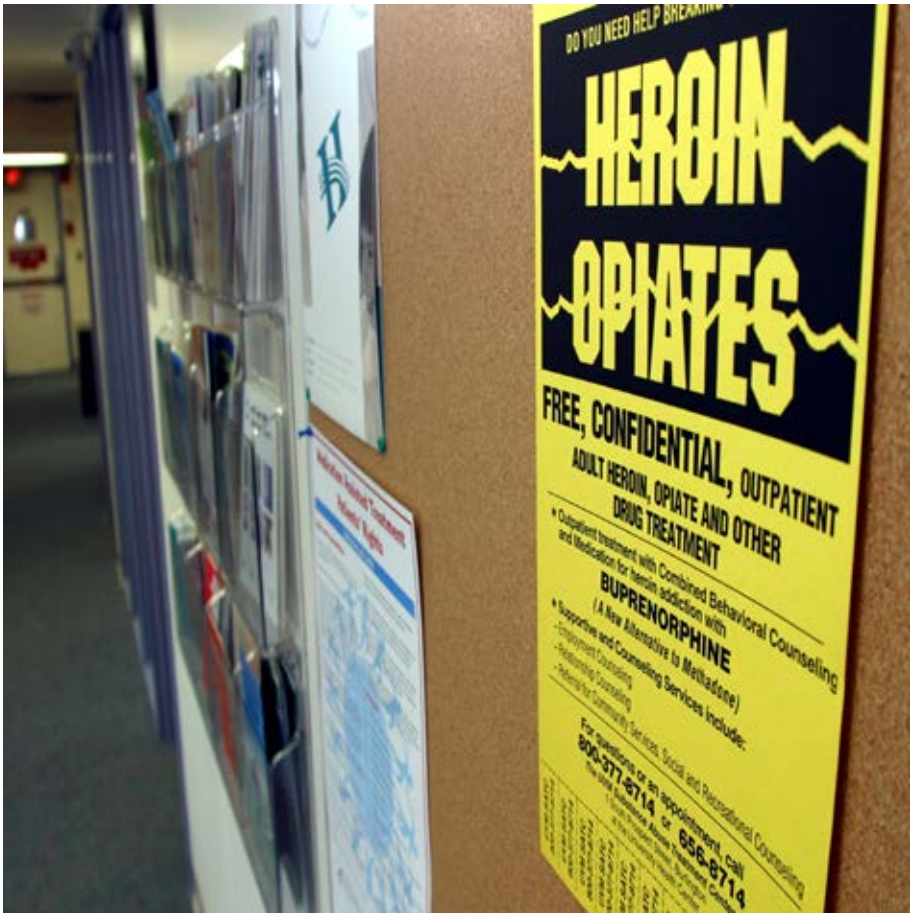
Funding, competing interests, data sharing See the full paper on bmj.com for details of funding. No competing interests declared. No additional data available.

includes buprenorphine, methadone, or naltrexone—drugs that promote and sustain recovery—should be available throughout healthcare and criminal justice systems. Harm reduction services, including syringe exchanges, overdose education, naloxone distribution, and safe injection facilities, are also needed to prevent overdose and facilitate health improvement.

The work by Martin and colleagues reminds us that even as policy makers pursue additional regulatory approaches to reduce opioid prescribing, the overdose crisis will likely worsen so long as supply side interventions are not coupled with evidence based measures to cut demand and reduce harm. More fundamentally, this analysis raises questions about drug scheduling as a tool of public health regulation. The US scheduling scheme inexplicably holds such disparate substances as cannabis, heroin, and psilocybin to be equally dangerous. It is high time to rethink how, why, and when this regulatory framework is deployed to curb drug related harms.

Cite this as: *BMJ* 2018;361:k2480

Find the full version with references at http://dx.doi.org/10.1136/bmj.k2480



Effects on abstinence of nicotine patch treatment before quitting smoking

The Preloading Investigators

Cite this as: *BMJ* 2018;361:k2164
Find this at: http://dx.doi.org/10.1136/bmj.k2164

Study question Does using a nicotine patch for four weeks while smoking as usual before attempting to quit help people achieve long term abstinence from smoking?

Methods The study population comprised adults aged 18 years or more who smoked daily, showed signs of tobacco dependence, and sought help to overcome this dependence. People were randomised to prepare for a quit attempt but smoke as usual for four weeks either wearing a 21 mg nicotine patch (preloading arm, n=899) or receiving standard smoking cessation pharmacotherapy and a behavioural intervention of comparable intensity (control arm, n=893). The primary outcome was biochemically confirmed prolonged abstinence at six months. The authors recorded adverse events during the period of preloading.

Results for abstinence at six months, defined by Russell standard criteria*

Effect	Adjusted effect size† (95% CI)	P value	Adjusted effect size‡ (95% CI)	P value
Estimated risks	17.5% preloading arm, 14.4% control arm			
Risk ratio	1.21 (0.98 to 1.50)	0.08	1.27 (1.03 to 1.57)	0.03
Risk difference	3.02 (-0.37 to 6.41)	0.08	3.80 (0.41 to 7.18)	0.03

*Involves a grace period of two weeks after quit day, when lapses do not count against abstinence.
†Adjusted for research centre—primary analysis.
‡Adjusted for research centre, previous longest abstinence, baseline strength of urges to smoke, and varenicline prescribed at one week after quit day (six weeks after baseline).

Study answer and limitations No strong evidence was found that preloading led to increased abstinence. Biochemically validated abstinence at six months was achieved by 157 (17.5%) participants in the preloading arm and 129 (14.4%) in the control arm: difference 3.0% (95% confidence interval −0.4% to 6.4%). The beneficial effect may have been masked by a concurrent reduction in the use of varenicline in people using nicotine preloading, and future studies should explore ways to mitigate this unintended effect. Preloading appeared safe: eight serious adverse events occurred in each arm.

What this study adds With current UK guidelines, use of a nicotine patch before quitting is unlikely to increase the proportion of people who stop smoking in the long term. With changes to guidelines and advice to smoking cessation services, however, it may lead to a worthwhile increase in smoking abstinence.

Funding, competing interests, data sharing This trial was funded by the National Institute for Health Research Health Technology Assessment 09/110/01. GlaxoSmithKline donated nicotine patches to the National Health Service in lieu of NHS treatment costs. The authors will share data that is in the interests of public health and provided they have not planned similar analyses
Trial registration Current Controlled Trials ISRCTN33031001.