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Fentanyl: the many challenges ahead.

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### Authors

Mars, Sarah G  
Rosenblum, Daniel  
Ciccarone, Daniel

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## Fentanyl: the many challenges ahead

*Addressing the challenges presented by illicitly produced fentanyl will require bold, evidence-based policies instead of recycling the stale strategies that have failed. While some approaches are already known to protect or improve health, further research and international data sharing will be needed as the epidemic continues to develop.*

We welcome the insights, comments and recommendations of all the respondents to our earlier published report [1–4]. We agree fully with Dr Wakeman's assessment that further crackdowns on the fentanyl supply would probably have disastrous effects on opioid users, favoring the more potent, more concealable analogs. Rather than offering strategies to resolve the current fentanyl problem, the existing system of global prohibition is probably its cause, and it is time to consider alternative remedies. In Portugal, drug possession and acquisition have become civil rather than criminal offences and an evidence-based drug strategy has been introduced to prevent drug use, expand treatment for dependence and dissuade others from continued use. This has shown encouraging results, and deserves further study as a possible paradigm [5,6].

Dr Bisaga makes many excellent points about the challenges fentanyl presents to existing opioid treatment modalities and the need for more empirical data for their revision. Buprenorphine induction is known to precipitate withdrawal among people who are opioid-dependent but the protracted withdrawal from short-acting fentanyl use reported by Dr Bisaga is puzzling. Research among active heroin injectors has found that, while some experience suspected fentanyl as having a short duration of effect, others report it lasting for many hours, even in cases of high opioid tolerance [7]. Further studies of illicitly manufactured fentanyl pharmacodynamics, including analogs, mixtures, adulterants and contaminants, are needed to understand this apparent contradiction. A modified Zurich or Bernese method, utilizing microdoses of buprenorphine while tapering full agonist opioids [8], appears promising. Research on full agonist substitution therapies, e.g. using hydromorphone, as well as those with a longer pedigree, such as heroin maintenance therapy, should also be pursued [9].

We strongly concur with Mounteney and colleagues that surveillance, along with international data sharing, are essential for perceiving the commonalities and differences in the global fentanyl epidemic [10]. In dividing these into macro regions, however, we would take issue with the North American/European split. It is certainly the case that Europe and the United States differ in their health-care arrangements, treatment services and opioid supplies, but Canada also presents some contrasts with

the United States. Like the United States, Canada's opioid pill prescribing has outstripped the rest of the world, but it has different heroin sources and a system of universal health-care, although less comprehensive than in some European countries. Canada also has progressive harm reduction and treatment policies, including more than 25 supervised consumption sites and government-approved prescription of heroin for the treatment of opioid use disorder.

We agree that diverted pharmaceutical fentanyl presents a different case to fentanyls that are illicitly manufactured. Pharmaceutical fentanyl, often in the form of patches, is easily identifiable, so users' demand can play an active role in the market. However, the replacement of heroin by illicitly manufactured fentanyl in its disguised form, regardless of whether heroin's demand is high in the United States or low in Europe, is a further piece of evidence that the switch to illicitly produced synthetics is driven by supply factors and not by demand.

### Declaration of interests

D.C. reports consultant fees from Mallinckrodt Pharmaceuticals and Nektar Therapeutics outside the submitted work.

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SARAH G. MARS<sup>1</sup> , DANIEL ROSENBLUM<sup>2</sup> & DANIEL CICCARONE<sup>1</sup>

*Department of Family and Community Medicine, University of California, San Francisco, CA, USA<sup>1</sup> and Department of Economics, Dalhousie University, Halifax, Canada, NS, B3H 4R2<sup>2</sup>*  
E-mail: sarah.mars@ucsf.edu

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