

# Letters

## RESEARCH LETTER

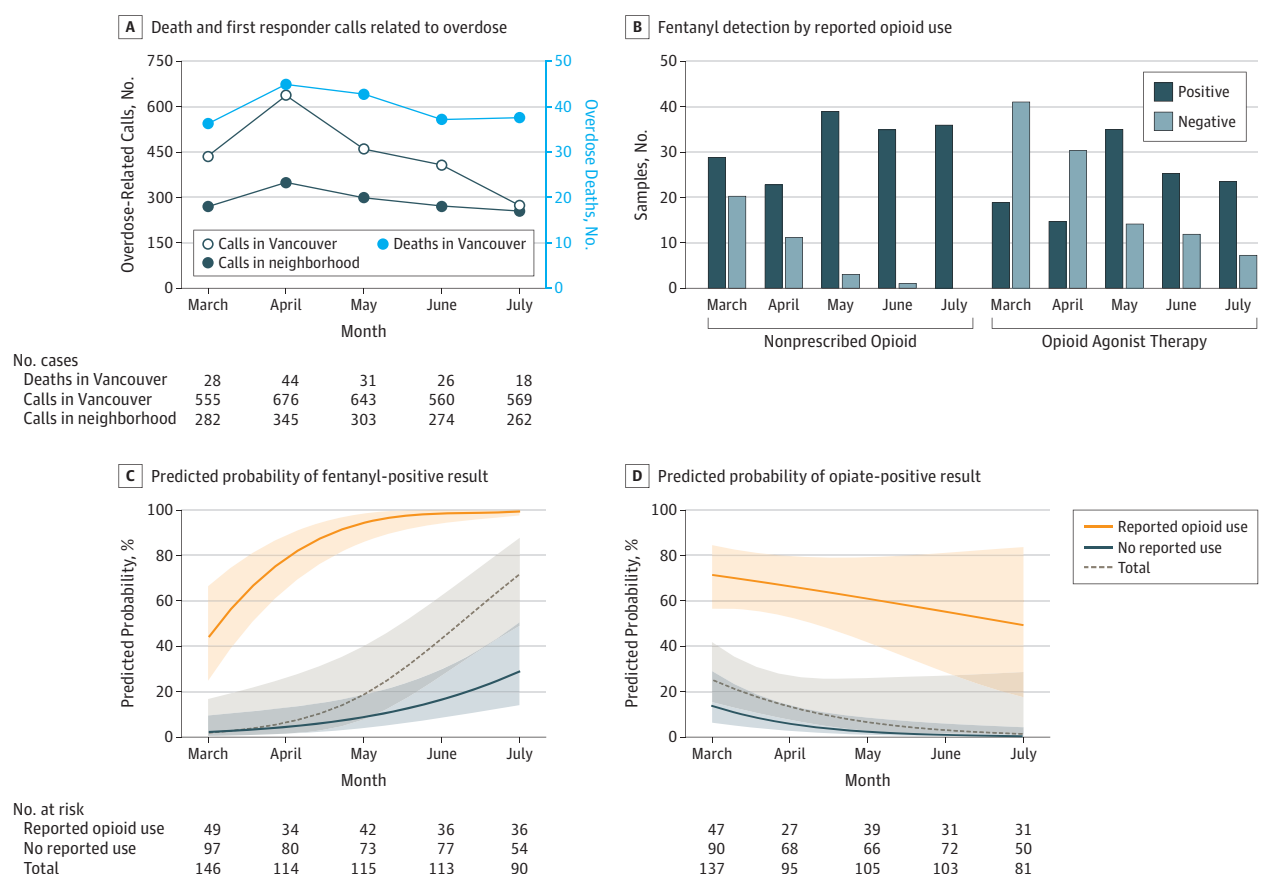
### Rapid Change in Fentanyl Prevalence in a Community-Based, High-Risk Sample

Planning for the implications of nonprescribed fentanyl use relies on multisource forensic<sup>1,2</sup> or clinical samples.<sup>3,4</sup> Complementing these descriptions, we report a prospective longitudinal study of change in urine fentanyl prevalence in a high-risk, community-based sample.<sup>5</sup>

**Methods** | Directly assessed participants were from a health outcomes study of people living in an impoverished neighborhood of Vancouver, Canada.<sup>5</sup> For context, overall over-

dose deaths (Vancouver) and first responder calls (Vancouver and neighborhood-specific) were obtained from the British Columbia Coroner's Office and Vancouver Police and Fire statistics for the study period (March 1 to July 31, 2017). Participants attended monthly visits and reported prescribed and nonprescribed drug use during the previous week, including fentanyl, buprenorphine, codeine, heroin, hydromorphone, methadone, morphine, and oxycodone. Participants (N = 237) contributed 595 urine samples that were tested for fentanyl/norfentanyl, opiates (morphine, heroin, and codeine), and methadone using detection strips (BTNX Inc). Agreement between reports and detection was assessed by  $\kappa$  statistic. Repeated measures logistic mixed-

Figure. Community-Based Studies of Fentanyl From March 1 to July 31, 2017



The British Columbia Coroner's Office reports of overdose deaths in Vancouver and overdose calls to first responders (police and fire department) for Vancouver and for the neighborhood from which participants were recruited (A). Numbers of urine samples with fentanyl detected are shown for participants using nonprescribed opioids and for those taking prescribed opioid agonist therapy (B). The probability of urine samples being positive for fentanyl (C) or opiates (heroin, morphine, or codeine) (D) changed during a 5-month

period and differed according to reported use of nonprescribed opioids in the week before urinalysis. Samples were tested for fentanyl/norfentanyl (sensitivity 10 ng/mL, with cross-reactivity for acetylfentanyl, butyrylfentanyl, carfentanyl, fluorofentanyl, 4-fluoroisobutyryl fentanyl, furanylfentanyl, 3-methylfentanyl, sufentanil, and thiofentanyl) and for opiates (heroin, morphine, and codeine). Shading represents the 95% confidence interval.

**Table. Factors Associated With Changes in Urine Fentanyl and Opiate Detection in Nonprescribed Opioid Users Between March and July 2017**

Characteristic	Unadjusted Models		Model 1 <sup>a</sup>		Model 2 <sup>b</sup>	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
<b>Urine fentanyl detected (n = 229 individuals; 575 observations)</b>						
Time, mo	2.28 (1.61-3.23)	<.001	3.31 (1.66-6.58)	<.001	2.05 (1.30-3.24)	.002
Intercept						
Age, y	0.92 (0.85-0.99)	.02	0.91 (0.84-0.98)	.02	0.98 (0.94-1.02)	.29
Female	5.22 (0.91-30.05)	.06	6.63 (1.03-42.62)	<.05	1.89 (0.72-4.97)	.19
Nonprescribed opioid use	30.64 (7.36-127.64)	<.001	NA	NA	34.47 (7.27-163.43)	<.001
Slope						
Nonprescribed opioid use	2.49 (1.20-5.18)	.01	NA	NA	2.34 (1.11-4.93)	.03
<b>Urine opiate<sup>c</sup> detected (n = 215 individuals; 518 observations)</b>						
Time, mo	0.32 (0.15-0.69)	.003	0.46 (0.19-1.11)	.08	0.39 (0.21-0.74)	.004
Intercept						
Age, y	1.00 (0.96-1.04)	.87	0.99 (0.95-1.04)	.76	1.01 (0.98-1.05)	.44
Female	3.39 (0.93-12.31)	.06	3.49 (0.92-13.28)	.07	2.16 (0.86-5.41)	.10
Nonprescribed opioid use	14.24 (6.07-33.39)	<.001	NA	NA	15.89 (4.09-61.71)	<.001
Slope						
Nonprescribed opioid use	2.21 (1.01-4.85)	<.05	NA	NA	2.01 (0.90-4.51)	.09

Abbreviations: NA, not applicable; OR, odds ratio.

<sup>a</sup> Fixed effect of time in the whole cohort, adjusting for age and sex.

<sup>b</sup> Fixed effects of nonprescribed opioid use on baseline and rate of change of detection over time, adjusting for age, sex, and time. To test for the possible effects of missing data, we examined associations between predictor and

outcome measures and the number of visits made. There were no significant associations. The analysis was rerun 5 times with multiple imputation to assess the possible effects of missing visits; the OR and P values were similar.

<sup>c</sup> Detected opiates included morphine, heroin, and codeine.

effects models with random intercept and slope were used to estimate associations between detection and reported opioid use in the prior week. Fixed effects of recent nonprescribed opioid use over time were estimated adjusting for age and sex. The study was approved by the institutional review boards at the University of British Columbia and Simon Fraser University, and participants provided written informed consent.

**Results** | Between March and April 2017, an upsurge occurred in overdose deaths and first responder calls (Figure, A). Directly assessed participants had a mean (SD) age of 46.4 (12.2) years, were mostly men (184 of 237 [78%]), and were marginally housed or street homeless. Participants had a mean education of 10.2 years. Injection drug use in the past week was reported by 110 of 231 participants (48%). During the 5-month period, nonprescribed opioid use was reported by 91 of 237 individuals (38%), including 57 of 103 individuals (55%) who were prescribed opioid agonist therapy (hydromorphone, methadone, buprenorphine, morphine, or heroin). Fentanyl was detected in 229 of 590 urine samples (39%), including 116 of 222 samples (52%) from participants prescribed opioid agonist therapy (Figure, B). Overall, 83 of 91 participants (91%) reporting nonprescribed opioid use had at least 1 fentanyl-positive sample; 15 of these 83 (18%) reported taking fentanyl (11 of whom reported daily use). Opiates were detected in 196 of 581 urine samples (34%). Agreement between self-report and detection was low for fentanyl ( $\kappa = 0.12$ ) and moderate or greater for other opioids

( $\kappa$  range, 0.54-0.84). The probability of fentanyl detection doubled each month (odds ratio, 2.28;  $P < .001$ ) (Figure, C and Table). With self-reported nonprescribed opioid use, fentanyl detection probability was greater (odds ratio, 34.47;  $P < .001$ ) and increased at a faster rate over time (odds ratio, 2.34;  $P = .03$ ). In contrast, opiate detection decreased over time (odds ratio, 0.32;  $P = .003$ ) (Figure, D and Table). By July 2017, all samples from participants reporting nonprescribed opioid use were fentanyl-positive.

**Discussion** | Fentanyl-positive urine samples increased rapidly during a 5-month period while opiate-positive samples declined. In Vancouver, as elsewhere,<sup>6</sup> the initial phase of the opioid epidemic was associated with diverted pharmaceuticals. This changed as nonpharmaceutical fentanyl entered the market as a heroin additive. The low concordance between reported fentanyl use and detection is consistent with unawareness of exposure. In the early months, as fentanyl-positive samples rapidly increased in the participants, an increase in overdose calls to first responders occurred in the neighborhood, and fatal overdoses increased city-wide. Some amelioration occurred by July 2017 when fentanyl-positive urine samples were ubiquitous among participants reporting nonprescribed opioid use. Tolerance to the adverse effects of higher potency opioids may be developing among users, as some individuals report actively seeking fentanyl.<sup>6</sup> Fentanyl was detected in half of the participants in opioid agonist therapy programs in our study, which raises concern for increasing tolerance.<sup>3</sup> Our fentanyl assay

demonstrates cross-reactivity with other fentanyl analogues. Rapid and specific tests for fentanyl and related analogues are urgently needed, along with innovative treatments.

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**Study concept and design:** Jones, Panenka, Barr, MacEwan, Thornton, Honer.  
**Acquisition, analysis, or interpretation of data:** Jones, Jang, Panenka, Barr, Thornton, Honer.

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## COMMENT & RESPONSE

### Corollary Discharge and Psychosis—Origin of the Model

**To the Editor** I recognize that an educational review cannot include exhaustive citations. However, I believe that these articles could briefly acknowledge the origin of their major ideas. The review by Poletti et al<sup>1</sup> in *JAMA Psychiatry* on abnormal corollary discharge and psychosis cites only relatively recent articles. The idea that corollary discharge mechanisms exist in the control systems of thought was first proposed in 1978.<sup>2</sup> At the levels of consciousness, these mechanisms would distinguish endogenous from environmentally stimulated mental activity. The 1978 article<sup>2</sup> outlined the reasoning and evidence pointing to the operation of corollary discharge feed-forward systems at the highest sensory-motor levels (in the conceptualization by John Hughlings Jackson, FRS). It illustrated how impairment of such mechanisms would produce many psychotic symptoms, including auditory hallucinations, thought control, and other confusions of self and agency.

These ideas were further developed with the late Mario Guazzelli, MD, in the *British Journal of Psychiatry* in 1999<sup>3</sup> in which we also implicated abnormal basal ganglia planning systems in the establishment of delusions. In 2011, I emphasized that dreaming offers a research opportunity to study altered consciousness (and its brain mechanisms) when corollary discharge systems are reversibly disabled in individuals without brain abnormalities; impaired corollary discharge systems could be the biological link that underlies the historically recognized similarities of madness and dreaming.<sup>4</sup>

Poletti et al<sup>1</sup> also speculate that the defect in corollary discharge systems emerges during neurodevelopment. This possibility was specifically noted in an article<sup>5</sup> that proposed that (1) the human brain undergoes a profound reorganization during adolescence driven by synaptic pruning and (2) defects in this late maturational process might cause mental illness (notably schizophrenia) by impairing corollary discharge control systems.<sup>5</sup> I think the article by Poletti et al<sup>1</sup> would have been even more valuable, especially for students, if it had touched on this intellectual history, which is not hopelessly remote because each of the articles cited here is easily retrievable. Moreover, each contains some unexplored research suggestions that are still relevant.

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