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Commentary

# Fentanyl self-testing outside supervised injection settings to prevent opioid overdose: Do we know enough to promote it?

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ABSTRACT

Since 2013, North America has experienced a sharp increase in unintentional fatal overdoses: fentanyl, and its analogues, are believed to be primarily responsible. Currently, the most practical means for people who use drugs (PWUD) to avoid or mitigate risk of fentanyl-related overdose is to use drugs in the presence of someone who is in possession of, and experienced using, naloxone. Self-test strips which detect fentanyl, and some of its analogues, have been developed for off-label use allowing PWUD to test their drugs prior to consumption. We review the evidence on the off-label sensitivity and specificity of fentanyl test strips, and query whether the accuracy of fentanyl test strips might be mediated according to situated practices of use. We draw attention to the weak research evidence informing the use of fentanyl self-testing strips.

This journal has drawn attention to the urgent need for developing harm reduction interventions in response to the harm producing effects of fentanyl in the heroin supply, which are linked to appreciable increases in rates of opioid overdose in some settings (Ciccarone, 2017). Fentanyl and its analogues (*i.e.* fentanyls) are linked to the significant increase in fatal opioid overdoses in North America since 2013 (United Nations Office on Drugs and Crime, 2017b). Despite widespread media attention, and repeated public health alerts, fatal overdoses continue to rise (Seth, Scholl, Rudd, & Bacon, 2018; Special Advisory Committee on the Epidemic of Opioid Overdoses, 2018). In 2016, 19,413 people died from unintentional overdoses involving synthetic opioids other than methadone in the United States, representing a two fold increase from 2015 (Seth et al., 2018). In Canada, there were 2,946 opioid-related deaths in 2016. Preliminary data indicate that 2,923 people died of opioid-related overdose between January and September 2017, with 72% of these involving fentanyl or fentanyl analogues (compared to 55% in 2016) (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2018). Fentanyl-related overdoses have also been documented throughout Europe, as well as in Asia, North Africa, and Oceania (United Nations Office on Drugs and Crime, 2017a). Since 2014, six fentanyl variations have been identified in the UK drug market, with a spate of overdoses attributed to fentanyl occurring in the North East of England in 2017 (BBC, 2017; Bryant, 2017). The case for a rapid harm reduction response is self-evident (Ciccarone, 2017). Calls have been made for upscaling community-based overdose prevention interventions, especially the peer distribution of naloxone, alongside the development of drug checking and drug testing interventions designed to detect the presence of fentanyl in the drug supply (Ciccarone, 2017; Fairbairn, Coffin, & Walley, 2017). In this commentary, we consider the feasibility and acceptability of drug testing strips as a means for users to self-minimise their overdose risk related to unintentional fentanyl use. We endorse the need to act urgently, yet note that self-testing interventions are not without risk or uncertainty.

## Fentanyl and overdose risk

Fentanyl is estimated to be 50–100 times 'stronger' than morphine (Centers for Disease Control and Prevention, 2018). Public health messaging commonly references the relative potency by weight of fentanyl compared to morphine despite the fact that opioid equianalgesic conversion tables are both variable and inconsistent (Centers for Disease Control and Prevention, 2018; Shaheen, Walsh, Lasheen, Davis, & Lagman, 2009). Lethality, rather than potency, is a more reliable risk indicator; however, there is currently no standard or comparable measure of acute fentanyl lethality in humans. The median lethal dose (LD50) for fentanyl in rats is 3.1 mg/kg, compared to 22.5 mg/kg for heroin, suggesting a seven-fold increase in toxicity – though the relative lethality in rats may not equate to the relative

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lethality in humans (International Programme on Chemical Safety (INCHEM), 2017; National Center for Biotechnology Information, 2017a). Despite the lack of certainty about the relative strength of fentanyl, it is incontrovertible that fentanyl (and many of its analogues) is lethal at much lower doses than other opioids, and is significantly more potent by weight when compared to heroin.

The increase in fatal overdoses since 2013 has been largely attributed to the use of heroin adulterated with non-pharmaceutical fentanyls and, to a lesser extent, diverted pharmaceutical fentanyl (Daniulaityte et al., 2017; Gladden, Martinez, & Seth, 2016; Massey et al., 2017; Seth et al., 2018; United Nations Office on Drugs and Crime, 2017b). Illegally produced fentanyls provide a potent, low-cost and low-bulk synthetic opioid – attractive as an addition to high-cost and/or low-purity heroin. It is posited that restrictions in the heroin supply due to Taliban control of opium production have contributed to the most recent influx of fentanyl-contaminated heroin into Europe (Mounteney, Giraudon, Denissov, & Griffiths, 2015). Nearly all of the fentanyl entering the United States originates in either China or Mexico (United States Drug Enforcement Administration, 2017). Most of the heroin in the US comes from Mexico and is both inexpensive and of relatively high purity; thus, the motivation for introducing fentanyls to the US heroin market is unclear (United States Drug Enforcement Administration, 2016).

The contamination of illegal drugs, such as heroin, with fentanyl makes it difficult for even the most experienced drug user to anticipate and mitigate the likelihood of overdose. Those with less experience, who are often most vulnerable to overdose, are less likely to consume drugs in the company of those who have experience of, and access to, naloxone (Frank et al., 2015; Neira-Leon et al., 2011). Despite the effectiveness of naloxone in reversing opioid overdose (Clark, Wilder, & Winstanley, 2014), US states and many Canadian provinces have been slow to facilitate naloxone distribution and actively endorse its use (Cressman et al., 2017; Human Rights Watch, 2017).

Fentanyl is often implicated as the cause of excess fatal overdoses; however, fentanyl analogues are thought to be contributing (either alone or in combination with fentanyl) to a significant proportion of these deaths (United Nations Office on Drugs and Crime, 2017b). Evidence from a sero-survey of unintentional fatal overdoses in Ohio showed the presence of multiple fentanyl analogues among fentanyl-positive decedents including: acrylfentanyl, carfentanil, and furanylfentanyl (Daniulaityte et al., 2017). In a recent report of fentanyl-related deaths across 10 US states, fentanyl analogs were detected in toxicology from 720 (14%) of 5,152 opioid overdose deaths including: carfentanil (in 389 deaths, 7.6%), furanylfentanyl (in 182 deaths, 3.5%), and acetylfentanyl (in 147 deaths, 2.9%) (O'Donnell, Halpin, Mattson, Goldberger, & Gladden, 2017). Fentanyl analogues are not always included in toxicological tests, and are often difficult to detect, suggesting that toxicological surveys may underestimate their occurrence (O'Donnell et al., 2017).

In March 2017, the UN Commission on Narcotic Drugs, in an attempt to curb illegal manufacturing, scheduled two fentanyl precursors and a fentanyl analogue, bringing them within the ambit of the UN drug treaty control framework (United Nations Office on Drugs and Crime, 2017a). There is little indication that supply-side controls will have an impact on availability; rendering harm reduction initiatives, largely in the form of risk reduction messaging, the primary means through which people who use drugs (PWUD) can mitigate their risk. Risk reduction advice includes not using drugs alone, taking a 'test hit' or smoking (of brown heroin) a sample of drugs before injecting, and ensuring that naloxone is available for bystander administration (Australian Injecting & Illicit Drug Users League, 2013; Ciccarone, 2017; Release, 2017; Toward the Heart, 2018). Health Canada actively encourages PWUD to consume drugs at a supervised injection facility (Health Canada, 2017). Supervised injection facilities have contributed to population-level reductions in fatal overdose (Marshall, Milloy, Wood, Montaner, & Kerr, 2011), and offer potential in reducing fentanyl-related overdose (Ciccarone, 2017).

Recently, there have been calls for promoting point-of-use drug testing as a means of detecting fentanyl to prevent unintentional fentanyl use and related overdose risk (Harris, 2017; Stewart, 2017; Vancouver Coastal Health, 2017a, 2017b). Fentanyl self-test strips (*i.e.* lateral flow immunochromatographic assays), when dipped into a solution containing dissolved drugs, can indicate the presence of fentanyl. As the test strips have only recently become available we are faced with a considerable amount of uncertainty regarding the evidence in support of their use, and their potential to reduce fentanyl overdose risk. Specifically, what do we know of their sensitivity, specificity, availability, and feasibility, including harm-reducing relative to harm-producing potential? Crucially, do we know enough to act, to upscale the promotion and distribution of self-testing interventions among opioid users? We emphasise the critical importance of integrating self-testing interventions inside a broader package of harm reduction intervention and support.

## Testing for fentanyl and fentanyl analogues

In Canada, fentanyl test strips are licensed as an *in vitro* diagnostic medical device for urinalysis and, as such, may only be sold directly to laboratories or health care professionals. However, the same test strips are also sold as a forensic test and can thus be used, off-label, to test drugs dissolved in solution. Forensic tests do not require licensing and may be lawfully sold to anyone. On 7 July, 2016, Vancouver Coastal Health began an evaluation of the off-label application of the test strips at the Insite Supervised Injection Site (Stewart, 2017). The evaluation found that 86% of all drug samples (including heroin, cocaine, *etc.*), and 90% of the 'heroin' samples, tested positive for fentanyl (Vancouver Coastal Health, 2017a, 2017b). This may be an overestimate, however, as most of the checks (62%) were performed post-consumption, and it is likely that PWUD may be more inclined to test drugs about which they have become suspicious (Lysyshyn, Dohoo, Forsting, Kerr, & McNeil, 2017; The Vancouver Sun, 2017). It also raises concerns about the potential excessive sensitivity of urinalysis tests when used off-label with drug solution. Currently, "[the test strips] could possibly pick up levels of fentanyl that are well below psychoactive doses from the air or contamination of powder during handling in the supply chain" (Exchange Supplies, 2018). A high frequency of positive test results, particularly when received post-consumption with no associated ill-effects, can lead to complacency, limit risk-reduction measures, and may impact testing acceptability among users.

In November 2017, Judy Darcy, Minister of Mental Health & Addictions, announced that the Ministry is expanding the use of fentanyl test strips to all supervised injection sites in British Columbia (CBC News, 2017). Formalised initiatives to promote fentanyl test strips appear to be limited to supervised facilities. Caution about the sensitivity and specificity of off-label use is reflected in Health Canada's recent warning that: "[s]ome individuals and organizations are using test strips to detect fentanyl by dissolving a small amount of drugs in a solution. These test strips have not been designed for direct use by consumers in this way, which could lead to false negative results" (Health Canada, 2017). As noted above, false positives – or positive results at below psychoactive dosage levels, may also have detrimental impact.

Clear evidence on the sensitivity and specificity of fentanyl test strips when used off-label is crucial for informing associated harm reduction strategies. BNTX Inc, the manufacturer of the test strips used in Vancouver, report that the strips are > 98% accurate at detecting fentanyl in urine (BTNX Inc, 2017). The potential for low specificity regarding psychoactive dose and associated toxicity is not addressed. The test strips are apparently able to detect, "many other fentanyl analogues such as carfentanil, acetylfentanyl, butyrylfentanyl, 3-methylfentanyl, ocfentanil, [and] sufentanil" (BTNX Inc, 2017). The recent Fentanyl Overdose Reduction Checking Analysis Study (FORECAST) compared the BTNX fentanyl testing strips, to a Raman spectroscopy (i.e. TruNarc)