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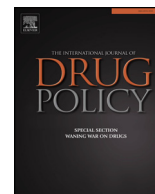
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## Commentary

## 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, Denisov, & 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 (BNTX 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, ofentanil, [and] sufentanil" (BNTX Inc, 2017). The recent Fentanyl Overdose Reduction Checking Analysis Study (FORECAST) compared the BNTX fentanyl testing strips, to a Raman spectroscopy (i.e. TruNarc)

machine, and a Fourier-transform infrared spectroscopy (i.e. Bruker Alpha) machine (Johns Hopkins Bloomberg School of Public Health, 2018). The study set out to determine the detection limit, sensitivity, and specificity of the three technologies. The preliminary data from the study indicate that the self-test strips, when used for off-label testing, and compared to the other two technologies, had the lowest detection limit (0.13 mg/ml) and the highest sensitivity (96% and 100% for the respective test sites) and specificity (90% and 98%) for fentanyl. The test strips were also successful in identifying fentanyl analogues (acetylfentanyl, furanylfentanyl, and furanylfentanyl in combination with heroin) (Johns Hopkins Bloomberg School of Public Health, 2018). Additional evaluation of these strips conducted by DanceSafe and the University of California San Francisco found that they performed better than other test strips on the market and detected most fentanyl analogues, including carfentanil at “miniscule concentrations” (DanceSafe, 2017). However, a preliminary study of the efficacy of the test strips found that seven out of 70 drug samples tested returned erroneous or invalid results leading Health Canada to limit its endorsement of drug-checking services to approved supervised consumption sites only, “where individuals have access to personnel who are trained in overdose response” (Health Canada, 2017; Ireland, 2017).

Health Canada’s response may appear to be overly cautious, given the 90% accuracy of the test strips and the critical need to respond to high rates of fatal overdose. The frequency of drug use among PWUD with a high tolerance (who may inject up to six times a day) may, however, render this relatively high accuracy problematic. It is unclear also whether sensitivity and specificity might differ according to the situated practices of fentanyl test strip use. Drug preparation practices differ geographically – determined, in part, by the type of heroin available (Ciccarone & Harris, 2015). It is unknown whether the use of acidifiers in drug preparation will affect test accuracy. The solution into which drugs are dissolved has been shown to reduce the accuracy of reagent tests (Quest & Horsley, 2007). This is important in the European context, where brown (base) heroin requires citric acid, vitamin C, or another acidifier to prepare it for injection. Situated practices of street injection, where drug preparation is often – of necessity – more hurried and constrained, may also impact test strip acceptability and use (Rhodes et al., 2007). The two to five minutes required for the test result to register might, for example, be an impossibility in a street injecting situation or for those experiencing acute withdrawals.

Despite these uncertainties, and a lack of peer-reviewed evidence to date about the efficacy and effectiveness of self-testing in fentanyl overdose prevention, test strips are becoming increasingly available for home use. The test strips are distributed by various harm reduction agencies, and are available to order online (Bebinger, 2017; DanceSafe, 2017; Exchange Supplies, 2018; O’Brien, 2017). This can be seen as pragmatic – and needed – response to the exigencies of an overdose epidemic, but the vacuum (of situated evidence, of comprehensive and supportive harm reduction interventions) in which this response is occurring requires critical reflection.

### Self-testing of club drugs using reagent kits

In the absence of sufficient research specific to fentanyl testing, we can consider the potential harm reducing impact of interventions for testing club drugs. Self-testing for MDMA, for example, involves placing a tablet into a reactive solution which changes colour indicating the presence of any number of substances. Evidence from their evaluation show that sensitivity and specificity is reduced with considerable potential to misinterpret results when used by people unfamiliar with the reagent tests (Murray et al., 2003). Given these uncertainties, experts do not recommend their use as a harm reduction tool, recommending instead the use of more rigorous testing methods (e.g. infrared spectroscopy) that are carried out by a trained technician and which provide accurate results, as well as a precise breakdown of a pill’s constituents (European Monitoring Centre for Drugs and Drug Addiction, 2001;

Murray et al., 2003). Similarly, a study of a reagent test for detecting potentially incapacitating concentrations of  $\gamma$ -hydroxybutyric acid (GHB) and ketamine in drinks determined that the accuracy of the test in a laboratory setting was 100%, but reduced to 65% (sensitivity 50%, specificity 91.6%) when applied by users (Quest & Horsley, 2007).

Even when self-test kits are effective and accurately interpreted with respect to the presence of MDMA, they may not indicate the presence of other substances, which may be individually harmful or which might result in cumulative toxicity (Schneider, Galettis, Williams, Lucas, & Martin, 2016). Additionally, the user is often unable to anticipate the effect of the drug until after it is consumed, regardless of what is indicated by the test (i.e. confirming that presence of a drug does not protect against idiosyncratic adverse effects that are responsible for many MDMA-associated fatalities). Factors inherent to the individual (e.g. tolerance, metabolism) may contribute to individual vulnerability and may not be taken into account, particularly when the pill itself is presumed to be the locus of risk (Schneider et al., 2016). Finally, MDMA self-test kits give no indication of the strength of a pill (Winstock, Wolff, & Ramsey, 2001).

Though self-testing of club drugs suggests the potential for both inaccurate and incomplete results, there are additional important concerns about the proper use and interpretation of these self-tests when administered by a lay user. Studies of self-testing of club drugs has demonstrated that self-testing is of limited value if not delivered within a package of harm reduction services including the provision of accurate information for reducing the risk of adverse outcomes, and for intervention in the case of overdose (European Monitoring Centre for Drugs and Drug Addiction, 2001).

### What do we need to know about fentanyl self-testing?

Given the severity of the opioid overdose epidemic in North America and the emergence of fentanyl-adulterated heroin in multiple countries, there is an urgent need to evaluate drug self-testing in the context of situated opioid use (Socias & Wood, 2017). Fentanyl test strips are currently being distributed for self-testing outside of supervised injection facilities, despite a limited evidence-base – including any published ethical deliberation – informing their design and implementation. In order to understand the potential effect of fentanyl self-testing, it is critical to appreciate how the test strips will be used and interpreted in the lived contexts of everyday opioid use, and whether they will be perceived acceptable among potential users of the technology. There is a need also, to consider the potential of any unintended consequences that might increase risk or harm – beyond the obvious risk of false negatives – and how these might be balanced against the alternatives, of which, currently, there are few.

### Use

Fentanyl test strips require that drugs are diluted in water before the test strip can be applied. Only one of the test kits currently available includes a ‘test buffer bottle’ for diluting and testing a drug sample (Exchange Supplies, 2018). The majority of the available test kits include a test strip only; in this case, it is likely that drug preparation would occur, followed by application of the test strip to the drug solution or to the cooker residue after drug consumption. With the drugs already in solution, the user’s obvious options to mitigate harm involve incremental dosing, swallowing, or simply disposing of the drugs.

Incremental dosing or taking a ‘test hit’ or ‘taster shot’ prior to injecting the remaining dose is likely to be a common response – a risk reduction measure often employed when the user suspects that the drug has been adulterated, or to reduce the likelihood of overdose after a period of abstinence (Preston & Derricott, 2017). There are no data to evidence the effectiveness of incremental dosing for fentanyl and its analogues; the enhanced potency of many fentanyls (particularly of carfentanil) may render this approach ineffective in reducing the risk of

overdose. The dissolution profile of fentanyl, and its analogues, may also pose problems when incremental dosing (National Center for Biotechnology Information, 2017a, 2017b). Brown heroin, which is widely available throughout Europe, may dissolve at a slower rate in an acid solution than fentanyl, initially leaving heroin residual in the cooker, and a higher relative concentration of fentanyl in the drug solution. Though this is not a risk when dissolving white heroin (which is the predominant form of heroin in North America), fentanyl and its analogues may still be unevenly distributed between samples. Indigenous harm reduction strategies may develop in response to such situations – such as intranasal use (i.e. using a nasal spray device).

### Effect

Fentanyl is known to change the nature of the drug use experience and there is evidence that this may be desired among some people who use drugs (Ciccarone, Ondocsin, & Mars, 2017; Harris, 2017; Johns Hopkins Bloomberg School of Public Health, 2018). In such circumstances a positive test result may be sought after, or at least not act as a disincentive to use – particularly among those experiencing opioid withdrawal. It is crucial, therefore, that community acceptable strategies to mitigate associated risks of fentanyl use are evidenced and disseminated. Learning from those who purposefully and safely use illicit fentanyl – alongside study of situated responses to positive test results will be invaluable. During the 2010/2011 heroin shortage in the UK, despite widespread knowledge of adulteration (largely, in this case, with benzodiazepines), and associated negative experiences (such as blackouts, memory loss), people continued to use heroin feeling that the risk was unavoidable given the immediate need to alleviate withdrawal. Indigenous harm reduction strategies, such as testing for adulterants by viewing how heroin ‘ran’ when heated on a foil, were not always successful (Harris, Forseth, & Rhodes, 2015).

One limitation of the test strips is that they do not give any indication of how much fentanyl – or fentanyl analogues – is present. As some fentanyl analogues (e.g. carfentanil) are toxic in significantly lower doses than fentanyl, it seems unlikely that the test can be calibrated to reduce sensitivity to fentanyl without increasing the risk of false negatives in drugs that contain only carfentanil for example. Part of the potential of the test strips as a harm reduction tool stems from their cross-reactivity with many fentanyl analogues. Given that many analogues are lethal in lower doses than fentanyl, and given that they have been found to be present in the absence of fentanyl (O'Donnell et al., 2017), reducing the sensitivity of the test strips to fentanyl – thereby increasing the specificity – may reduce the overall utility of the test. Contamination of injection equipment may also result in a positive test result and, though many people who use drugs do not share or reuse syringes, sharing and/or reusing spoons is not uncommon (McGowan, Harris, & Rhodes, 2013). It is unclear if a test which routinely indicates a non-fatal concentration of fentanyl, or indicates the presence of a less potent analogue, will promote complacency as people witness or experience non-fatal/pleasurable use of drugs for which a positive test result has been indicated.

### Acceptability

There is currently limited evidence on the acceptability of the test strips among people who use drugs. The Insite evaluation reported that of the average 600 daily supervised injection site users, an average of only 4.7 checks were performed per day (Lysyshyn et al., 2017). Reports that “clients who checked prior to consumption and got a positive result were 10 times more likely to reduce their dose, and clients who reduced their dose were 25% less likely to overdose” (Vancouver Coastal Health, 2017a, 2017b) refer therefore, to a small minority of clients who chose to test their drugs. The FORECAST study reported that the majority of their 256 research participants (73%) expressed moderate to high interest in knowing if fentanyl is present in their

drugs, with 70% indicating that knowing their drugs contained fentanyl would inspire them to modify their behaviour; however, the study did not report specifically on the acceptability of fentanyl test strips among PWUD (Johns Hopkins Bloomberg School of Public Health, 2018).

In America, recent increases in drug use have largely occurred in demographics with historically low heroin use (e.g. women, the privately insured, and people with higher incomes) (Centers for Disease Control and Prevention, 2015). Shifts in the profile of American drug users are thought to reflect transitions from prescription opioid use to illegal opioid use (Compton, Jones, & Baldwin, 2016). This has ramifications for engagement with harm reduction services, as service access is generally lower among women and those of higher socio-economic status (Harris et al., 2015). Access to harm reduction services is likely to be lower among these demographics, and among occasional users, due to limited knowledge about available services or a hesitancy to engage with services perceived to cater to the stigmatised, erroneously archetypal, ‘drug user’. Drug-using populations are becoming more diverse geographically, with suburban users less likely to have access to harm reduction services than those in urban catchment areas (Jozaghi & Marsh, 2017). Ultimately, a considerable proportion of those at risk of fentanyl-related overdose are people who are less likely to engage in harm reduction interventions. It is unclear if test strips – even if they are effective – would reach those who are most at risk of obtaining fentanyl-adulterated drugs. If they do reach those at risk, then their use by those who are most likely to use drugs in a manner that is uninformed by complimentary harm reduction recommendations (e.g. not using drugs alone, or without naloxone) is problematic.

### Do we know enough?

We draw attention to the weak research evidence informing the use of fentanyl self-testing strips. Drug use and harm reducing intervention effects are subject to multiple situated contingencies (Rhodes, 2009). How the effect of an intervention of harm reducing potential is made manifest is contingent upon its local meanings and implementations (Rhodes, Closson, Papparini, Guise, & Strathdee, 2016). In considering calls to upscale the promotion of fentanyl test strips to reduce overdose risk, we emphasise the critical, urgent, and pragmatic potential of qualitative and ethnographic research as a key dimension of implementation science (Messac, Ciccarone, Draine, & Bourgois, 2013). We point to a track record in the application of rapid situation assessment methods in the field of drug injection and harm reduction to hit home the feasibility potential of developing rapid responses in implementation science (Rhodes, Stimson, Fitch, Ball, & Renton, 1999). We thus call for qualitative work, delivered within a rapid assessment framework, to investigate the use, feasibility and acceptability potential of fentanyl self-testing interventions, including alongside alternatives, such as supervised-testing interventions and other overdose prevention initiatives (including the peer distribution of naloxone). Importantly, we draw attention to the need to investigate the unexpected and unintended effects of self-testing interventions, including any risk potential. We note the importance of such qualitative research combining with data about the pharmacokinetics and pharmacodynamics of fentanyl and its common analogues to inform the harm reduction advice offered alongside the distribution of test strips. In addition, further *in vitro* and off-label laboratory testing of the test strips is crucial to determining their accuracy and the range of detectable analogues.

Research is needed in order to capture and evidence situated indigenous responses to emergent drug harm risks, particularly when aligned with the use of new technologies such as self-testing. Now well-evidenced public health responses to drug harms, such as needle and syringe programs (NSP), stem from early community-led action to combat the rise of HIV among PWID. Widespread ‘underground’ needle and syringe distribution by activists in North American cities in the late 1970s and early 1980s provide an example of initiatives which arose in the absence of controlled intervention studies, also in a context of

prohibitions against the use of government funds for NSP evaluation and/or promotion (Friedman et al., 2007). This context provides an opportunity for implementation science to work alongside communities to evidence and test the efficacy of emergent fentanyl risk reduction initiatives.

It is critical to act to reduce the overdose risks related to fentanyls. A cautious approach is one which develops commensurate with the relative knowns and unknowns of research and other evidence concerning the effect potential of harm-reducing interventions. An approach which involves the distribution of test strips (with clear guidance on the interpretation of results) alongside low threshold access to naloxone, and integrated inside broader harm reduction responses, may serve to reduce the immediate risks of fatal overdose. Fentanyl and its analogues are incredibly fast-acting requiring naloxone be administered immediately; therefore, updated information on the use of naloxone to reverse fentanyl overdose should also be provided alongside test strips. Further, discouraging indigenous harm reduction methods that are unlikely to reduce the risk of fentanyl overdose (e.g. determining the presence of fentanyl by visually examining drugs), and encouraging the use of drugs only when in the company of someone equipped with naloxone, may mitigate the risk of false negatives and/or complacency. Such risk reduction practices at once offer opportunities for embedding rapid situation assessment as part of intervention responses so as to reflect immediately on how they work and whether they might be up-scaled elsewhere.

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## Conflicts of interest

None.

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