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The opioid epidemic and injection drug use: MIPIE and health harms related to the injection of prescription opioids

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America's 21st century opioid epidemic is distinguished by the high proportion of people using heroin and illicitly-manufactured fentanyl who initiated their opioid use with prescription opioids (POs) that were either prescribed to them or diverted and used for nonmedical reasons (Jones, Logan, Gladden, & Bohm, 2015). Among this new generation of opioid users, many have turned to injection drug use (IDU) as their primary route of drug administration. This transition pattern has contributed to a nationwide increase in the number of people who inject drugs (PWID) (Suryaprasad et al., 2014), with a particularly sharp increase in the number of young people (< 40 years) injecting opioids (Valdiserri et al., 2014; Zibbell, Hart-Molloy, Barry, Fan, & Flanigan, 2014).

In contrast to previous generations of PWID, most of whom came from socially disadvantaged and disproportionately minority neighborhoods in urban areas, this new population of people injecting opioids is largely non-Hispanic white, varied in socioeconomic status, and heavily concentrated in non-urban areas of the country, places with sparse or no pre-existing populations of PWID (Cicero, Ellis, Surratt, & Kurtz, 2014). While IDU is a well-established risk factor for HIV and HCV infection, emerging evidence suggests that injecting POs is independently associated with HCV infection risk (Havens et al., 2013; Lake & Kennedy, 2016), with pill injectors at higher risk for HCV infection than PWID who do not inject POs (Zibbell et al., 2014). Scientific evidence has not yet established the mechanism(s) underlying the association between PO injection and HCV infection; thus, further research into the specific mechanics used by PWID to prepare and inject POs is urgently needed.

Broz et al.'s report in the February 2018 issue of the *International Journal of Drug Policy* represents a significant contribution to this effort. First, it is one of only a few reports in the research literature (to our knowledge, it is the first in-depth report based on field research conducted in the U.S.) to present a detailed, ethnographically-informed account of injection practices specific to POs. Second, the semi-structured interviews from which their findings are based were conducted with people injecting POs in Scott County, Indiana, a rural area

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[☆]A Response to Broz et al., Multiple Injections per Injection Episode: High-risk Injection Practice among People Who Injected Pills during the 2015 HIV Outbreak in Indiana

Conflict of interest

The authors have no conflicts of interest to declare.

that, in 2015, experienced the first HIV outbreak attributed to PO injection (Conrad et al., 2015). Through interviews with residents of Scott County who injected drugs, Broz et al. identified a phenomenon they refer to as “multiple injections per injection episode” (MIPIE) that was commonly employed by local PWID to inject OpanaER pills. They further suggest that this high-risk injection practice facilitated and accelerated the area’s HIV outbreak.

OpanaER is extended-release oxymorphone developed by Endo Pharmaceuticals whose abuse-deterrent formulation includes both a crush-resistant mechanism intended to prevent misuse from crushing and snorting the drug, as well as an extended-release technology to facilitate the slow release of the drug through the digestive tract. The chemical excipients that allow for the extended release of the drug form a gelatin-like compound in the gut when exposed to water; this property has the unintended effect of turning a drug solution made from the pills into a highly viscous gel (Bartholomäus et al., 2013).

In order to circumvent the pills’ abuse-deterrent and extended-release (ER) technologies, Scott County respondents described using a cumbersome process to prepare OpanaERs into an injectable solution. This first involved heating a pill to override the crush-resistant chemicals, then adding water to the crushed pill until the resulting solution was sufficiently liquid to be drawn into a syringe and injected. Because this process required a greater volume of water (> 1 ml) than is typically used to prepare powdered drugs like heroin, cocaine or methamphetamine for injection, the 1 ml insulin syringes used by local PWID were not large enough to hold the solution and multiple injections were necessary to consume a full dose in one sitting. As a result, PO injectors in Scott County reported performing up to 35 injections per day, thereby increasing the number of opportunities for exposure to blood-borne pathogens. Because MIPIE in this sample typically occurred in a context of group injection, with people pooling money to buy diverted OpanaERs and then dividing the drug solution among them – and in a policy environment that provided drug users with little to no access to sterile syringes – the risk for exposure to HIV and HCV was considerable. Therefore, the authors suggest, MIPIE was likely a major factor responsible for the rapid dissemination of HIV and HCV through Scott County’s injecting community.

Descriptions of similar procedures used to inject other PO pills have been reported by Roy et al. in Montreal (Roy, Arruda, & Bourgois, 2011) and by our team in New York City (Mateu-Gelabert, Guarino, Jessell, & Teper, 2015). Together with Broz et al’s findings, these reports provide strong evidence that distinct and unsafe injection practices associated with PO injection are fairly widespread in both urban and non-urban areas where the nonmedical use of POs is prevalent. Broz et al. expand this evidence by identifying a highly plausible behavioral link between the injection of a particular PO formulation and documented cases of HIV and HCV infection: MIPIE. Situating MIPIE in the context of existing literature, it is our opinion that Broz and her colleagues correctly surmise that MIPIE is a likely mechanism underlying the observed association between PO injection and HCV infection (Bruneau, Roy, Arruda, Zang, & Jutras-Aswad, 2012; Zibbell et al., 2015).

The finding that MIPIE was being performed due to structural factors (i.e., OpanaER’s abuse-deterrent and extended-release properties) and not individual choice (e.g., needle fixation) bodes ill for HCV elimination efforts given the prevalence of PO pill injection in

many regions across the U.S. (Havens et al., 2013; Mateu-Gelabert et al., 2015; Zibbell et al., 2014). Although Endo Pharmaceuticals agreed in July 2017 to withdraw OpanaER from the U.S. market at the request of the U.S. Food and Drug Administration, other POs with similar abuse-deterrent technologies remain available. Federal and state public health agencies should be on alert for sharp increases in new HCV infections in states experiencing endemic PO diversion and misuse, as localized HCV outbreaks among people injecting POs have been increasingly reported (Centers for Disease Control & Prevention, 2008, 2011a, 2011b, 2012; Zibbell et al., 2015). That we continue to see HCV outbreaks within social networks of PWID indicates that unsafe injection practices are still occurring in many communities. Also, because these HCV outbreaks are caused by IDU, increases in acute HCV infections may also serve as proxy surveillance indicators for detecting areas where IDU is endemic and potentially vulnerable to outbreaks of other injection-related diseases and negative sequelae (Van Handel et al., 2017). For example, Scott County's HIV outbreak occurred in a community of PWID that had been experiencing high rates of HCV infection for many years prior (Peters et al., 2016).

An additional concern suggested by Broz et al.'s findings is that high-volume PO solutions could motivate the use of larger syringes (> 1 ml). However, these higher-volume syringes, often referred to as *high dead-space syringes*, may have the unintended consequence of heightening HIV/HCV risk. Zule and Bobashev (2009) found that *high dead-space syringes* retain greater amounts of post-injection fluid in the "dead-space" between the needle and the syringe tip than *low dead-space syringes*, allowing them to transfer larger amounts of contaminated, post-injection blood when shared amongst injection partners.

In addition to exacerbating known injection-related risks, there is some evidence that injecting abuse-deterrent PO formulations can lead to unanticipated health outcomes. For example, shortly after the introduction of the tamper-resistant formulation of OpanaER in 2012, reports linked a TTP-like blood clotting disorder to the injection of this particular Opana formulation, thought to be a function of the specific compounds contained in the pill's crush-resistant technology (Fiore, 2015). Further, extended manipulation of a pill in a non-sterile environment increases the likelihood of bacterial exposure. Using fingers to crush and mix a pill in solution, along with the MIPIE effect of producing a higher aggregate number of daily injections, could compound PWID's vulnerability to soft-tissue bacterial infections and acute sepsis (i.e., "cotton fever"). More research is needed to determine if PO injectors are more likely to experience bacterial infections associated with IDU (e.g., abscesses, cellulitis, endocarditis) than people who inject drugs other than PO pills.

As the PO epidemic has facilitated the expansion of IDU into new, largely rural and suburban areas of the U.S., it has placed a heavy burden on existing medical infrastructures, exposing a serious lack of opioid use disorder treatment and primary prevention in many parts of the country. Medical services in some of the most affected areas (e.g., Appalachia, the Rust Belt, the Deep South) are already limited and at-capacity with few additional resources to sufficiently address this burden. Additionally, medical personnel in these regions may have limited experience treating PWID for opioid use disorders and injection-related medical complications and may require additional training to reduce stigma and improve treatment delivery.

Equally important is the establishment of comprehensive harm reduction services, including syringe services programs, which are currently nonexistent, prohibited or extremely limited in many high-burden states. Harm reduction services may want to consider implementing or augmenting safer injection education to address the specific risks associated with injecting POs, including the HIV/HCV risks associated with MIPIE, the use of micron filters for pill-based solutions, and the potential for cross-contamination in group injection situations. Given the likelihood of additional HCV and HIV outbreaks in areas with widespread opioid use and IDU, public health officials at the federal, state and local levels should consider coordinating efforts across the medical system, the drug treatment industry, and harm reduction programs to develop integrated services for people with substance use disorders.

As a final note, research indicates that about 80% of young people who use heroin initiated their opioid use with the nonmedical use of POs (Jones, 2013; Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014), often during adolescence. In our study of young adults who use opioids in New York City, we found that PO misuse was initiated at age 16.7 on average, with first drug injection occurring several years later at the average age of 20.3 (Mateu-Gelabert et al., 2017). This lag time between initiation of opioid misuse and onset of drug injection provides a critical window of opportunity for offering secondary prevention efforts (Grebely & Dore, 2011). Innovative interventions to prevent the escalation of opioid misuse – transitions from POs to heroin to injection drug use – should be developed and widely delivered to America's youth. Ideally, a comprehensive, opioid-focused prevention program would be multi-modal and include the following components: outreach programs tailored to reach and engage young people, including those who have yet not transitioned to heroin or IDU; the development of harm reduction education specifically geared to people using and injecting POs; and expanded access to low-threshold, low-cost medication-assisted treatment (particularly with buprenorphine and methadone) for all persons with opioid use disorder, including persons under 18.

Broz et al. raise the stakes for why it is important for public health to further investigate the individual/structural factors and health risks associated with PO injection. We need to better understand the risks associated with the nonmedical injection of POs, including extended-release and abuse-deterrent formulations, with the goal of mitigating or preventing the cascade of negative consequences experienced by the most vulnerable and hidden among us.

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