

The moderating effect of psychedelics on the prospective relationship between prescription opioid use and suicide risk among marginalized women

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Abstract

Background/aims: Given high rates of depression and suicide among marginalized women, and increasing calls to integrate trauma-informed biomedical and community-led structural interventions, this study longitudinally examines the potential moderating effect of psychedelic use on the relationship between other illicit drug use and suicide risk.

Methods: Data (2010–2017) were drawn from a community-based, prospective open cohort of marginalized women in Vancouver, Canada. Extended Cox regression analyses examined the moderating effect of psychedelic use on the association between other illicit drug use and incidence of suicidal ideation or attempt over follow-up.

Results: Of 340 women without suicidal ideation or attempt at baseline, 16% ($n=53$) reported a first suicidal episode during follow-up, with an incidence density of 4.63 per 100 person-years (95% confidence interval 3.53–6.07). In unadjusted analysis, psychedelic use moderated the relationship between prescription opioid use and suicide risk: among women who did not use psychedelics, prescription opioid use increased the hazard of suicide (hazard ratio 2.91; 95% confidence interval 1.40–6.03) whereas prescription opioid use was not associated with increased suicidal ideation or attempt among those who used psychedelics (hazard ratio 0.69; 95% confidence interval 0.27–1.73) (interaction term p -value: 0.016). The moderating effect of psychedelics remained significant when adjusted for confounders (interaction term p -value: 0.036).

Conclusions: Psychedelic use had a protective moderating effect on the relationship between prescription opioid use and suicide risk. In the context of a severe public health crisis around prescription opioids and lack of addiction services tailored to marginalized women, this study supports calls for innovative, evidence-based and trauma-informed interventions, including further research on the potential benefits of psychedelics.

Keywords

Women, psychedelics, hallucinogens, suicide prevention, substance use, moderating effect

Introduction

Marginalized women, such as street-involved sex workers or women who use drugs, experience a disproportionately elevated risk for suicide stemming from complex and interrelated socio-structural factors (Gu et al., 2014; Roxburgh et al., 2006; Shannon et al., 2015; Ulibarri et al., 2013; Zhang et al., 2016). In North America, marginalized and street-involved women (i.e. women who experience poverty, inadequate shelter, and elevated rates of health and drug-related harms) (Bungay, 2013; Shannon et al., 2007) continue to face severe forms of stigma, violence, and criminalization, including social exclusion, ongoing trauma from historical experiences of childhood abuse, and concurrent mental health and substance use issues that are known to be key drivers of depression and suicide (Hawton and van Heeringen, 2009; Li et al., 2011; Whiteford et al., 2013). Additionally, Indigenous women in North America are vastly overrepresented among street-based sex workers and experience devastating multigenerational effects as a result of colonialism and racial policies, including a high burden of mental illness and suicide and displacement from land and home communities (Benoit et al., 2003; Bingham et al., 2014).

Rates of suicide vary significantly across settings and populations, however, global research and evidence demonstrate that

nearly half (45%) of marginalized women (injection drug using sex workers) surveyed in China reported suicide ideation in the last six months (Gu et al., 2014); nearly one-fifth (19%) of female sex workers in India reported suicide attempts in the last three months (Shahmanesh et al., 2009); and nearly three-quarters (74%) of street-based sex workers in Sydney, Australia reported lifetime suicidal ideation or attempt (Roxburgh et al., 2006).

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Among a sample of trans women with a history of sex work, 64% reported ever attempting suicide (Nemoto et al., 2011).

Substantial structural barriers to accessing safe and non-judgmental health and support services exist for marginalized and street-involved women sex workers (Dell et al., 2011; Duff et al., 2014; Shannon et al., 2015), and few evidence-based mental health or addiction interventions are tailored to the needs of such key populations both in Canada and internationally (Benoit et al., 2003; Jeal et al., 2015). Research and intervention efforts have paid inadequate attention to developing addiction supports as part of a complex trauma-informed care package that includes community-driven and structural interventions. In the context of significantly elevated risk of suicide, there remains an urgent need to develop clinical addiction treatments tailored to the needs of marginalized women alongside community/sex worker-led interventions within a trauma-informed care framework.

Re-emerging evidence demonstrates that use of psychedelics – chemical compounds such as lysergic acid diethylamide (LSD), psilocybin, mescaline, methylenedioxymethamphetamine (MDMA), and dimethyltryptamine (DMT) – may be associated with improvements in mental wellbeing and addiction issues (dos Santos et al., 2016; Hendricks et al., 2015; Sessa, 2012; Tupper et al., 2015), yet the literature is characterized by large gaps and a paucity of evidence on how psychedelics might influence suicide risk. Findings from early studies conducted in the 1950s and 1960s indicated important utility of psychedelics for treating mental health and substance use disorders, however, political concern over recreational use resulted in a decades-long gap in research (Dyck, 2015; Sessa, 2012).

Renewed scientific inquiry and evidence is now lending mounting support to the therapeutic potential of psychedelics to treat addictions (Bogenschutz et al., 2015; Brown, 2013; Johnson et al., 2014; Krebs and Johansen, 2012), as well as ameliorate treatment-resistant depression, anxiety, and post-traumatic stress disorder (PTSD) (Carhart-Harris et al., 2016a; Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Osório et al., 2016; Ross et al., 2016). Two large population studies among the US adult population found significantly reduced psychological distress and suicidality associated with non-medical (naturalistic) psychedelic use (Hendricks et al., 2015; Krebs and Johansen, 2013).

Most recently, a longitudinal study by our team demonstrated that naturalistic psychedelic use predicted reduced suicidality among a community-based cohort of marginalized women in Vancouver, Canada, while other illicit drug use and childhood trauma predisposed women to suicidality (Argento et al., 2017b). In the context of these findings demonstrating a significant relationship between psychedelic use and reduced risk of suicide, the present study aimed to further explore the potential moderating effect of psychedelics on the relationship between other illicit drug use and suicide risk among women in this setting.

Methods

Data for this study were obtained from an open, prospective, community-based cohort of over 900 women sex workers in Vancouver, Canada, known as AESHA (An Evaluation of Sex Workers Health Access). The study period for this analysis was January 2010–February 2017, providing an updated sample from our previous study that included data up to August 2014 (Argento et al., 2017b). Eligibility included cis and trans women,

age 14 years or older, that exchanged sex for money within the past 30 days at baseline. Consenting participants completed interviewer-administered questionnaires at enrollment and bi-annually. Interview, outreach, and nursing staff included experiential individuals (current/former sex workers) with substantial community experience. As previously described (Shannon et al., 2007), participants were recruited across Metro Vancouver using time-location sampling and community mapping strategies, with day and late-night outreach to outdoor sex work locations (i.e. streets, alleyways), indoor sex work venues (i.e. massage parlors, micro-brothels, and in-call locations), and online. Weekly outreach by outreach/nursing teams operating a mobile van, as well as regular contact encouraging drop-in to women-only spaces at the research office, contribute to an annual retention rate of >90% for AESHA participants. A Community Advisory Board of over 15 community and sex work agencies, as well as representatives from the health authority and policy experts, provides input and guidance to the research. All participants receive an honorarium of \$40 CAD at each bi-annual visit for their time, expertise and travel. The study holds ethical approval through Providence Health Care/University of British Columbia Research Ethics Board.

The main questionnaire elicits responses related to socio-demographics (e.g. gender identity, sexual orientation, ethnicity, housing), the work environment (e.g. access to services, violence/safety, policing, incarceration), client characteristics (e.g. types/fees of services, condom use), intimate partners (e.g. sexual history, cohabitation, financial support), trauma and violence (e.g. lifetime and childhood trauma, exposure to intimate partner and workplace violence), and comprehensive injection and non-injection drug use patterns. The clinical questionnaire asks about overall physical, mental, and emotional health, and human immunodeficiency virus (HIV) testing and treatment experiences to support education, referral, and linkages with care.

Statistical analyses

The outcome of interest was a first episode of self-reported suicide risk, defined as responding "yes" to having thought about or attempted suicide in the last six months. Analyses were thus restricted to AESHA participants who had never thought about or attempted suicide at baseline and completed at least one follow-up visit. Time-fixed variables examined included: age, gender/sexual minority (lesbian, gay, bisexual, trans, queer, or two-spirit (LGBTQ2S)), Indigenous ancestry (inclusive of First Nations, Metis, and Inuit), being an im/migrant worker (versus Canadian born), education (high school or greater), and physical and/or sexual childhood abuse (before age 18 years). Variables treated as time-updated covariates based on bi-annual follow-up data included: HIV/sexually transmitted infection (STI) serostatus, recent homelessness, recent physical and/or sexual violence by clients, recent police harassment and/or arrest, and primary place to solicit clients. Time-updated lifetime injection and non-injection drug use variables included use of psychedelics (LSD/acid, magic mushrooms/psilocybin, ecstasy/MDMA), cannabis, crack, cocaine, crystal methamphetamine, heroin, and illicit prescription opioid use (any street methadone/suboxone, dilaudid, morphine, oxycontin, percocet/vicodin/demerol, talwin, fentanyl, or T3s/T4s).

Using extended Cox regression with interaction terms, unadjusted hazard ratios (HRs) and adjusted HRs (AHRs) and 95%

Table 1. Unadjusted and adjusted hazard ratios for the moderating effect of psychedelics on the association between other illicit drug use and suicide risk among marginalized women in Vancouver, Canada ($n=340$).

Illicit drug use	Psychedelic use hazard ratio (95% CI)	No psychedelic use hazard ratio (95% CI)	Interaction term p -value	Psychedelic use adjusted hazard ratio ^a (95% CI)	No psychedelic use adjusted hazard ratio ^a (95% CI)	Interaction term p -value
Prescription opioids	0.69 (0.27–1.73)	2.91 (1.40–6.03)	0.016	0.64 (0.25–1.68)	2.59 (0.94–7.14)	0.036
Cocaine	0.39 (0.12–1.29)	4.69 (1.93–11.43)	0.001			n/s
Crack	1.31 (0.17–10.25)	4.08 (1.57–10.61)	0.326			n/s
Crystal meth	1.98 (0.69–5.73)	4.51 (2.21–9.22)	0.206			n/s
Heroin	0.88 (0.31–2.53)	2.15 (1.04–4.46)	0.170			n/s

CI: confidence interval.

^aFinal multivariable model adjusted for heroin use, HIV serostatus, indigeneity, and childhood abuse.

confidence intervals (CIs) were calculated to estimate the moderating effect of psychedelics on the relationship between other illicit drug use and incidence of suicidal ideation or attempt. Significant associations at the $p < 0.10$ level in bivariate analysis were subsequently fitted into separate multivariable confounder models. A manual stepwise approach was used to determine the most parsimonious models, whereby hypothesized confounders that altered the association of interest by $< 5\%$ were systematically removed (Maldonado and Greenland, 1993). All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA). Two-sided p -values are reported.

Results

A total of 340 women without suicide ideation or attempt who completed at least one follow-up visit were eligible for inclusion in the present analysis. During follow-up, 16% ($n=53$) reported a first episode of suicide ideation or attempt in the last six months, corresponding to an incidence density of 4.63 per 100 person-years (95% CI 3.53–6.07). The median age at baseline was 36 years (interquartile range (IQR) 29–43), one-third (35%; $n=120$) reported Indigenous ancestry, and nearly one quarter (23%; $n=79$) identified as a gender and/or sexual minority. At baseline, 36% ($n=124$) reported experiencing recent workplace violence in the last six months (e.g. physical and/or sexual abuse by clients, police, or predators posing as clients), and more than half (56%; $n=189$) reported a history of physical and/or sexual childhood abuse. One-quarter (25%; $n=86$) reported homelessness in the last six months. At baseline, 32% ($n=108$) of participants reported ever using prescription opioids. Nearly half of participants (47%; $n=161$) had ever used heroin, 56% ($n=189$) had ever used cocaine, 62% (211) had ever used crack, and close to one-third (32%; $n=109$) had ever used crystal methamphetamine. At baseline, 28% ($n=95$) of participants reported ever using a psychedelic substance, and of those, 74% ($n=70$) had used MDMA, 39% ($n=37$) had used LSD, and 36% ($n=34$) had used psilocybin/magic mushrooms.

As indicated in Table 1, unadjusted extended Cox regression analysis demonstrated that psychedelic drug use significantly reduced the hazard of suicide ideation or attempt by modifying the effect of using prescription opioids and cocaine. Among participants who had never used a psychedelic drug, prescription

opioid use was associated with nearly three times greater hazard of suicide risk (HR 2.91; 95% CI 1.40–6.03), whereas the hazard was not significant among those who had used a psychedelic drug (HR 0.69; 95% CI 0.27–1.73) (interaction term p -value: 0.016). Among women who had never used a psychedelic drug, cocaine was associated with nearly five times greater hazard of suicide ideation or attempt (HR 4.69; 95% CI 1.93–11.43), compared to no significant hazard among women who also used a psychedelic drug (HR 0.39; 95% CI 0.12–1.29) (interaction term p -value: 0.001). In the final multivariable confounder models, the moderating effect of psychedelic use on the relationship between prescription opioid use and suicide risk remained significant (interaction term p -value: 0.036).

Discussion

The present analysis provides longitudinal evidence that naturalistic psychedelic use modifies the effect of other illicit drug use to reduce the hazard for suicide among marginalized women in this setting. In unadjusted analyses, psychedelic drug use was demonstrated to have a protective effect on suicide risk by modifying the effect of using prescription opioids and cocaine. The protective moderating effect of using psychedelics on the association between using prescription opioids and suicide risk remained statistically significant after controlling for potential confounders (heroin use, HIV seropositivity, Indigenous identity, and childhood abuse).

This study among marginalized and street-involved women sex workers – a population that reports disproportionately elevated rates of suicide risk – further examined the association between psychedelic use and its protective effect on incidence of suicidal ideation or attempt. Findings demonstrate temporal evidence that psychedelic use moderates the effect of using other illicit drugs to reduce hazard of suicidal ideation or attempt, and contribute to a growing body of research citing benefits to health and wellbeing associated with psychedelic drug use in both clinical and non-clinical settings (Argento et al., 2017b; Carhart-Harris et al., 2016a; dos Santos et al., 2016; Griffiths et al., 2016; Hendricks et al., 2015; Krebs and Johansen, 2013; Ross et al., 2016; Sanches et al., 2016).

While rates of suicide among women who are marginalized and stigmatized in society are heterogeneous within and across populations and settings, global research has estimated that

19–75% of marginalized sex workers (e.g. women who are also street-involved, use drugs, or identify as a gender or sexual minority) report recent suicidal ideation or attempt (Gu et al., 2014; Jung, 2013; Lau et al., 2010; Nemoto et al., 2011; Roxburgh et al., 2006; Shahmanesh et al., 2009). Street-involved sex workers report elevated rates of severe depression, anxiety, and PTSD – up to 74% among women in a US study (Surratt et al., 2012) – as well as violence, trauma, and childhood abuse, all of which predispose women to other sexual and drug use-related risks and harms (Argento et al., 2017a; Deering et al., 2014; Roxburgh et al., 2006; Stolz et al., 2007), including suicide (Gu et al., 2014; Hawton and van Heeringen, 2009; Shahmanesh et al., 2009; Zhang et al., 2016). Street-involved sex workers in Miami and Vancouver who reported recent physical/sexual abuse or victimization were more likely to use prescription opioids non-medically (Argento et al., 2015; Surratt et al., 2006), and in Vancouver, recent and historical violence independently predicted initiation of crystal methamphetamine injection (Argento et al., 2017a), consistent with the literature indicating that illicit drugs may be used to self-medicate for emotional trauma or mental health problems (Fast et al., 2014; Romero-Daza et al., 2005; Tull et al., 2010).

Recent observational work has documented significant associations between naturalistic use of psychedelics and reduced psychological distress and suicidality (Argento et al., 2017b; Hendricks et al., 2015; Krebs and Johansen, 2013), as well as reduced recidivism and intimate partner violence among correctional populations in the US (Hendricks et al., 2014; Walsh et al., 2016). In clinical settings, recent randomized controlled trials have reported significant reductions in depression and anxiety with psilocybin among cancer patients (Griffiths et al., 2016; Ross et al., 2016), increased psychological wellbeing with psilocybin and LSD (Carhart-Harris et al., 2016b; Kraehenmann et al., 2015), and long-term improvements among patients with treatment-resistant PTSD with MDMA-assisted psychotherapy (Mithoefer et al., 2013, 2018; Oehen and Schnyder, 2013). Additionally, emerging research lends considerable support to the potential of psychedelics to treat substance use issues (Bogenschutz and Johnson, 2015; Sessa, 2012; Sessa and Johnson, 2015; Walsh, 2016). For example, previous studies demonstrate psychedelic substances may have important therapeutic utility for treating alcohol (Bogenschutz et al., 2015; Krebs and Johansen, 2012), tobacco (Johnson et al., 2014), cocaine, and opioid use disorders (Alper et al., 1999; Brown, 2013; Mash et al., 2001). Notably, a recent US survey of 44,000 adult respondents with a history of illicit opioid use found psychedelic drug use was significantly associated with a 40% reduced risk of past year opioid abuse (Pisano et al., 2017). Accumulating evidence supports potentially therapeutic benefits of psychedelics; however, the associations uncovered in the present analysis cannot be determined as causal. It is possible that women who have used psychedelics may possess certain psychological or temperamental characteristics (e.g. openness to experience, curiosity, or spirituality) that women who have not used psychedelics do not possess. Such potential confounding variables were not examined in the study and warrant further investigation.

The complex mechanisms by which psychedelics moderate the relationship between opioid use and suicide risk likely involve activity at the serotonin (5-HT)_{2A} receptors (Anisman

et al., 2008; Bogenschutz and Johnson, 2015). Evidence suggests that opioid use, as well as major depression and suicide, is associated with increased binding of 5-HT_{2A} receptors, while psychedelics down-regulate these receptors (Anisman et al., 2008; Bogenschutz and Johnson, 2015; Müller and Homberg, 2015; Vollenweider and Komter, 2010). Psychedelics may enhance recall of autobiographical memories and may facilitate the positive reprocessing and reconciliation of traumatic memories (Bogenschutz and Pommy, 2012; Carhart-Harris et al., 2012b), thereby potentially reversing the association between drug use (as a coping mechanism for emotional trauma) and suicide risk (O'Connor and Nock, 2014; Ulibarri et al., 2013), particularly among marginalized women who experience high rates of violence, childhood abuse, and trauma. Nascent neuroimaging research posits that the influence of psychedelics on an area in the brain known as the default mode network (DMN) may help to explicate how psychedelics work to modulate mood and states of consciousness (Carhart-Harris et al., 2014; Carhart-Harris et al., 2012a). Indeed, it has been hypothesized that the DMN is the physical counterpart to the ego (Carhart-Harris et al., 2014) and that ego-dissolution occasioned by psychedelic experiences might facilitate enhanced insights and self-reflection (Nour et al., 2016). Finally, the tendency of psychedelics to elicit powerful “mystical-type” experiences (Griffiths et al., 2006) influences key characteristics such as personal meaningfulness, life satisfaction, spirituality, and connectedness that play a crucial role in reducing problematic substance use and associated risk of suicide (Bogenschutz and Johnson, 2015; Garcia-Romeu et al., 2014; Watts et al., 2017). Notably, having a more intense mystical-type experience was significantly correlated with high success in tobacco smoking cessation in a preliminary study of psilocybin-assisted therapy: 80% abstinence rates were observed at six-month follow-up and 67% at 12-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2014, 2017).

Given the complex etiology of suicide risk among marginalized women and compounded impacts of trauma, psychological distress, and substance use on health and safety, the present analysis highlights the potential of psychedelics to disrupt risk pathways by having a protective moderating effect on the relationship between other drug use and suicidal ideation or attempt. This study underscores the critical need for evidence-based, innovative, and alternative approaches to addressing substance use issues and risk of suicide among marginalized women, and supports the advancement of further research on the therapeutic utility of psychedelic substances, alongside counseling and trauma-informed care models.

Limitations

Data were self-reported and may be subject to recall bias. This study examined highly sensitive and stigmatized risk variables, such as violence, childhood abuse, and illicit drug use, which introduce the potential for social desirability bias. Suicide risk is influenced by complex socio-structural variables, which have not all been measured in this study. Although lifetime psychedelic use was demonstrated to modify the effect of other illicit drug use on incidence of suicidal ideation and attempt, the associations cannot be determined as causal. However, the use of Cox regression to analyze first episodes of suicidal ideation or attempt enabled the determination of a temporal relationship between the

moderating effect of lifetime psychedelic use and suicide risk. Due to a lack of statistical power, analyses evaluating the frequency or timing of use of specific psychedelics were not feasible, and doses and contexts of use could not be determined. The present study included a diverse sample of women who work in both street-based and off-street settings, yet findings cannot be fully generalizable to other populations.

Conclusion

This study demonstrated that psychedelic use had a significant and protective moderating effect on the relationship between illicit prescription opioid use and incidence of suicidal ideation or attempt among a cohort of marginalized women. In the context of a severe public health crisis around the misuse of prescription opioids in North America and lack of addiction services tailored to marginalized women, this study supports calls for innovative and evidence-based approaches to mitigate risks and harms. This includes more rigorous scientific inquiry into the potential benefits of psychedelics, alongside trauma-informed care and structural interventions (e.g. housing, policy reforms, violence supports) among marginalized women that address the underlying drivers of depression and suicide.

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