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Short communication

Depression – A major but neglected consequence contributing to the health toll from prescription opioids?

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ABSTRACT

Prescription opioid analgesic (POA) use is common especially in North America, and associated with extensive morbidity and mortality. While medical and non-medical POA use have been documented to be associated with mental health problems, and specifically depression, newly emerging epidemiological evidence suggests that incident depression post-initiation of POA use may be common. Neurobiological – specifically regarding impacts of POAs on brain functioning – and/or psycho-social processes may be relevant pathways; these must be better understood, also to guide clinical practice for interventions. Incident depression outcomes may be an added component to the extensive health toll from widespread POA use.

1. Introduction

More prescription opioid analgesics (POAs) are consumed in North America than any other international jurisdiction; moreover, the volume of POAs used has multifold increased in both the US and Canada over the past decade (Kenan et al., 2012; Manchikanti et al., 2012; Fischer et al., 2014b). In Canada, one in five adults have used an analgesic in the past year (Health Canada, 2014; Murphy et al., 2015). Importantly, these sharp increases in medical POA use have occurred alongside steeply rising levels of POA-related morbidity and mortality. For example, there have been some 16,000 POA-related overdose deaths, 366,000 emergency department and 170,000 treatment admissions annually in the US since 2010; similar rates of mortality, health care utilization and treatment at population-proportionate levels are either measured or estimated for Canada (Warner et al., 2014; Yokell et al., 2014; SAMHSA, 2014), amounting to what has been widely described as an 'epidemic' and acute public health crisis in North America (Manchikanti et al., 2012; Fischer and Argento, 2012; Volkow and McLellan, 2011).

2. Epidemiological evidence

While the health burden from POAs is fairly well-documented (Webster et al., 2011; King et al., 2014; Fischer et al., 2013) there is emerging evidence that POA use (including problematic use, e.g., non-medical, abuse) is associated with mental health disorders, and mainly depression. Specifically, several studies have found that individuals with current or historical mental health problems – including depression – are more likely to use POAs, and to use them chronically. For example, adjusted rates of prevalent long-term POA use were 2–4 times higher among depressed non-cancer pain patients than those without depression in Washington State and Northern California insurance plan populations; furthermore, a diagnosis of depression was associated with a higher POA dose regimen in both studies (Braden et al., 2009). Chronic POA use was more common in those with mental health or substance use disorders (SUD) compared to those without among chronic non-cancer pain patients in a national insurance plan (8% vs 3%) and the Arkansas Medicaid plan (20% vs 13%) population; POA use

Abbreviations: BSWH, Baylor Scott and White Health; MDE, major depressive episode; NMPOU, non-medical prescription opioid use; OR, Odds Ratio; SIMD, substance-induced major depression; VHA, Veterans Health Administration; HR, hazard ratio; MED, morphine equivalent dose; NSDUH, National Survey on Drug Use and Health; POA, prescription opioid analgesic; SUD, substance use disorder

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increased at greater rates in both populations among those with mental health or SUD compared to those without (Edlund et al., 2010). Co-occurring mental health disorders predicted (Odds Ratio [OR] 3.15 and 1.96, respectively) regular POA use in the 1997–98 and 1998–2001 waves of the US' Healthcare for Communities survey (Sullivan et al., 2005, 2006). Moderate/severe depression was found in 46% of n=1514 non-cancer chronic pain patients with POA prescriptions in Australia; this proportion was higher in younger/middle-age groups (19–54 years) (Campbell et al., 2015).

Furthermore, multiple systematic review/meta-analyses and large-scale studies involving adult and adolescent populations have documented associations between common mental health problems, including depression, and POA misuse or disorders. Specifically, presence of depressive symptoms predicted (OR: 1.2) non-medical prescription opioid use (NMPOU) among adult respondents in the 2002–04 National Survey on Drug Use and Health (NSDUH) (Becker et al., 2008). Fourteen (14.2) percent of adolescents (12–17 years) reporting past-year NMPOU, compared to 6.1% of non-reporters, had a past-year major depressive episode (MDE) in the 2008–12 NSDUH (Edlund et al., 2015). The pooled prevalence of depression symptoms among substance abuse treatment patient samples reporting NMPOU was 27% – and thus substantially elevated from general population norms (Goldner et al., 2014) – and depression symptoms were associated with NMPOU (OR: 1.2–4.3) among general population samples (Fischer et al., 2012) in respective systematic reviews. Patients – in the context of non-pain symptoms – were 1.75 times more likely to have NMPOU if exhibiting moderate depression, and 2.42 times if exhibiting severe depression in a sample of non-cancer chronic pain patients (21–80 years) with no history of substance abuse (Grattan et al., 2012). Of n=606 Australian cohort participants regularly tampering with POAs, 61% reported moderate/severe depression at baseline (2014) (Larance et al., 2015).

Notably, recent studies have found evidence for the possibility of incident depression developing after initiation of POA use. Concretely, baseline NMPOU (lifetime) was associated with incidence of mental health problems (including major depression; OR: 1.4) between waves 1 and 2 of the National Epidemiologic Study on Alcohol and Related Conditions (Martins et al., 2012). Analysis adjusted for co-variates (e.g., pain) found that patients in a Veterans' Administration population (n=49,770) with POA prescriptions >90 days featured elevated risks of new onset depression than those with lower POA duration (HR=1.25 for 90–180 days; HR=1.51 for >180 days) (Scherrer et al., 2014). In adjusted analyses, an increase in POA prescriptions to >50 mg MED, compared to non-use, was associated with elevated risk (OR: 2.65) of new onset depression among patients with chronic lower back pain (Scherrer et al., 2015). Among adolescents in the NSDUH (2008–12) with both lifetime NMPOU and MDE, 27.2% had NMPOU onset pre-MDE and 25.8% had onset of both in the same year (Edlund et al., 2015). Adolescents in the NSDUH with NMPOU had an OR of 1.3 of incident MDE, compared to those with no lifetime NMPOU (Ali et al., 2015). Among young (18–25 years) injection drug users in Chicago, past-year POA misuse was associated (OR: 1.81) with past-year substance-induced major depression (SIMD); with POA misuse occurring pre-SIMD in 64% of applicable cases (Mackesy-Amiti et al., 2015). New-onset depression post-POA use was observed in 9–12% of Veterans Health Administration (VHA), Baylor Scott and White Health (BSWH) and Henry Ford Health system patient populations (2000–2012) (Scherrer et al., 2016a). Risk of new-onset depression increased with duration of POA use after adjusting for pain conditions; compared to 1–30 day use, hazard ratio (HR) ranges across cohorts were 1.18–1.33 for 31–60 day use, and 1.35–2.05 for 61–90 day use (Scherrer et al., 2016a). Furthermore, patients with baseline depression exposed to POAs had a significantly greater risk of depression recurrence compared to unexposed in the VHA (HR=2.17) and BSWH (HR=1.77) cohorts (Scherrer et al., 2016b). These data suggest that new onset depression following exposure to POAs may be causally related.

3. Possible pathways

While potential pathways of POA misuse arising following the onset of depression (e.g., as 'self-medication'), or co-occurring with depression as a result of shared vulnerabilities (i.e., involving common underlying mechanisms), have been reasonably well-explained (Markou et al., 1998; Goldner et al., 2014; Khantzian, 1997), a theoretical framework describing the development of depression following initiation of POA misuse has not been developed. However, there are several lines of evidence that point to possible mechanisms. The precipitation model has been proposed to explain that substance use may induce psychiatric symptoms or disorders (Fergusson et al., 2009) possibly through neural plasticity or modified neurotransmitter function (Brady and Sinha, 2005; Weiss et al., 1992; Koob and Le Moal, 1997), by activation of dormant genetic mechanisms (Langbehn et al., 2006) or through psychosocial factors. Neuroscientific evidence suggests that POA use and depression involve changes in overlapping brain structures and mechanisms, and that they "may be linked by some shared neurobiology," specifically that drug abuse behaviors may lead to 'drug-induced depression' (Markou et al., 1998; Lingford-Hughes and Nutt, 2003; Zellner et al., 2011).

Specific areas of the brain that are implicated in both POA use and depression are the medial prefrontal cortex, amygdala, hippocampus, and ventromedial parts of the basal ganglia (Drevets et al., 2008). Magnetic resonance imaging techniques showed significant changes in amygdala volume and functioning with a small sample of POA-dependent patients when compared to healthy controls; POA dependence was associated with structural and functional changes in brain regions implicated in affect, impulse control, reward and motivational functions (Upadhyay et al., 2010). Significant changes in various brain region structures – including the amygdala – were demonstrated in a small sample of POA-using patients pointing to "structural and functional changes in reward and affect-processing circuitry"; these changes were morphine-dose dependent and persisted several months after POA-cessation (Younger et al., 2011). Similar changes in amygdala volume were described for un-medicated depressed patients in a meta-analytic study (Hamilton et al., 2008). The observed brain function changes with POA use may depend on the specific POAs involved, yet lend strong support for the hypothesized neurobiological link between POA misuse and depression (Schlaepfer et al., 1998; Kosten and George, 2002; Butelman et al., 2012).

Recent in-vivo neuro-imaging studies corroborate these theoretical dynamic structural brain changes. POA use may cause a 'resetting' of neurotransmitter mechanisms and dysregulation of receptors (Grenald et al., 2014) that could lead to depression. Dopaminergic and endogenous opioid receptor systems may be dysregulated when addiction develops, in the expression of depression as a form of neurobiological imbalance of brain reward and stress processes (Le Merrer et al., 2009; Zellner et al., 2011; Shurman et al., 2010; Lutz and Kieffer, 2013). Lowered testosterone levels as a result of repeated opioid use may also be a causal mechanism for new onset depression (Bawor et al., 2015; Smith and Elliott, 2012). Furthermore, psychosocial factors may contribute to the precipitation of depression following POA use. For example, prolonged POA use – e.g., for chronic pain – could contribute to negative self-image or lead to decreased functionality, each potentially leading to the development of depressive symptoms (Pincus et al., 2002; Fishbain et al., 1997; Campbell et al., 2003).