Understanding Risk Factors for Opioid Overdose in Clinical Populations to Inform Treatment and Policy

Tae Woo Park, MD, Lewei (Allison) Lin, MD, Avinash Hosanagar, MD, Amanda Kogowski, Katie Paige, and Amy S.B. Bohnert, PhD

Overdoses involving opioid analgesics represent a significant public health problem in the United States. We reviewed the literature on risk factors for overdose, with a focus on studies that examine clinical populations of patients receiving opioids for pain and potential risk factors for overdose in these populations. A structured review resulted in 15 articles published between 2007 and 2015 that examined risk factors for fatal and nonfatal overdose in patients receiving opioid analgesics. Opioid dosage was the factor most consistently analyzed and also associated with increased risk of overdose. Other risk factors include concurrent use of sedative-hypnotics, use of extended-release/long-acting opioids, and the presence of substance use and other mental health disorder comorbidities. Future research is needed to better characterize populations taking opioids for pain to help clarify discrepancies between existing studies and identify previously unexplored risk factors for overdose. Given that policy and clinical practice have shifted as a result of prior studies reviewed here, further efforts in understanding patient groups and opioid-related prescribing practices associated with overdose risk have great potential to impact policy and practice in the treatment of pain while improving the safety around opioid prescribing.

Key Words: clinical populations, opioid analgesics, overdose, poisoning, risk factors

(T Addict Med 2016;xx: xxx–xxx)

The number of drug overdose deaths has risen to historically unprecedented levels in the United States over the past 15 years. As a result, unintentional drug overdose was the leading cause of injury death in 2013 (Centers for Disease Control and Prevention, 2015). The increase in overdose deaths has largely been driven by deaths that involved opioid analgesics, and the rate of opioid analgesic-related overdose deaths specifically has nearly quadrupled between 1999 and 2011 (Chen et al., 2014).

An important factor behind these trends was that opioid analgesic availability increased substantially between 2002 and 2010 due to increased prescribing. Availability has decreased slightly between 2011 and 2013, and surveillance systems are indicating that opioid overdose deaths have followed a similar pattern (Dart et al., 2015). These patterns may reflect the implementation of initiatives aimed at improving opioid prescribing, and also other prevention efforts.

Despite growing awareness of the risks related to opioid analgesic use, opioids will likely continue to be prescribed to patients for the treatment of both acute and chronic noncancer pain. Current treatments for chronic noncancer pain, including nonopioid treatments, have limited efficacy (Turk et al., 2011). Although the use of opioids for chronic pain is controversial, some patients do report benefit from treatment (Furlan et al., 2006; Noble et al., 2010). Consequently, an important aspect of improving the quality of opioid prescribing is determining when it is safe and appropriate (Becker et al., 2013). Identifying patient groups and opioid-related prescribing practices that are associated with overdose risk can assist clinicians and policymakers in maintaining appropriate access to pain care while reducing the potential harms of opioid prescribing.

Previous studies have reviewed risk factors related to opioid analgesic overdose (Webster et al., 2011; Paulozzi, 2012; King et al., 2014), but the number of primary studies examining overdose risk factors is increasing rapidly and updates to these reviews are needed. In particular, because there are now a number of higher-quality studies that attempt to control for confounding and do not rely on ecologic data (and thus avoid ecologic biases), a newer review is able to restrict to higher-quality studies. A more recent review examined the risks generally of long-term opioid therapy for chronic pain, including overdose, but the rigorous methods used to determine inclusion in the review precluded many relevant studies that might aid clinical decision-making (Chou et al., 2015). The present study reviews the literature with a focus on risk factors for opioid analgesic-related overdose. What are risk factors for opioid overdose in clinical populations of patients receiving opioids for pain management?
We then summarize findings from these studies and discuss possible directions for future research.

METHODS

Search Strategy

We conducted a systematic electronic search of peer-reviewed literature with the aim of finding studies that involved fatal and nonfatal overdoses in patients who are prescribed opioids for pain. We searched the PubMed database for studies in English that were in print from April 1, 1963 through August 20, 2015, involving opioid-related overdoses in adult clinical populations. We used the search terms “opioid” AND (“overdose” OR “poisoning” OR “toxicity”) AND “patient”.

Search Results and Exclusion Criteria

The search resulted in 1790 articles. We then performed a careful review of the content of the articles identified in our search. We excluded articles that: (1) were review papers, opinion pieces, or editorials; (2) used data limited to case reports; (3) did not test associations between risk factors and opioid overdose; (4) did not involve clinical populations; or (5) did not involve opioids prescribed for treatment of pain.

We first examined the methods across studies to characterize the similarities and differences between studies approach and contextualize potential differences in findings between studies. We then examined the specific types of risk factors included in each study and identified the primary finding of each study, and also additional factors examined.

Of note, although the patient and treatment characteristics considered in the reviewed papers may be better termed “risk indicators” because the methods preclude a high degree of confidence that the relationships studied are always causal, we have used the more common term “risk factor” here.

RESULTS

Characteristics of Selected Studies

After a detailed review, we found 15 out of 1790 articles described studies that were relevant to the present study and did not meet any of the exclusion criteria (Table 1).

Study Design

All studies included in this review were observational in nature. There were 9 cohort studies, 4 case-control studies, and 2 case-cohort studies. The data for all studies were generated prospectively and thus were not subject to recall bias, but no study was based on prospective assessment of enrolled participants; instead, all studies relied on 1 or more type of administrative or surveillance data. Follow-up time differed between studies ranging from 15 days (Miller et al., 2015) to 13 years (Kaplovitch et al., 2015) (Table 2).

Data Sources

All studies utilized data from patients in the United States or Canada. All but 2 studies utilized administrative claims data from various health systems and programs, including Medicaid, the Veterans Health Administration (VHA), the Ontario Provincial Drug Program, and commercial insurance plans. The administrative claims data generally were used to obtain data regarding demographic, clinical characteristics, medications, and healthcare utilization. Data from state prescription monitoring programs (PMPs) were utilized in 2 studies (Paulozzi et al., 2012; Baumblatt et al., 2014) to measure the prescription of controlled substances. To measure outcomes, death certificate data were used to determine overdose as a cause of death in 8 studies (Dunn et al., 2010; Bohnert et al., 2011; Gomes et al., 2011; Paulozzi et al., 2012; Baumblatt et al., 2014; Kaplovitch et al., 2015; Park et al., 2015; Ray et al., 2015). The other studies utilized International Classification of Diseases diagnostic codes recorded for outpatient, inpatient, and/or emergency department patient encounters.

Population

Studies differed with regards to specific opioid types and formulations included. All studies included schedule II and III opioids. One study included patients who received a prescription for any controlled substance (drugs in schedules II, III, or IV and carisoprodol) in the control group (Paulozzi et al., 2012). Approximately a quarter of patients in the control group of that study did not receive an opioid during the study period. One study only included extended-release/long-acting (ER/LA) opioids (Hartung et al., 2007), another study only compared those receiving long-acting morphine to methadone (Ray et al., 2015), and 2 studies only included schedule II or III opioids (Liang and Turner, 2015; Turner and Liang, 2015). Two studies included buprenorphine (Paulozzi et al., 2012; Zedler et al., 2014). The majority of studies (11 of 14 studies) included methadone, but 2 studies excluded liquid methadone (Miller et al., 2015; Park et al., 2015) and 2 other studies excluded methadone entirely (Bohnert et al., 2011; Gomes et al., 2011). Two studies included schedule IV opioids such as codeine cough suppressants and tramadol (Braden et al., 2010; Zedler et al., 2014). One study excluded fentanyl (Bohnert et al., 2011) and another excluded hydrocodone (Gomes et al., 2011). Four studies included patients who received opioids starting in 1997 (Dunn et al., 2010; Gomes et al., 2011; Kaplovitch et al., 2015; Ray et al., 2015), whereas the rest of the studies included only patients who received opioids during or after 2000.

Several studies sought to examine specific subgroups of patients receiving opioids, although the methods used to define subgroups varied. Three studies examined patients receiving chronic opioid therapy for pain by requiring multiple opioid prescriptions in 90 days without significant gaps between prescriptions (Braden et al., 2010; Dunn et al., 2010; Yang et al., 2015). Another study only included patients who received one or more opioid prescriptions at least 91 days after their first opioid prescription (Kaplovitch et al., 2015). Two studies required a chronic pain diagnosis (Dunn et al., 2010; Miller et al., 2015). Another study examined patients with a chronic pain diagnosis along with 3 other patient subgroups: acute pain, cancer, and substance use disorders (Bohnert et al., 2011). Five studies excluded patients with cancer and 6 studies excluded palliative care and/or hospice patients.
## TABLE 1.  Studies That Test Associations Between Potential Risk Factors and Overdose

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Dates</th>
<th>Data Source(s)</th>
<th>Sample Size</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Overdose Outcome</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumblatt et al., 2014</td>
<td>Case-control study</td>
<td>2009–2010</td>
<td>Tennessee PMP and Tennessee Death Statistical System</td>
<td>Cases: n = 932, controls: n = 11,840</td>
<td>≥1 opioid prescription in PMP</td>
<td>Opioid analgesic-related fatal OD of unintentional or undetermined intent</td>
<td>Increased risk of OD associated with: 4 or more prescribers (OR = 6.5), 4 or more pharmacies (OR = 6), and more than 100 MME/d (OR = 11.2) Risk increased with increasing number of prescribers, pharmacies, and daily opioid dosages</td>
</tr>
<tr>
<td>Bohnert et al., 2011</td>
<td>Case-cohort study</td>
<td>2004–2008</td>
<td>VHA administrative data and National Death Index</td>
<td>Cases: n = 750, subcohort: n = 154,684</td>
<td>≥1 opioid analgesic fill and received medical services, excluded palliative care and hospice patients</td>
<td>Opioid analgesic-related fatal OD of unintentional or undetermined intent</td>
<td>Increased risk of OD associated with ≥50 MME/d compared with 1 to 20 MME/d in 4 patient groups: chronic pain, cancer, acute pain, and substance use disorders Risk increased further with ≥100 MME/d Factors most strongly associated with alcohol or drug-related encounter were: substance use disorder diagnoses, opioid daily dosage, and ER/LA opioids</td>
</tr>
<tr>
<td>Braden et al., 2010</td>
<td>Retrospective cohort study</td>
<td>2001–2004</td>
<td>Claims data from commercial insurance plans (HealthCore) and Arkansas Medicaid</td>
<td>HealthCore total: N = 38,491, cases: n = 622, Arkansas Medicaid total: N = 10,159, cases: n = 264</td>
<td>Prescribed opioids for at least 90 continuous d over 6 mos, excluded nursing home residents, hospice patients, and cancer patients</td>
<td>Alcohol or drug-related encounter which included: (1) alcohol intoxication, withdrawal, or overdose, (2) drug intoxication or withdrawal, and (3) nonfatal drug overdose</td>
<td>Risk increased further with ≥100 MME/d</td>
</tr>
<tr>
<td>Dunn et al., 2010</td>
<td>Retrospective cohort study</td>
<td>1997–2005</td>
<td>Automated healthcare data from Group Health Cooperative, a Washington state health system</td>
<td>Total: N = 9940, cases: n = 51</td>
<td>≥3 opioid prescriptions in first 90 d of new episode of opioid use and diagnosis of noncancer pain, excluded cancer patients</td>
<td>Opioid-related fatal and nonfatal OD of any intent</td>
<td>Increased risk of OD associated with 50 to 99 MME/d (HR = 3.7) and 100 MME/d (HR = 8.9) compared with 1 to 20 MME/d</td>
</tr>
<tr>
<td>Gomes et al., 2011</td>
<td>Case-control study</td>
<td>1997–2006</td>
<td>Ontario Public Drug Benefit Program, Ontario Cancer Registry, Canadian Institute for Health Information, Ontario Health Insurance Plan, and Ontario Registered Person databases</td>
<td>Cases: n = 498, controls: n = 1714</td>
<td>≥1 opioid analgesic fill, excluded cancer and palliative care patients</td>
<td>Opioid-related fatal OD of any intent</td>
<td>Increased risk of OD associated with 50 to 99 MME/d (OR = 1.9), 100 to 100 MME/d (OR = 2.0), and ≥200 MME/d (OR = 2.9) compared with &lt;20 MME/d</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Dates</td>
<td>Data Source(s)</td>
<td>Sample Size</td>
<td>Inclusion/Exclusion Criteria</td>
<td>Overdose Outcome</td>
<td>Main Findings</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hartung et al., 2007</td>
<td>Retrospective cohort study</td>
<td>2000–2004</td>
<td>Oregon Medicaid claims data</td>
<td>Total: N = 5684, number of opioid-related adverse events unclear</td>
<td>≥1 long-acting opioid analgesic fill of ≥28 days supply</td>
<td>Opioid-related adverse events, including nonfatal OD</td>
<td>Decreased risk of opioid-related adverse event associated with long-acting oxycodone compared with long-acting morphine (HR = 0.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased risk of OD symptoms in methadone compared with long-acting morphine in those with noncancer pain (HR = 1.6)</td>
</tr>
<tr>
<td>Kaplovitch et al., 2015</td>
<td>Retrospective cohort study</td>
<td>1997–2010</td>
<td>Ontario Public Drug Benefit Program, Ontario Cancer Registry, Canadian Institute for Health Information, Ontario Health Insurance Plan, and Ontario Registered Person databases</td>
<td>Total: N = 32,499, cases: n = 59</td>
<td>≥3 months of opioid treatment, new users only, excluded cancer patients</td>
<td>Opioid-related fatal OD of unintentional, intentional, and undetermined intent; deaths involving another drug at concentration high enough to cause death were excluded</td>
<td>Increased risk of OD associated with being male (HR = 2.0)</td>
</tr>
<tr>
<td>Liang and Turner, 2015</td>
<td>Retrospective cohort study</td>
<td>2009–2012</td>
<td>Aetna Health Maintenance Program data</td>
<td>Total: N = 206,869, Cases: n = 1385</td>
<td>≥2 schedule II or III opioid analgesic prescriptions, excluded cancer and opioid maintenance patients</td>
<td>Nonfatal OD from any drug of any intent</td>
<td>Increased risk of OD associated with daily opioid dosage in dose-response fashion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased risk of OD associated with higher total MME (daily opioid dose × days of supply in previous 6 mos) among those prescribed 50 to 99 MME/d</td>
</tr>
<tr>
<td>Miller et al., 2015</td>
<td>Retrospective cohort study</td>
<td>2000–2009</td>
<td>VHA administrative data</td>
<td>Total: N = 840,606, Cases: n = 319</td>
<td>New users of opioid analgesics, ≥1 opioid analgesic fill, chronic noncancer pain, excluded hospice patients</td>
<td>Nonfatal OD from any drug of unintentional or undetermined intent</td>
<td>Increased risk of OD associated with ER/LA opioids than short-acting opioids (HR = 2.3), particularly in the first 2 wks of initiating treatment (HR = 5.3)</td>
</tr>
<tr>
<td>Park et al., 2015</td>
<td>Case-cohort study</td>
<td>2004–2009</td>
<td>VHA administrative data and National Death Index</td>
<td>Cases: n = 2400, subcohort: n = 420,386</td>
<td>≥1 opioid analgesic fill and received medical services, excluded palliative care, hospice, and opioid maintenance patients</td>
<td>Fatal OD from any drug of unintentional, intentional, or undetermined intent</td>
<td>Increased risk of OD associated with concurrent receipt of opioids and benzo diazepines (HR = 3.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk of OD associated with benzodiazepines increased as benzodiazepine dosage increased</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Dates</td>
<td>Data Source(s)</td>
<td>Sample Size</td>
<td>Inclusion/Exclusion Criteria</td>
<td>Overdose Outcome</td>
<td>Main Findings</td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Paulozzi et al., 2012</td>
<td>Case-control study</td>
<td>2006–2008</td>
<td>New Mexico PMP and New Mexico Office of the Medical Investigator</td>
<td>Cases: n = 300, controls: n = 5993</td>
<td>≥1 record in PMP</td>
<td>Opioid-related fatal, unintentional OD</td>
<td>Increased risk of OD associated with opioid type, particularly methadone, fentanyl, hydrocodone, and oxycodone</td>
</tr>
<tr>
<td>Ray et al., 2015</td>
<td>Retrospective cohort study</td>
<td>1997–2009</td>
<td>Tennessee Medicaid data, death certificate data, and a statewide hospital discharge database</td>
<td>Total: N = 38,756, cases: n = 43</td>
<td>≥1 long-acting morphine or methadone fill, excluded cancer or other serious illness, &quot;drug abuse&quot; (other than alcohol or tobacco), and recent hospitalization</td>
<td>Opioid-related fatal OD of any intent</td>
<td>Increased risk of OD associated with methadone compared with long-acting morphine (HR = 2.5)</td>
</tr>
<tr>
<td>Turner and Liang, 2015</td>
<td>Retrospective cohort study</td>
<td>2009–2012</td>
<td>Aetna Health Maintenance Program data</td>
<td>Total: N = 206,869, cases: n = 1385</td>
<td>≥2 schedule II or III opioid analgesic prescriptions, excluded cancer and opioid maintenance patients</td>
<td>Nonfatal OD from any drug of any intent</td>
<td>Risk of OD higher among patients with depression in all opioid dosage categories except ≥100 MME/d</td>
</tr>
<tr>
<td>Yang et al., 2015</td>
<td>Retrospective cohort study</td>
<td>2008–2010</td>
<td>MarketScan Medicaid claims data</td>
<td>Total: N = 90,010, cases: n = 1237</td>
<td>≥3 opioid prescriptions for ≥90 d with no gaps &gt;31 d between prescriptions</td>
<td>Opioid-related nonfatal OD of any intent</td>
<td>Increased risk of OD associated with: overlapping opioid prescriptions (2 prescriptions of the same drug that overlapped by ≥25% of the days prescribed) (HR = 3.0) and ≥4 pharmacies (HR = 1.8)</td>
</tr>
<tr>
<td>Zedler et al., 2014</td>
<td>Case-control study</td>
<td>2010–2012</td>
<td>VHA administrative data</td>
<td>Cases: n = 817, controls: n = 8170</td>
<td>≥1 opioid analgesic fill</td>
<td>Opioid-related nonfatal toxicity or unintentional overdose</td>
<td>Increased risk of OD most strongly associated with ≥100 MME/d (OR = 4.1), history of opioid dependence (OR = 3.9), and hospitalization in 6 months before OD (OR = 2.9)</td>
</tr>
</tbody>
</table>

OD, overdose.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design/ Demographics</th>
<th>Medical Comorbidities</th>
<th>Mental Health Comorbidities</th>
<th>Substance Use Disorder Comorbidities</th>
<th>Pain Conditions</th>
<th>Other Variables Examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohnert et al., 2011</td>
<td>Risk of OD decreased as age increased in all patient groups. Black patients had a lower risk of OD compared with white patients in those with chronic pain or substance use disorders.</td>
<td>Decreased risk of OD was associated with COPD, CVD, and sleep apnea in those with chronic pain.</td>
<td>Increased risk of OD associated with nonsubstance use psychiatric disorders in those with chronic pain, cancer, and substance use disorders.</td>
<td>Increased risk of OD associated with substance use disorders in those with chronic pain, cancer, and acute pain.</td>
<td>Increased risk of OD associated with injuries and acute pain in those with chronic pain.</td>
<td>Decreased risk of OD associated with chronic bodily pains in those with acute pain.</td>
</tr>
<tr>
<td>Braden et al., 2010</td>
<td>Decreased risk of alcohol or drug-related encounter associated with older age in HealthCore sample. Increased risk associated with being female in Medicaid sample.</td>
<td>Increasing risk of alcohol or drug-related encounter as number of mental health disorders increased in both samples.</td>
<td>Increased risk of alcohol or drug-related encounter with alcohol, nonopioid, and opioid use disorders in both samples.</td>
<td>Decreased risk of alcohol or drug-related encounter with neck pain and arthritis and/or joint pain in both samples.</td>
<td>Increased risk of alcohol or drug-related encounter with greater days of supply of sedative/hypnotic medication in both samples.</td>
<td>Increased risk of OD associated with “as needed” only compared with regularly scheduled prescriptions in those with cancer.</td>
</tr>
<tr>
<td>Park et al., 2015</td>
<td>Increased risk of OD associated with being male.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paulozzi et al., 2012</td>
<td>Increased risk of OD associated with older age.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turner and Liang, 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al., 2015</td>
<td>Black patients had a lower risk of OD compared with white patients.</td>
<td>Increased risk of OD associated with history of depression.</td>
<td>Increased risk of OD associated with history of alcohol abuse.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 2 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Demographics</th>
<th>Medical Comorbidities</th>
<th>Mental Health Comorbidities</th>
<th>Substance Use Disorder Comorbidities</th>
<th>Pain Conditions</th>
<th>Other Variables Examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zedler et al., 2014</td>
<td>Increased risk of OD associated with older age</td>
<td>Increased risk of OD associated with a range of medical comorbidities including: chronic pulmonary disease, renal disease, skin ulcers, metastatic solid tumor, use of warfarin, moderate to severe liver disease, pancreatitis, and sleep apnea</td>
<td>Increased risk of OD associated with bipolar disorder Decreased risk in those with ADHD</td>
<td>Increased risk of OD associated with substance abuse and opioid dependence</td>
<td>Increased risk of OD associated with traumatic injury</td>
<td>Increased risk of OD with hospitalizations of 1 d or greater in length</td>
<td></td>
</tr>
</tbody>
</table>

White patients and patients of other races had a higher risk of OD compared with black patients.

Increased risk of OD associated with being widowed.

Those living in the West had a higher OD risk than those living in the Northeast.

Decreased risk of OD in those with rheumatologic disease.

Decreased risk in those with ADHD.

Increased risk of OD associated with being widowed.

Those living in the West had a higher OD risk than those living in the Northeast.

Several studies were not included in this table because they involved case-control studies with matching or because risk estimates for variables other than the main outcomes were not reported.

ADHD, attention deficit hyperactivity disorder; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; OD, overdose.
Opioid Dosage

Confounders Studied

Results of Adjusted Models: Main Overdose Risk Factors Studied

Opioid Dosage

Among all of the studies that reported on the relationship between opioid dosage and overdose, the finding that higher dosages were associated with an increased risk of overdose compared with the lowest-risk group category (typically 1 to <20 MME/d) was universally true, irrespective of the study design, data source, population, or how opioid dosage was measured. All studies that tested different opioid dosage categories found a dose-response relationship. There was some inconsistency between studies regarding the lowest opioid dosage category that was associated with an increased overdose risk. Four studies found an increased risk associated with opioid doses between 20 and <50 MME/d (Bohnert et al., 2011; Zedler et al., 2014; Liang and Turner, 2015; Yang et al., 2015), but one of them only in a chronic pain patient subgroup (Bohnert et al., 2011). Two studies found an increased risk associated with 50 to <100 MME/d and higher (Dunn et al., 2010; Gomes et al., 2011). One study tested both the assumed dosage and average dosage approaches to measuring opioid dosage and found that each approach had a similar dose-response relationship between dose and overdose risk, but the opioid dosage in the assumed dosage approach had larger risk estimates (Gomes et al., 2011).

One study examined the total quantity of opioid taken in a 6-month interval (not divided by the number of days), and also daily dosage (Liang and Turner, 2015). For example, a week of 50 MME/d would equal a total quantity of 350 MME. They found that at the 50 to <100 MME daily opioid dosage category, receiving a higher total quantity of opioid further increased overdose risk. They did not find a similar relationship in any of the other daily opioid dosage categories, including the highest category of ≥100 MME/d.

Other Opioid Treatment Characteristics

Several other characteristics of opioid prescribing were tested in the included studies. Three studies calculated risk of overdose associated with duration of action of the opioid analgesic (Braden et al., 2010; Zedler et al., 2014; Miller et al., 2015). They found that ER/LA opioids were associated with an increased overdose risk compared with short-acting opioids. One study found the greatest overdose risk from ER/LA opioids to be during the first 2 weeks after initiation of treatment (Miller et al., 2015). Two studies did not categorize opioid medications by duration of action, but instead examined the risks associated with specific opioid formulations. One of these found an increased overdose risk with fentanyl, hydromorphone, methadone, and oxycodone (Paulozzi et al., 2012), and the other found an increased risk of overdose with hydrocodone and oxycodone and a decreased risk with tramadol (Zedler et al., 2014). Two studies particularly focused on the comparison of morphine with methadone (Hartung et al., 2007; Ray et al., 2015) because the latter has pharmacological properties that could increase risk of overdose. One found an increased risk of overdose symptoms in methadone compared with long-acting morphine (Hartung et al., 2007), and the other found an increased risk of overdose death in methadone compared with long-acting morphine (Ray et al., 2015).

Two studies examined overlapping prescriptions (2 prescriptions of the same formulation that overlapped by ≥25% of the days prescribed), which may be a marker of early refills (Paulozzi et al., 2012; Yang et al., 2015). Both the studies by Paulozzi et al. (2012) and Yang et al. (2015) found that having overlapping opioid prescriptions was strongly associated with increased risk. Additionally, 1 study found that prescription schedule (“as needed,” regularly scheduled, or both) was not associated with overdose risk after adjusting for other factors (Bohnert et al., 2011).
Other Medications

Several studies examined concurrent prescription of other medications and their association with overdose. Three studies examined the sedative-hypnotic class of drugs (Braden et al., 2010; Dunn et al., 2010; Yang et al., 2015), and 3 studies specifically examined benzodiazepines (Zedler et al., 2014; Park et al., 2015; Turner and Liang, 2015). One study that examined benzodiazepines also studied antidepressants and zolpidem (Turner and Liang, 2015), and another examined antidepressants and antipsychotics (Zedler et al., 2014).

Although results were fairly consistent across studies regardless of measures, definitions for how other medication use was measured differed across studies. Four studies examined the number of days of supply of medications during a time interval before the index date (Braden et al., 2010; Dunn et al., 2010; Zedler et al., 2014; Turner and Liang, 2015). Braden et al. (2010) examined the supply of sedative-hypnotics per 30 days and found it to be associated with an increased risk of alcohol or drug-related adverse event. Another study examining the number of days of supply of sedative-hypnotics found that there was an increased overdose risk relative to people not receiving any sedative-hypnotics, but the risk did not further increase with the number of days sedative-hypnotics were prescribed (Dunn et al., 2010). The Turner and Liang (2015) study used a similar method as that used by Dunn et al. (2010) and found that overdose risk increased with increasing duration of benzodiazepine treatment. In the same study, among those with depression, long-term antidepressant therapy (at least 90 days during a 180-day interval) was associated with a decreased overdose risk. Additionally, zolpidem, a nonbenzodiazepine hypnotic, was associated with increased overdose risk in those without an anxiety disorder, but not in those with an anxiety disorder. One study considered benzodiazepines, antidepressants, and antipsychotics prescribed during a 6-month “look-back period” and found that each was associated with an increased overdose risk. Zedler et al. (2014). Finally, Park et al. (2015) measured the overdose risk only during times when benzodiazepines were prescribed to be taken concurrently with opioids and found that benzodiazepines were associated with an increased overdose risk in a dose-response fashion.

Prescriber and Pharmacy Shopping

Two studies in this review tested the number of prescribers or pharmacies utilized by patients (Baumblatt et al., 2014; Yang et al., 2015), commonly referred to as “doctor shopping” or “pharmacy shopping.” The Baumblatt et al. (2014) study found that use of ≥4 pharmacies or prescribers in the past year was both associated with an increased overdose risk. The Yang et al. (2015) study considered several potential definitions of pharmacy shopping and determined that a threshold of ≥4 pharmacy visits in 90 days was a useful indicator of increased overdose risk.

Demographics

A number of studies reported findings on patient demographic characteristics and their associations with overdose risk, although this was not the primary focus of any studies. Overdose risk decreased with older age in all subgroups of 1 study (Bohnert et al., 2011) and in the private insurance subgroup of another study (Braden et al., 2010). In contrast, older age was associated with an increased risk in 2 other studies (Paulozzi et al., 2012; Zedler et al., 2014), and was not associated with overdose risk in another study (Yang et al., 2015). Being male was associated with increased overdose risk in 2 studies (Paulozzi et al., 2012; Kaplovitch et al., 2015) and being female was associated with an increased overdose risk in the Medicaid subgroup of another study (Braden et al., 2010). Another study found no association between sex and overdose risk (Yang et al., 2015). Black patients were found to have a lower overdose risk than white patients in all 3 studies that examined race (Bohnert et al., 2011; Zedler et al., 2014; Yang et al., 2015). One study examined region of the United States and found that those living in the West had a higher overdose risk than those living in the Northeast (Zedler et al., 2014).

Comorbidities

Four studies reported associations between comorbidities and overdose risk. Substance use disorder diagnoses were associated with an increased overdose risk in all studies that reported on the relationship (Braden et al., 2010; Bohnert et al., 2011; Zedler et al., 2014; Yang et al., 2015). Mental disorders were also found to be associated with increased overdose risk when studied. Patients diagnosed with depression were found to have increased overdose risk compared with those without depression in all opioid dosage categories except in those receiving ≥100 MME/d (Turner and Liang, 2015). Depression (Yang et al., 2015) and bipolar disorder (Zedler et al., 2014) were associated with increased overdose risk. One study examined nonsubstance use psychiatric disorders and found an association with increased overdose risk in subgroups of patients defined by having chronic pain, cancer, or substance use disorders (Bohnert et al., 2011). Although 1 study (Braden et al., 2010) found that the Charlson comorbidity index was unrelated to overdose risk, other studies found that specific medical disorders such as chronic pulmonary disease, sleep apnea, and skin ulcers were associated with increased risk. Bohnert et al. found that chronic obstructive pulmonary disease, cardiovascular disease, or sleep apnea was associated with decreased risk in patients with chronic pain conditions. Regarding pain comorbidities, 1 study found that back pain and headache were associated with increased overdose risk, and neck pain and arthritis were associated with a decreased risk (Braden et al., 2010). Another study found that traumatic injury was associated with an increased overdose risk (Zedler et al., 2014).

DISCUSSION

Comparability of Studies

The methodology of the included studies was variable in several key ways. One difference was in the study population. Some studies focused on the chronic pain population, whereas others included any patient who received opioid analgesics. Nonetheless, in a study that examined 4 different patient subgroups, similar associations were found between opioid dose and overdose (Bohnert et al., 2011). Also, 4
studies included patients who received opioids starting in 1997 (Dunn et al., 2010; Gomes et al., 2011; Kaplovitch et al., 2015; Ray et al., 2015), before the start of the rapid rise in the number of opioid prescriptions in North America. Prescribing practices, particularly those concerning patient selection, may have been different in these earlier studies, and therefore the relationships between risk factors and overdose may have differed in these studies. Additionally, follow-up times varied among studies. Longer follow-up times allow for the possibility of more overdose outcomes which can increase the power of studies to detect associations. Also, risk factors associated with overdose may vary between the period of early use versus long-term use.

Studies also differed on the definition of overdose. First, many utilized death certificate data to confirm death and the cause of death, whereas others used overdose-related diagnosis codes in administrative claims data from inpatient, outpatient, and emergency department encounters to identify overdose events. Both methods likely undercount overdose events. Both types of studies would not include overdoses that are less severe and do not receive treatment or result in death, and studies based on death certificate data may also not be able to characterize risk for overdose in circumstances where the overdose is likely to be survived, generally. Studies relying on encounters with the healthcare system to assess overdose events may bias results if the factors being considered in relation to overdose risk are related to the likelihood of accessing health services or the likelihood that death occurs before treatment can be obtained. There are insufficient data available to draw strong conclusions about whether the type of overdose measurement relates to risk factors, although it is notable that the well-replicated finding of opioid dosage has been consistent across sources of data. Second, some studies restricted the outcome to overdose caused by opioid analgesics, whereas others included all substances. Although the former approach has the benefit of focusing on those overdoses with the greatest potential to be directly related to the opioid use, there is potentially problematic variation in the use and interpretation of toxicology screening by locality. Nonetheless, 1 study reported sensitivity analyses that compared deaths caused by opioid analgesics and/or benzodiazepines compared with all drug overdoses and found little difference in overdose risk (Park et al., 2015). That study also found little difference in overdose risk when comparing deaths that included suicides to deaths where intent was undetermined or unintentional.

Studies also differed in the number and type of patient and treatment characteristics included in adjusted models. One study reported hazard ratios for overdose after controlling in a stepwise fashion for 3 covariate groups: demographics, clinical conditions, and other drugs (Liang and Turner, 2015). The authors found that hazard ratios for overdose were particularly sensitive to clinical conditions. Therefore, studies that controlled for clinical conditions likely provide more robust evidence than those that do not.

There were also important similarities across the studies. All studies were observational studies that utilized health databases, either administrative claims, or prescription drug monitoring program databases. None involved prospective data collection. Methods for measuring opioid exposure were largely similar across studies. All studies utilized prescription data that included medication type, strength, and days of supply. Although there were 2 approaches used to calculate opioid dosage, 1 study found that increasing opioid dosages were associated with increasing overdose risk using both methods (Gomes et al., 2011).

Summary and Implications of Overdose Risk Factors

Opioid Dosage

Increasing daily opioid dosage was associated with increasing overdose risk in all studies that examined this relationship. It is important to note that a high opioid dosage may be a marker for other characteristics associated with overdose. Some of the opioid-prescribing guidelines published after several of the earliest studies on opioid dosage and overdose have recommended lower prescribing maximums than prior guidelines (Nuckols et al., 2014), though doses should be determined on a case-by-case basis after weighing risks and benefits for individuals. In addition, studies used fairly broad opioid dosage categories. Other analytic techniques may be able to better determine whether there is a specific threshold after which risk increases noticeably.

Other Opioid Treatment Characteristics

Other characteristics of opioid prescribing were found to be associated with increased risk of overdose. Among these characteristics, the most consistent finding was the increased risk associated with ER/LA opioids. In 1 study, patients who were initiated on ER/LA opioids had higher daily opioid dosages and were more likely to have depression, drug use disorder, and chronic pain (Miller et al., 2015). Thus, similar to high opioid dosage, initiation with an ER/LA opioid prescription may be a marker for other characteristics associated with overdose. Overdose risk has also been associated with oxycodone, hydromorphone, and methadone (Hartung et al., 2007; Paulozzi et al., 2012; Zedler et al., 2014; Ray et al., 2015). All studies included schedule II and III opioids. Several studies included schedule IV opioids, which may be associated with a lower risk of overdose. By including opioids that are potentially less lethal, these studies may have underestimated the strength of association between overdose and risk factors such as opioid dose. Opioid prescribing involving a significant overlap in prescriptions of the same drug has been identified as an overdose risk in 2 studies. This is likely to represent early opioid refills, a potential sign of opioid misuse (Starrels et al., 2011). Though this overlap in prescriptions could represent other clinically indicated patterns of opioid use, this pattern may be a useful indicator for payer or health system processes for identifying and intervening with high-risk patients.

Other Medication Use

All studies that examined sedative-hypnotics or benzodiazepines (a type of sedative-hypnotic drug) found an increased risk of overdose associated with their use. However,
benzodiazepines may be a marker for symptom severity, which may be associated with overdose risk. Nevertheless, because of the consistency of this finding across studies and the plausibility of a biological mechanism of combined effects on the central nervous system, benzodiazepines and other sedative-hypnotics should be used with caution in patients taking opioids for pain.

**Prescriber and Pharmacy Shopping**

Two studies focused on the number of prescribers and pharmacies used by a patient as overdose risk factors. A high number of prescribers or pharmacies used by a patient to obtain opioid prescriptions may represent high-risk opioid behavior, including opioid misuse and/or diversion, and also possession of a larger total quantity of opioids and other controlled substances. These findings suggest that use of prescription monitoring programs may help providers, payers, and health systems identify high-risk behavior.

**Demographics**

Among patient demographic characteristics, the only consistent finding in the included studies was a decreased overdose risk associated with being black. Black patients are less likely to receive opioids for pain during emergency department visits (Pletcher et al., 2008), a disparity that potentially leads to both undertreatment of pain and a decreased risk of overdose. Additionally, black patients may be less likely to receive a thorough death investigation, which may have influenced the results of studies that used death certificate data (Huguet et al., 2012). One study focused on sex as the primary overdose risk factor and found that men had approximately twice the risk of overdose death than women (Kaplovitch et al., 2015).

**Comorbidities**

Among comorbid conditions, substance use disorder diagnoses were most consistently identified as being associated with overdose risk. In particular, substance use disorder diagnoses seem to have the strongest associations with overdose risk among comorbidities. With regards to other mental health disorders, 1 study demonstrated greater overdose risk in depressed patients across different daily opioid dose categories (Turner and Liang, 2015). The study also found that among those with a depression diagnosis, longer-term antidepressant prescription was associated with a decreased overdose risk. The interactions between mental health conditions and their treatment tested in this study provide a useful framework for understanding these potentially complicated relationships, and further research examining the impact of mental health and substance use disorder treatment on overdose risk is needed. With regards to medical disorders, the specific disorders examined and the findings associated with those disorders varied widely across studies. Of note, diagnoses in administrative databases tend to have lower-than-moderate sensitivity and high specificity, and reliance on these sources of data may have introduced bias (Wilchesky et al., 2004). Research on overdose risk factors would benefit from a more comprehensive study of medical comorbidities to identify those patients at greatest risk for adverse outcomes of opioid treatment. Nonetheless, settings where individuals with substance use disorders and other mental health conditions are treated are likely important for opioid overdose prevention efforts.

**Recent CDC Guidelines for Opioid Prescribing for Chronic Pain**

Recently, the Centers for Disease Control released guidelines for prescribing opioids for chronic pain (Dowell et al., 2016). These guidelines discuss risk factors for opioid-related harms including overdose, utilizing a combination of expert opinion and literature review, and made recommendations aimed at primary care clinicians who treat patients with chronic pain. Several of these recommendations were aligned with findings from the present review including reassessing risks and benefits of opioid therapy when prescribing opioid dosages ≥50 MME/d, avoiding initiating opioid therapy with ER/LA opioids, avoiding prescribing concurrent benzodiazepines and opioids, and incorporating strategies to mitigate risk of overdose when prescribing opioids to patients with a history of substance use disorder.

**Limitations and Future Research**

Though a number of large observational studies examining risk factors for overdose have now been completed, there are several areas of inquiry that remain understudied. Notably, no overdose studies involve prospective assessment of enrolled participants, making it difficult to assess for potentially important risk factors such as the level of disability associated with pain and severity of addiction, and mental health symptoms. Because overdose death is a relatively rare event among those prescribed opioid analgesics, a prospective cohort study of overdose deaths may be difficult to accomplish given the required sample size, but studies could focus on groups with highest risk of overdose based on known risk factors. Given the challenges of conducting prospective cohort studies on this issue, other novel approaches such as using systems dynamic modeling to examine strategies to mitigate opioid overdose at the population level (Wakeland et al., 2015) may be helpful in thinking about system-wide interventions.

No studies included in this review measured actual medication-taking behavior or use of other substances. Thus, implications from these studies may have more relevance for provider decision-making about pharmacotherapies than they do for patient education. A substantial minority of patients either under or overutilize their pain medications (Lewis et al., 2010). In 1 study, more than 40% of patients who died of an opioid analgesic-related overdose were not prescribed an opioid at the time of death (Bohnert et al., 2011). Furthermore, most studies included in this review did not report how opioid dose was calculated with overlapping prescriptions, introducing further heterogeneity in ascertaining doses across studies. Improved measurement of actual medication and other drugs ingested may give a clearer picture of the risk factors involved in overdose. In addition, understanding the relationship between specific opioid-related aberrant behaviors with overdose risk (eg, taking more opioid than prescribed vs taking for reasons other than pain) may help inform prevention.
Further limitations include exclusion of non-English-language articles, meta-analysis was not attempted, and publication bias was not assessed. As this is a fast growing area of research, our findings could change based on new evidence published since the literature review was conducted (eg, Dasgupta et al., 2016), and in the future.

It is unclear what impact prescriber and health system characteristics may have on overdose risk. In Ontario, Canada, prescribers in the highest quintile of opioid-prescribing frequency issued opioid prescriptions 55 times more often than the lowest quintile (Dhalla et al., 2011), and those with the highest level of opioid prescribing also had the most patients die of opioid analgesic-related overdose. A study of facility-level practices in the VHA and the risk of suicide attempt may serve as a good model for a similar study that could examine overdose risk (Im et al., 2015).

A recent study developed a risk index for overdose in VHA patients using risk factors most highly associated with overdose (Zedler et al., 2015). They found that the risk index tool performed well in identifying patients prescribed opioid analgesics most at risk of overdose. Further work refining such a tool to tailor risk factors to specific patient populations, and testing its applicability in other populations, may aid clinical decision-making in prescribing opioids for pain and targeting risk mitigation efforts (eg, take-home naloxone for overdose reversal).

Lastly, there is growing evidence of genetic variation in opioid metabolism that could explain variation in overdose risk beyond the risk factors easily studied through the available data (Bruehl et al., 2013), but new genetic data collection initiatives may allow further exploration of this topic.

CONCLUSIONS

Overdoses involving opioid analgesics have increased dramatically in the United States. Opioid dosage is the risk factors with the most accumulated evidence of a relationship with overdose. Concurrent sedative-hypnotic use, use of ER/LA opioids, and the presence of substance use and other mental health disorders are also consistently found to be associated with increased overdose risk. Thus, these factors are important for reconsideration of treatment practices and identification of high-risk groups for risk-reduction interventions.

Future research is needed to better characterize populations taking opioids for pain to help clarify current risk factors. Future research may also discover new risk factors for overdose, which may emerge as treatment patterns change in response to heightened awareness of the risks of opioids and greater use of risk mitigation tools. A better understanding of patient groups and opioid-related prescribing practices associated with overdose risk may assist clinicians and policymakers in helping to treat pain while improving the safety of opioid prescribing.

REFERENCES


