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Neurocognitive impairments and brain abnormalities resulting from opioid-related overdoses: A systematic review

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Abstract

Background: Non-fatal opioid-related overdoses have increased significantly over the past two decades and there have been increasing reports of brain injuries and/or neurocognitive impairments following overdose events. Limited preclinical research suggests that opioid overdoses may cause brain injury; however, little is known about such injuries in humans. The purpose this systematic review is to summarize existing studies on neurocognitive impairments and/or brain abnormalities associated with an opioid-related overdose in humans.

Methods: PubMed, Web of Science, Ovid MEDLINE and PsyINFO were searched, without year restrictions, and identified 3099 articles. An additional 24 articles were identified by reviewing references. Articles were included if they were published in English, reported study findings in humans, included individuals 18 years of age or older, and reported an objective measure of neurocognitive impairments and/or brain abnormalities resulting from an opioid-related overdose. Six domains of bias (selection, performance, attrition, detection (two dimensions) and reporting were evaluated and themes were summarized.

Results: Seventy-nine journal articles, published between 1973–2020, were included in the review. More than half of the articles were case reports (n = 44) and there were 11 cohort studies, 18 case series, and 6 case-control studies. All of the studies were categorized as at-risk of bias,

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Contributors

ELW initially developed the concept and all authors contributed to the development of the protocol. ELW conducted the search and initial review of the identified articles. Once eligible articles were imported into COVIDENCE; ELW, JJM and FC reviewed the abstracts and full articles to determine inclusion. Disagreements were resolved by SDC. JJM and FC developed the coding scheme for the diagnoses and symptoms. ELW extracted the data elements into the database, which was reviewed by JJM and FC to ensure agreement and accuracy. ELW drafted the manuscript which was reviewed by all authors, who provided input and review of all revisions.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2021.108838.

few controlled for confounding factors, and methodological differences made direct comparisons difficult. Less than half of the studies reported toxicology results confirming an opioid-related overdose; 64.6 % reported brain MRI results and 27.8 % reported results of neuropsychological testing. Only two studies had within subject comparative data to document changes in the brain possibly associated with an overdose. Despite these limitations, existing publications suggest that brain injuries and neurocognitive impairments are associated with opioid overdose. Additional research is needed to establish the incidence of overdose-related brain injuries and the potential impact on functioning, as well as engagement in treatment of substance use disorders.

Conclusions: Respiratory depression is a defining characteristic of opioid overdose and prolonged cerebral hypoxia may cause brain injuries and/or neurocognitive impairments. The onset, characteristics, and duration of such injuries is variable and additional research is needed to understand their clinical implications.

Keywords

Opioid-related overdose; Neurocognitive impairments; Brain abnormalities; Systematic review

1. Introduction

Worldwide, the large majority of deaths associated with illicit drug use has been attributed to opioids (80 %; World Drug Report, 2020). The United States (U.S.) is leading the world in rates of illicit opioid use and its associated morbidity and mortality. These increases in drug overdose deaths in the U.S. have occurred in “waves.” The first wave beginning in the late 1990s was characterized by increased prescribing and subsequent illicit use of pharmaceutically manufactured opioids, the second wave starting in 2010 was related to a shift to heroin use, and the third wave starting in 2013 was due to increased sales and use of illicitly manufactured fentanyl and its chemical analogs (Ciccarone, 2019). Most recently, a fourth wave appears to be emerging with an increase in psychostimulants, such as methamphetamines, involved in overdose deaths (Cano and Huang, 2021). Opioids have been identified in many of these stimulant-related fatalities. In 2020, the provisional number of drug-related overdose deaths in the U.S. is 88,295; the highest number ever recorded (Ahmad et al., 2021; O’Donnell et al., 2020).

Deaths resulting from opioid-related overdose are only the tip of the iceberg however, as there are significantly more non-fatal overdoses. Estimates of non-fatal overdoses are variable and likely underestimate the true prevalence because survivors and bystanders or lay responders often do not seek medical care (Seal et al., 2003). Australian researchers have estimated that 20–30 non-fatal overdoses occur for every overdose death (Darke et al., 2003). More recent U.S.-based studies estimate that 4–18 % of opioid-related overdoses treated in the pre-hospital or hospital setting result in a fatality (Chang et al., 2020; Lasher et al., 2019; Lowder et al., 2020; Dunn et al., 2010). Further, 46–92 % of people who use opioids illicitly either have experienced a non-fatal overdose or have witnessed an overdose during their lifetime (Winstanley et al., 2020; Bennett et al., 2011; Doe-Simkins et al., 2009). The influx of illicitly manufactured fentanyl, with markedly higher potency and low cost, has led to a greater risk of opioid overdose. In addition, early data suggest that opioid overdoses increased during the COVID-19 pandemic (Slavova et al., 2020). Despite the

high incidence of non-fatal overdoses, the associated morbidity has not been adequately characterized by empirical research.

An opioid overdose is classically defined as exposure to an opioid compound that results in the clinical signs of depressed mental status and/or unconsciousness, slow and shallow breathing, and constricted pupils. Opioid-induced respiratory depression may cause cerebral hypoxia (Kiyatkin, 2019; White and Irvine, 1999) and if untreated, it could lead to cardiorespiratory arrest and/or death. For the purposes of this review, however, we will define an overdose as the use of an opioid in an amount that results in over-sedation and/or respiratory depression requiring intervention by medical or non-medical persons. The necessary interventions usually include reversal of the opioid agonist effects by naloxone administration, respiratory support, and monitoring of mental status and breathing. Because the effects of naloxone are of short duration, a recurrence of opioid-induced respiratory depression may emerge. In the absence of effective interventions, fatalities may occur over a period of time that varies across cases depending mainly on opioid potency and efficacy and individual tolerance to opioids, with the likely critical time window for interventions to be administered ranging from a few minutes to just over an hour (Boyer, 2012).

Exogenous opioids induce respiratory depression through various sites in the cerebral cortex, subcortical regions and brainstem, targeting both voluntary and involuntary breathing neural circuits. Some of the respiratory pathways are parallel to, and overlap with analgesic pathways, likely increasing the propensity to overdose, as someone seeking pain relief may be inadvertently inhibiting their respiration (Montandm and Slutsky, 2019). Additionally, fentanyl and its analogs appear to have a greater propensity to produce chest wall rigidity that contributes to respiratory depression (Gill et al., 2019). It is likely that the hypoxic period before overdose reversal causes toxic injuries to multiple organs including the central nervous system (CNS), even when a fatal outcome is averted (Feng et al. 2015). In animal models, a large intravenous challenge dose of heroin produces a rapid and pronounced drop in oxygen levels in the brain (Solis et al., 2017). Several case studies in humans have suggested that opioid overdose can cause acute or delayed onset of leukoencephalopathy, as well as damage to brain areas sensitive to hypoxic ischemia including the hippocampus and cerebellum (Milroy and Parai, 2011; Salgado et al., 2010). Reduced oligodendroglia and myelin, and white matter damage and vacuolation have also been described (Milroy and Parai, 2011; Salgado et al., 2010; Barnett et al., 2001; Huisa et al., 2013).

In addition to histopathological changes in the brain, neurocognitive impairments have been reported following opioid overdose. One study showed memory and motor impairments in opioid-naïve rats after acute methadone-induced apnea that persisted for several days (Ahmad-Molaei et al., 2018). Neurocognitive sequelae from opioid overdoses in humans have not been rigorously or systematically studied; however, evidence of potential brain injuries have been documented as early as 1969 (Brust and Richter, 1976). In case studies, overdoses involving methadone or heroin resulted in a constellation of neurocognitive impairments that persisted for over three months or up to more than a year (Salgado et al., 2010; Barnett et al., 2001; Huisa et al., 2013). Investigators have described various findings after overdose reversal that ranged from amnesia, inattention and forgetfulness, to gait impairment and incontinence. The purpose of this systematic review is to summarize

existing studies on brain abnormalities and neurocognitive impairments associated with opioid-related overdoses.

2. Methods

2.1. Search strategy

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009) and the review protocol was registered (https://osf.io/v7ujg) on the Open Science Framework (OSF) Registry. PubMed, Web of Science, Ovid MEDLINE and PsyINFO were used to search for research articles indexed by August 2020. The search terms included 1) overdose, poisoning, drug-related death, toxicity or intoxication; 2) cognition, cognitive, hypoxia/hypoxic, anoxic/anoxia, brain injury, brain damage, neurocognition, neurocognitive, neurological, or encephalopathy; and 3) opioid, opiate, heroin, fentanyl, methadone, opium, hydrocodone, oxycodone, tramadol, narcotic or carfentanil (see Supplement, Table 1 for complete reporting of search strategy). Other related articles were identified by reviewing the references of articles identified in the search. Articles were included in the review if 1) the article was published in English, 2) reported data from human research studies or clinical cases, 3) included data on individuals 18 years of age or older, 4) reported data on cognition or brain abnormalities based on neuropsychological testing, neuroimaging or clinical diagnosis, and 5) the cognitive impairments or brain abnormalities were described as occurring subsequent to a suspected or confirmed overdose involving opioids. Adolescents were excluded from this study because more than 95 % of individuals that present to the emergency department for a non-fatal opioid-related overdose or die of an opioid-related overdose are older than 18 years of age (Vivolo-Kanter et al., 2020; Scholl et al., 2019). Suspected intentional and unintentional overdoses were defined as respiratory depression reversed by naloxone administration, self-reported use of opioids prior to the overdose, bystander reports of opioid use or evidence of opioid use observed at the scene of the overdose. Articles were excluded if data were based only on histology and if the article was classified as a non-systematic review, a commentary, or news. Studies that focused only on neurocognitive impairments associated with opioid use, without specification of overdose, were excluded. Similarly, articles that focused on neurocognitive impairments or brain abnormalities resulting from overdoses not involving opioids were excluded.

2.2. Quality assessment

Existing tools to assess bias of studies included in systematic reviews are study design specific; few apply to multiple study designs and none can be used to assess case reports/series, cohort, and case-control studies (Sanderson et al., 2007; Viswanathan et al., 2012). Hence, six recommended domains of bias were assessed including selection (does the design or analysis control for confounding factors), performance (did the researchers rule out concurrent intervention or unintended exposure(s) that could bias results), attrition (differential nonresponse, dropout, or loss to follow-up), detection (two dimensions: overdose detection using toxicology and brain injury detection using imaging or neurocognitive assessments), and reporting (conclusion supported by study design & objective measures) (Viswanathan et al., 2012). The scale used to rank bias risk in the

Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was applied to each domain (high risk, low risk, unclear) (Whiting et al., 2011). The QUADAS-2 is not scored, rather if all domains are rated as 'low risk' then the study is overall rated as 'low risk'. If one or more domains are rated as 'high risk' or 'unclear', then the study overall is rated as 'at risk of bias' (Whiting et al., 2011).

2.3. Data synthesis

Search engine results were imported into EndNote, which was used to identify and delete duplicate articles. One author (ELW) initially screened the titles and abstracts to identify those potentially meeting the inclusion criteria. After initial screening, eligible articles were imported into COVIDENCE systematic review software (COVIDENCE Systematic Review Software). At least two authors (ELW, JJM, FC) reviewed every article abstract to determine eligibility and a third author resolved disagreements. Articles requiring full review were uploaded into COVIDENCE and at least two authors (ELW, JJM, FC) independently reviewed the articles and reason for exclusion was coded using pre-specified criteria. If consensus was not achieved, a third or fourth author (SDC) would review and make a final determination.

An Excel case extraction form was used to facilitate synthesis of the study findings and it captured information on the year of publication, country in which the study was conducted, the sample size (overall and cases relevant to this review), study design (based on classifications used elsewhere (Zara et al., 2000)), diagnosis (when relevant), reported behavioral symptoms exhibited among cases, the measurement of cognitive impairments or brain abnormalities (MRI, CT scan, neuropsychological testing or clinical observation), positive drug toxicology reports (drugs and number positive), outcome and time to outcome. Reported symptoms were categorized as cognitive, dyskinesia, dysautonomic, mutism, unresponsiveness or emotional/psychiatric. These characteristics are reported at the study level because diagnosis, symptoms, drug/alcohol use and outcomes were not systematically reported across relevant cases/subjects. Three authors (ELW, JJM, FC) reviewed the case extraction form to ensure agreement on content and coding. The Excel data were imported into Stata/SE Version 15.1 (StataCorp., 2017) in order to generate descriptive statistics. The overall characteristics of the articles are reported and other factors were thematically organized into the following categories: 1) drugs used at time of the overdose, 2) assessment of cognitive impairments and brain abnormalities, 3) diagnosis and symptoms, and 4) outcomes.

3. Results

A total of 3099 articles were identified in the search (see Supplement, Table 1 for details) and 24 articles were identified by reviewing reference lists (see Fig. 1). Duplicate articles and those reporting the same study results, were excluded. There were several case reports of sudden onset of amnesia that were summarized in two articles by Barash et al. (Barash and Kofke, 2018; Barash et al., 2020). Articles summarized in Barash et al. (2018) were excluded (Benoilid et al., 2013; Small et al., 2016; Barash et al., 2017; Haut et al., 2017; Duru et al., 2018). Barash et al. (2020) expands upon their 2018 review to define opioid-

associated amnestic syndrome and minimal details were provided on the cases. Hence any articles not included in the Barash et al. 2018 paper that met the inclusion criteria for this review, were included (Taylor et al., 2019); noting that most had already been identified by our search (Butler et al., 2019; Jasne et al., 2019; Ramirez-Zamora et al., 2015). One study reported baseline (Dassanayake et al., 2012) and follow-up results (Oxley et al., 2015) in two articles and both articles were included as the results were non-duplicative. After reviewing 2270 abstracts, 2067 articles were excluded and an additional 124 articles were excluded after reviewing the full text. Two hundred thirty-nine articles were excluded because they did not describe research results or were non-systematic reviews. The vast majority of the articles were excluded because they either were not relevant to overdose (n = 1072), the overdose did not involve opioids or were reported in aggregate as drug overdoses (n = 165), or brain abnormalities or cognitive functioning were not reported (n = 103). Seventy-nine articles were included this review.

The 79 studies (see Table 1) reported results for 16,330 subjects and, after excluding control cases, 3498 subjects remained. The vast majority of cases (n = 2433) were from a single retrospective cohort study conducted in Canada (Morrow et al., 2019). The earliest publication was in 1973 (Richter et al., 1973) and three years later two other studies were reported (Ginsberg et al., 1976; Pearson et al., 1975); the next study was not published until more than a decade later (Revesz and Geddes, 1988). The majority of studies (60.8 %) were published in 2010 or later. Twenty-one countries were represented in the studies; 41.8 % of the articles reported studies conducted in the U.S. and 11.4 % reported studies conducted in Australia. More than half of the articles were case reports (n = 44) and there were 18 case series, 11 cohort studies, and 6 case-control studies. Six studies reported only post-mortem results of forensic brain autopsies of decedents presumed to die of drug (opioid) or overdose-related causes of death (Alturkustani et al., 2017; Andersen and Skullerud, 1999; Muller et al., 2018; Pearson et al., 1975; Oehmichen et al., 1996; Yarid and Harruff, 2015). Fifty-two studies reported brain MRI results, whereas only 23 studies reported the results of neurocognitive testing.

3.1. Quality of studies

All of the studies were determined to have at least one source of bias (see Table 2). Ninety-one percent of the articles were categorized as being at high risk of selection bias, which in part reflects the study designs and that randomization was not used in any of the studies. Among the six case-control studies, only three (Darke et al., 2000; McDonald et al., 2013; Muller et al., 2018) used matching to reduce selection bias. Eighty-two percent of the articles were categorized as being at high risk of performance bias because there were inadequate controls for exposures, other than a drug overdose, that could have contributed to the observed cognitive impairments or brain abnormalities. In terms of detection bias, 48.7 % of the studies were rated as being at high risk of bias due to their measurement of an overdose and only 11.4 % were rated as being at high risk of measuring either cognitive functioning or brain abnormalities. Four studies reported brain abnormalities or cognitive impairment based only on clinical observation (Morrow et al., 2019; Fatovich et al., 2008; Grigorakos et al., 2010; Pfister et al., 2016). Only two studies (Yarid and Harruff, 2015;

Zamora et al., 2015) fully acknowledged the potential for confounding and/or bias and hence did not make diagnostic conclusions.

3.2. Themes

3.2.1. Drugs used at the time of overdose—Forty-one studies reported toxicological drug results at the time of the overdose. Among the 330 subjects with drug toxicology results reported, only 3 were opioid negative. The majority reported the result as positive for opiates/opioids, without specification of opioid compounds. Eighteen subjects had a positive toxicology for methadone, 5 for fentanyl, 1 norfentanyl, and 1 reported a novel opioid synthetic compound (U-4770) (Koch et al., 2018). Non-opioid positive toxicology results that were reported included 17 subjects who tested positive for benzodiazepines, 15 subjects who tested positive for cocaine, 12 who tested positive for cannabis/cannabinoids, and 7 who tested positive for amphetamines/methamphetamines. The majority of articles (59.5 %) did not report on whether the cases had used alcohol, had a history of alcohol use, or had toxicology results positive for alcohol. Only eight articles reported toxicological testing for alcohol (Adrish et al., 2014; Barash and Kofke, 2018; Butler et al., 2019; Cerase et al., 2011; Cheng et al., 2019; Corliss et al., 2013; Corre et al., 2013; Pearson et al., 1975) and of these only two studies reported positive toxicology (Corre et al., 2013; Pearson et al., 1975).

3.2.2. Assessment of neurocognitive impairments or brain abnormalities—Forty-four percent of articles reported results from CT scans, 65.8 % reported brain MRI results and 29.1 % reported results of neuropsychological testing. Fourteen case reports/series used postmortem brain autopsy results to confirm brain abnormalities in decedents. Only two studies reported having pre-overdose brain imaging or neurocognitive testing which could be used to accurately measure change after the overdose (Butler et al., 2019; Molloy et al., 2006). Eighteen studies reported both brain MRI and neuropsychological testing. Of the 22 studies that reported findings from neuropsychological testing, 18 % did not specify the names of the tasks administered (only specifying the domain assessed). For studies that did report the specific tasks, there was a wide range in the extensiveness of the neuropsychological evaluations across the studies: some included only screening measures (e.g. Mini-Mental State Exam, Montreal Cognitive Assessment; 7 studies), some administered select measures (5 studies), and others utilized more comprehensive batteries (6 studies). When multiple neuropsychological measures were administered and specified, task selection also greatly varied as no more than two studies utilized the same neuropsychological measure. Few of the studies reported the specific neuropsychological test performed and none utilized the same test.

3.2.3. Diagnoses and symptoms—Sixty-seven studies reported subjects' diagnoses which included encephalopathy/leukoencephalopathy (40 studies), amnesia (7 studies), stroke (3 studies), other brain injury/damage/abnormalities (17 studies) and other medical conditions (7 studies). Seven articles reported subjects having amnesia, most of which were summarized by Barash et al. (2019; 2020) and three additional articles were identified in this review (Gottfried et al., 1997; Switzer et al., 2020; Torralba-Moron et al., 2017). Several other studies reported memory deficits that were not specifically diagnosed as amnesia (Arciniegas et al., 2004, Chang et al., 2009; Cheng et al., 2019; Khot et al., 2007; King

et al., 2015; Landais, 2014; Lefaucheur et al., 2017; Meyer, 2013; Shprecher et al., 2008; Switzer et al., 2020; Wijdicks, 2005). Across these 67 studies, the most frequently reported symptoms included the following: cognitive symptoms (n = 58 subjects), dyskinesia (n = 40 subjects), dysautonomia (n = 27 subjects), unresponsiveness (n = 23 subjects), emotional/psychiatric symptoms (n = 18 subjects), and mutism (n = 12 subjects). Specific cognitive deficits were related to: confusion/disorientation (n = 15), memory (n = 13), attention (n = 6), executive functions (n = 4), processing speed (n = 4), and speech (n = 3); 4 additional papers described unspecified cognitive deficits. Specific emotional/psychiatric symptoms included "odd" behavior (n = 6), apathy (n = 5), agitation/aggression (n = 3), inappropriate behavior, abulia, social withdrawal, and mania (n = 1 each). Two case reports found that two individuals did not have brain abnormalities following an overdose and no clinical observations suggesting cognitive impairment were reported (Adrish et al., 2014; Kuhlman and Gwathmey, 2018).

3.3. Outcomes and follow-up

The studies investigated clinical recovery after an overdose and the follow-up periods ranged from hospital discharge to five years. Eight studies reported outcomes at a year or greater follow-up (Achamallah et al., 2019; Barash and Kofke, 2018; Huisa et al., 2013; Jensen et al., 1990; Meyer, 2013; O'Brien et al., 2009; O'Brien and Todd, 2009; Quinn and Abbott, 2014; Shu et al., 2016; Villella et al., 2010). Among the forensic autopsy studies, data were not available on the timing of the overdose and the subjects' death. Thirteen subjects were reported to have fully recovered during the follow-up window, which ranged from three days to one year (Carroll et al., 2012; Cerase et al., 2011; Cohen and Hack, 2019; Corre et al., 2013; Huisa et al., 2013; Koch et al., 2018; Lefaucheur et al., 2017; Long et al., 2013; Meyer, 2013; Molloy et al., 2006; Mumma et al., 2009; Vila and Chamorro, 1997; Zamora et al., 2015). Sixteen had a partial recovery at follow-up, which ranged from three to nine months (Arciniegas et al., 2004; Barnett et al., 2001; Beeskow et al., 2018; Bileviciute-Ljungar et al., 2014; Cheng et al., 2019; Chang et al., 2009; Gupta et al., 2009; Jasne et al., 2019; Landais, 2014; Salazar and Dubow, 2012; Shprecher et al., 2008; Switzer et al., 2020; Vendrame and Azizi, 2007; Villella et al., 2010). The studies reported 36 subject deaths that occurred either prior to hospital discharge or within 6 weeks of the overdose.

4. Discussion

Seventy-nine articles, reflecting studies conducted in 21 countries, documented 3496 subjects that possibly had neurocognitive impairments and/or brain abnormalities associated with an opioid-related overdose. Two case reports found no evidence of post-overdose brain injuries based on neuroimaging (Adrish et al., 2014; Kuhlman and Gwathmey, 2018). As overdose deaths have increased over the past two decades, so have the number of published articles documenting brain injuries. Significant methodological differences across these studies limit direct comparisons and all of the studies were categorized as being at risk of bias. The primary methodological weaknesses of these studies included limited control of confounding factors that could explain the observed neurocognitive impairments and/or brain abnormalities, limited availability of objective measures to confirm that opioid-related overdose occurred, and variable follow-up periods. The vague specification of

study inclusion criteria and the limited number of opioid-positive toxicology reports are problematic. It is possible that some of the subjects in the studies were presumed to have experienced an opioid-related overdose because they had a history of opioid use and/or documented opioid use disorder without definitive evidence for an opioid overdose. The majority of individuals demonstrated persistent impairments at follow-up, and the overall number of deaths reported was 36 across all of the studies.

Twenty-nine of the studies reported a diagnosis of leukoencephalopathy, which is a form of encephalopathy that specifically affects white matter (Lyon et al., 2006). Spongiform leukoencephalopathy, a form of toxic leukoencephalopathy, occurs secondary to exposure to a wide variety of agents, including carbon monoxide poisoning and drugs of abuse, which subsequently damage white-matter tracts devoted to higher cerebral function (Filley and Kleinschmidt-DeMasters, 2001). Leukoencephalopathy can have an acute onset or a delayed onset that can occur 2–180 days after a hypoxic-ischemic brain injury (Arciniegas et al., 2004). Acute and delayed leukoencephalopathy, with and without spongiform, has been associated with inhalation of heroin fumes, which is known as ‘chasing the dragon’ (Wolters et al., 1982; Cordova et al., 2014; Kass-Hout et al., 2011; Blasel et al., 2010; Keogh et al., 2003). Most of the studies in this review reported a delayed onset of leukoencephalopathy; however, one recent case series reported sudden onset (Achamallah et al., 2019). Delayed-onset cases were less likely to report toxicological confirmation of opioid-related overdoses and it is largely unknown if an alternative exposure could have caused the observed brain injury. Some of the articles postulated that neurological impairments resulted from a particular method of opioid administration (e.g., inhalation or injection) rather than from an opioid overdose (Wijdicks, 2005; Filley and Kleinschmidt-DeMasters, 2001). Others have speculated that spongiform leukoencephalopathy is caused by an unidentified heroin adulterant or contaminant; however, there is insufficient evidence to support a causal mechanism (Cordova et al., 2014). Leukoencephalopathy associated with opioid use and/or overdose has been reported in multiple case reports dating as early as 1981 (Wolters et al., 1982), across multiple countries, involving different opioid compounds and various routes of administration (Alambyan et al., 2018).

Case reports of an “amnestic syndrome” associated with use of novel opioid synthetics have been reported in Massachusetts (Barash and Kofke, 2018; Small et al., 2016; Barash et al., 2017), California (Butler et al., 2019), West Virginia (Haut et al., 2017; Duru et al., 2018), and in France (Benoilid et al., 2013). Two cases were identified in this review that were not included in the amnesia cluster reported by Barash et al. (Barash and Kofke, 2018; Barash et al., 2020). Gottfried et al. (1997) reported a case of persistent anterograde and retrograde amnesia in a patient that experienced an overdose involving opioids, benzodiazepines, and amphetamines. A recent case report involving self-reported use of fentanyl, that was not confirmed by toxicology, described acute onset of anterograde amnesia (Butler et al., 2019). While Barash et al. make a strong case for a fentanyl-specific cause of the amnesia (Barash and Kofke, 2018), there is limited toxicological testing to confirm fentanyl as the explanatory factor. Several other articles reported that subjects experienced memory deficits, but few clinical details were provided on these deficits. Eight articles reported cases with memory problems lasting more than one month. Standard urine toxicology testing used

in clinical practice infrequently differentiates opioid compounds and rarely includes novel opioid synthetics.

The period after a non-fatal overdose is not well studied in humans, yet it is a critical one when interventions to decrease morbidity and mortality can be made. These potential treatment options would likely have to be adequate for patients who may have developed overdose-related cognitive impairments. Questions remain over appropriate post-overdose clinical management and the role of neuropsychological testing when initiating treatment for OUD. The studies in this review provide insufficient evidence to estimate the prevalence of brain injuries among individuals who experience a non-fatal overdose. Given that the majority of the studies were case reports/series, it is likely that bias exists in reporting high acuity injuries and hence even less is known about mild cognitive impairments that may occur. Dassanayake et al.' case control study (n = 175) found evidence of sufficient neurocognitive impairment among patients hospitalized for CNS-D-related overdose to conclude that they had an increased risk of motor vehicle accidents upon discharge (Dassanayake et al., 2012; Oxley et al., 2015).

Studies in this review rarely controlled for confounding factors that could explain brain injuries or neurocognitive impairments. Individuals who use drugs have a higher risk of traumatic brain injuries (Corrigan and Deutschle, 2008; McHugo et al., 2017), largely due to injuries sustained during periods of intoxication. Drugs may be adulterated or contaminated by substances known to be neurotoxic (Langston et al., 1983) or due to co-use of drugs known to be associated with neurocognitive deficits including alcohol and methamphetamines. Many individuals with OUD experience, on average, 3–6 non-fatal overdoses (Doe-Simkins et al., 2009; Heale et al., 2003; Winstanley et al., 2020; Sherman et al., 2008) and the effects of these overdoses could compound over time. In a rodent model, Zhu et al. (2005) found that the immature brain can tolerate longer periods of oxygen deprivation and hence age may influence the risk of overdose-related brain injuries. While a few case reports ruled out infectious diseases such as HIV or Hepatitis C (Barnett et al., 2001; Carroll et al., 2012; Hill et al., 2000; Oehmichen et al., 1996; Salazar and Dubow, 2012; Torralba-Moron et al., 2017; Villella et al., 2010), three reported cases did test positive for Hepatitis C (Carroll et al., 2012; Hsu et al., 2009; King et al., 2015); however, such testing was infrequently mentioned. Neurocognitive impairments in drug users, including extra-medical use of prescription opioids and heroin, may result from chronic use (Baldacchino et al., 2012; Gruber et al., 2007; Kroll et al., 2018) and it is difficult to disentangle compound-specific deficits in the context of polydrug use. There is limited research on the prevalence of neurocognitive impairments in individuals with OUD; one small cross-sectional study estimated that 39 % of patients seeking buprenorphine treatment had neurocognitive impairments (Arias et al., 2016). Four case reports tested for a "pseudodeficiency" of arylsulfatase A, which is caused by a genetic mutation that may make individuals more susceptible to post-hypoxic demyelination, and two of the cases tested positive (Barnett et al., 2001; Gottfried et al., 1997). There is also speculation that a cytochrome P4502D6 genetic polymorphism may increase the risk of leukoencephalopathy (Bach et al., 2012). However, there is insufficient evidence to understand the role that genes may play in increasing the risk of overdose-related brain injuries. Ideally, confirmation of an opioid-related overdose would be determined by a respiration rate less than 12 breaths

per minute (Boyer, 2012) and an opioid-positive toxicology. Articles were included in this review if participants experienced an opioid-related overdose and if drug toxicology data was missing, other objective measures were considered (e.g., reversal of respiratory depression after naloxone administration, secondary reports of opioid use from bystanders). For example, one study reported a case of post-hypoxic leukoencephalopathy following a suicide attempt involving multiple drugs (Loftsgard et al., 2017). This study was excluded because it was unknown whether the drug overdose involved opioids and they reported that the patient was not responsive to naloxone. It would have been overly-restrictive to exclude studies without opioid-positive toxicology and yet relevant studies may have been excluded. Terminology has changed over time and across disciplines. For example, some of the older articles used the term 'heroin intoxication' which was described in such a way to be consistent with what we now define as an opioid overdose (Oehmichen et al., 1996). The lack of standardized language on this topic, as demonstrated by the variation in the diagnoses and symptoms described in this review, complicate identification of relevant studies. Importantly, this review was unable to accurately characterize the symptoms of overdose-related brain injuries as symptoms were not systematically reported across the studies.

Despite the limitations of the articles included in this review, we know that opioid overdose can cause cerebral hypoxia and anoxia and that brain injury can occur within 3 – 6 min of oxygen deprivation. There is increasing awareness of the potential for overdose-related brain injuries, as evidenced by a 2019 U.S. Department of Health and Human Services (DHHS) report on health outcomes associated with non-fatal overdose (Zibbel et al., 2019). Variability in the onset and duration of symptoms described in these studies may complicate timely identification of brain injuries in patients that received medical treatment for an overdose. Initial management often occurs in the pre-hospital setting. Time with inadequate respiration likely predicts the extent of brain injuries and it is unknown if that critical information is systematically captured in the patients' electronic medical records (EMR). Emergency departments do not routinely conduct comprehensive toxicology on patients presenting with overdose and neurocognitive impairments in this population may be attributed to ongoing drug use, rather than associated specifically with an overdose. Because of the potential delayed onset of neurocognitive impairments, more complete documentation of the overdose event (e.g., Glasgow Coma Score; time, dose & route of naloxone administration; length of time unconscious) in the EMR may help determine whether the brain injury is related to cerebral hypoxia or anoxia. Clinicians may want to consider screening for acute brain injuries and/or neurocognitive impairments in individuals known to have experienced a prolonged period of hypoxia or anoxia due to an opioid overdose and consider monitoring for delayed onset for those with the highest risk. In clinical settings, comprehensive drug toxicology following an overdose could help identify specific opioid compounds and non-opioid drugs involved. These steps would be critical to determining, for example, whether fentanyl-related overdoses cause amnesia.

The findings of this review provide a strong rationale and directionality for future research. Rigorously designed prospective case control studies, that control for confounding factors, are needed to empirically measure changes in the brain and cognition that occur following opioid-related overdose. Importantly, standardized measures should be established

to quantify overdose-related brain injuries to ensure comparability across studies. The incidence and prevalence of opioid-related brain injuries is needed to inform clinical care and post-overdose management, particularly in terms of whether screening for brain injuries is warranted in this population. The pharmacodynamic effects of opioid compounds are different and it is plausible that this explains differential risk of brain injuries. For example, fentanyl has a rapid onset that may increase the period of inadequate respiration and chest wall rigidity structurally restricts respiration (Suzuki and El-Haddad, 2017). Concomitant use of CNS depressants will impair reflexes and asphyxiation can occur in tandem with respiratory depression. Any fall or head trauma in the peri-overdose period may also affect overdose outcomes. In all, there is a high level of variability seen in overdose events. In order to adequately control for confounding factors, within-subject study designs are needed to compare baseline and post-overdose neurocognitive functioning.

5. Conclusions

This is the first study to systematically summarize existing research on brain injuries and neurocognitive impairment associated with opioid overdoses. Non-fatal opioid-related overdoses are becoming more common in the context of the current opioid epidemic and there is a high probability that these hypoxic events result in neurocognitive impairments that in turn increase the risk of poor treatment outcomes. The fourth wave of the opioid epidemic may increase the incidence of overdose related brain injuries due to the known neurotoxicity of methamphetamine. Yet, to date, there is no systematic empirical evidence on the incidence of overdose-related neurocognitive impairments and no definitive evidence stating whether or not neurocognitive impairments that result in poor treatment outcomes are attributable to overdose. The reviewed studies lack standardized inclusion criteria, failed to adequately control for confounding factors, and do not harmonize outcome measures. The results reported are not yet sufficient to draw conclusive evidence on the incidence, magnitude, and consequences of opioid overdose-related brain injuries. Therefore, further investigation into these types of impairments is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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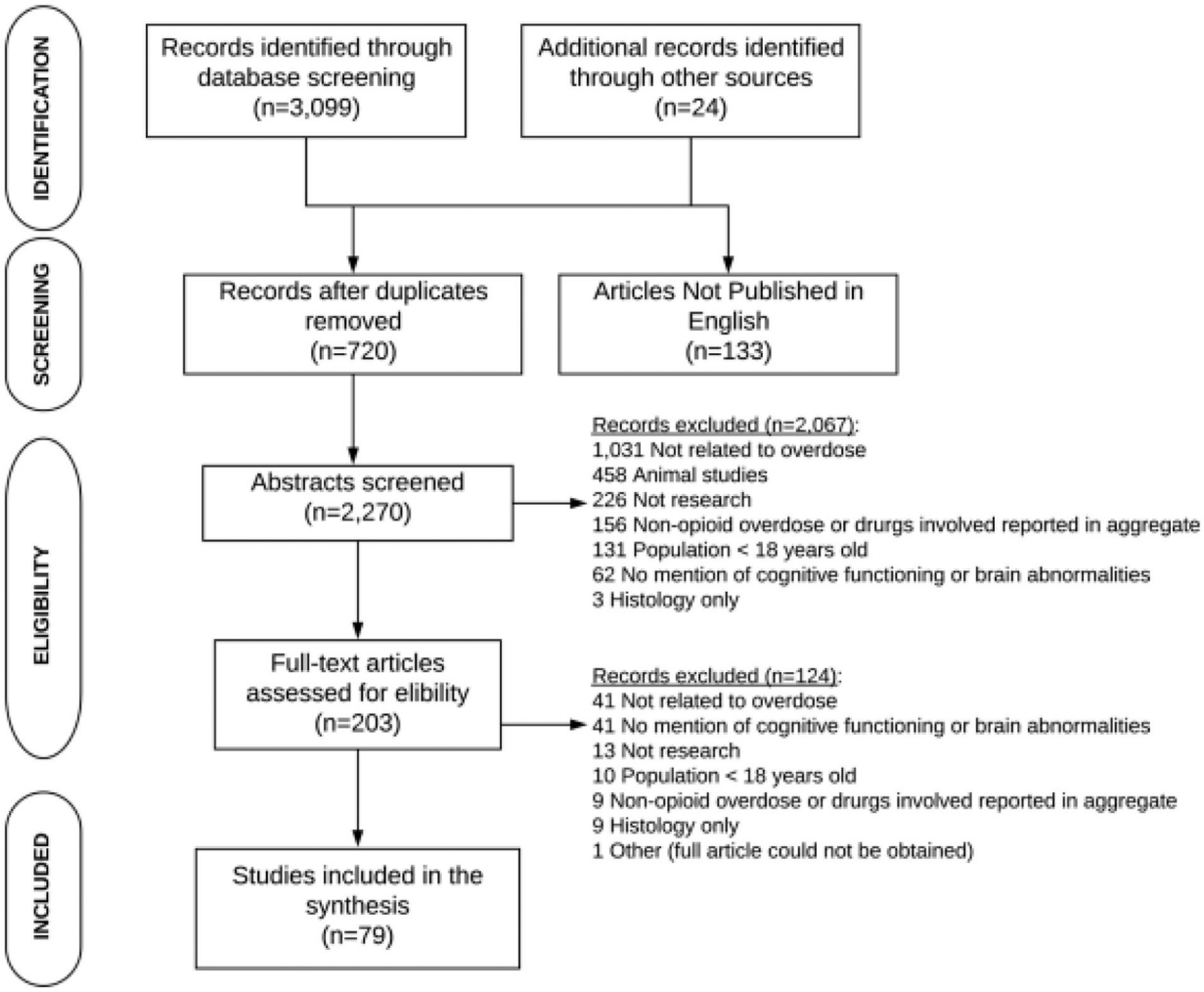

Fig. 1.

PRISMA Flow Diagram of Studies of Neurocognition and/or Brain Abnormalities Resulting from Opioid-Related Overdoses.

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Table 1

Study characteristics.

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
Achamallah et al. (2019)/ USA	Case series	3 (3)	Acute leukoencephalopathy (seizures, tremors, dysautonomia, rigidity, hyperthermia, tachycardia, fever, hypertension)	Brain MRI, CT scan	Opioids (3) Amphetamine (1) Benzodiazepines (1) Cannabis (1) Cocaine (1)	Persistent impairments (Month 2-Year 5)	• 21-year-old male was non-responsive following an opioid overdose; brain MRI revealed abnormalities in the corpus callosum; patient awoke on day 7 and transferred to long-term care; cognition and functioning improved by year 5; however, motor deficits persisted • 34-year-old male was found unresponsive after overdose involving opioids and amphetamines • 20-year-old male was found unresponsive; toxicology was positive for opioids, benzodiazepines, cocaine, and cannabis; on day 34, patient was transferred to long-term care facility and at month 8, he continued to have significant cognitive impairments, as well as motor dysfunction • All cases reported attributed to heroin inhalation
Adrish et al. (2014)/ USA	Case report	1 (1)	Renal failure, rhabdomyolysis, gluteal compartment syndrome (lower extremity weakness)	CT scan	Opioids (1)	No brain injury	• 42-year-old male found unconscious after injecting heroin; mental status improved within 36 h during hospitalization • Head CT scan was normal & discharged after ~one week in hospital to short-term rehabilitation for lower extremity weakness
Alquist et al. (2012)/ USA	Case report	1 (1)	Leukoencephalopathy (N/A)	Brain autopsy	Oxymorphone (1) Cocaine (1) Benzodiazepines (1) Cannabis (1)	Death (Day 5)	• 27-year-old male was found unconscious; patient had Glasgow Coma Score of 3 T and was admitted to the ICU, after no improvement by day 5 the family withdrew life support and the patient died • Postmortem brain autopsy revealed diffuse cerebral edema
Alturkustani et al. (2017)/ England	Retrospective cohort	5 (5)	Leukoencephalopathy (N/A)	Brain autopsy	Opiates (4) Cocaine (3) Cannabis (1) Benzodiazepines (1)	N/A	• Cases defined as autopsy reports from 2002 to 2013 that documented white matter changes due to drug use • White matter changes were multifocal and widespread

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• Evidence of bilateral globus pallidus necrosis suggests that cardiorespiratory arrest did not occur at the same time as white matter changes • Concluded that drug-induced hypoxic-ischemic injury caused leukoencephalopathy
Andersen and Skullerud (1999)/ Norway	Retrospective cohort	100 (92)	Brain abnormalities (N/A)	Brain autopsy	Unavailable	N/A	• Sample included deaths among IV heroin users from 1995 to 1996 • 92 % had heroin listed as a cause of death or known heroin use prior to death (7 deaths did not result from overdose) • Brain abnormalities were found in 38 of 100 cases: 25 had lesions of hypoxic origin, 6 had bilateral hippocampal sclerosis & 9 had pallidal lesions • Authors concluded that 5–10% of IV heroin users may have pallidal lesions
Arciniegas et al. (2004)/ USA	Case report	1 (1)	Delayed encephalopathy (memory impairments, speed processing, and executive functioning; incontinence, ideational dyspraxia, agraphesthesia)	Brain MRI, NP	Unavailable	Improved (Month 5)	• 24-year-old male was comatose ~18 h after an overdose; had history of stimulant and alcohol misuse, as well as OUD • MRI on day 2 confirmed hypoxic/ischemic injury with increased signal intensity in anterior periventricular areas and posterior periventricular white matter • Week 2 patient discharged from hospital and 9 days later he experienced gradual impairments in cognition • Patient readmitted to the hospital and 2nd MRI 1 week later revealed new lesions in frontal white matter • 5 weeks after hospital readmission, patient was transferred to acute neurorehabilitation unit; patient was severely cognitively impaired and incontinent • Cognitive testing 4 weeks later revealed impairments in executive functioning and attention • Patient’s arylsulphastase A was within normal range

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• Improvements occurred after administration of amantadine HC1 hydrochloride
Barash and Kofke (2018)/ USA	Case series	22 (21)	Sudden onset of amnesia (memory impairment, inattention, impaired executive functioning, problems with orientation)	Brain MRI, NP	Opioids (9) Cocaine (5) Cannabis (2) Cannabinoids (2) Benzodiazepine (3) Amphetamines (3) Buprenorphine (1) Barbiturates (1) Fentanyl (4) Norfentanyl (1)	Persistent impairments (4) (Week 8-Month 22)	• Synthesis of several case reports of sudden onset of amnesia following drug use that occurred 2012–2017 • Massachusetts cluster included 18 patients, 17 either had drug tested positive for opioids or patients had a history of opioid use (Small et al., 2016; Barash et al., 2017) • 1 case in France resulted from heroin inhalation (Benoilid et al., 2013) and 2 cases in West Virginia had confirmed fentanyl use (Duru et al., 2018) and cocaine use (Barash et al., 2017) • MRIs revealed hyperintense signal on both hippocampi • Patients had impairments in orientation and attention • Authors could not rule out an unknown contaminant in heroin/fentanyl as potential cause of amnesia • Follow-up not available for 10 cases • Authors conclude, based on epidemiological evidence of increased involvement of fentanyl in overdoses and animal studies of fentanyl, that there is association between fentanyl and hippocampal injury
Barnett et al. (2001)/ Australia	Case report	1 (1)	Delayed post-anoxic encephalopathy (rhabdomyolysis, incontinence, mutism, immobility)	Brain MRI, CT scan, NP	Unavailable	Partial recovery (Month 9)	• 45-year-old male sought inpatient drug treatment 8 days after IV heroin overdose that had caused a prolonged period of unconsciousness • At day 12, patient had impairments in cognitive functioning and left spatial hemineglect, brain CT was normal and MRI revealed signal change in the bilateral cerebral white matter • Testing ruled out Hepatitis and HIV • At 3 weeks after admission, patient was incontinent, mute, and immobile; subsequently patient was transferred to a nursing home

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• At 3 months, neuropsychological testing confirmed severe cognitive impairment • At 6 months, patient had significant improvements and was discharged from the nursing home • At 9 months, neuropsychological testing and MRI suggested near complete recovery of cognitive functioning, although loss of cerebral volume suggests some permanent damage
Beeskow et al. (2018)/ German	Case report	1 (1)	Delayed leukoencephalopathy (odd behavior, agitation, apathy, myoclonus, mutism)	Brain MRI	Unavailable	Partial recovery (Month 9)	• 51-year-old woman was comatose and unresponsive to opioid antagonist (naloxone not specified); toxicology not performed and suspected opioid-related overdose • CT scan revealed bilateral hyperintensities of the globus pallidus, MRI confirmed lesions • 3 weeks after hospitalization, patient displayed odd behavior, apathy and mutism • MRI at 5 weeks showed change and MRI at 9 months showed marked regression of leukoencephalopathy
Bileviciute-Ljungar et al. (2014)/ Sweden	Case report	1 (1)	Delayed leukoencephalopathy (cognitive impairment, gait impairment, spasticity, mania, aggressive, disorientation, incontinence)	Brain MRI, CT scan, NP	Methadone (1) Benzodiazepines (1)	Partial recovery (Month 7)	• 34-year-old male overdosed on methadone • Patient was in the ICU for 8 days; Montreal Cognitive Assessment (MoCA) score on Day 12 was 19/30; MRI on day 23 revealed white matter changes • Day 31 patient further deteriorated; cognitive testing confirmed impairment (2 SD below mean) in memory (working and long-term), attention, and visuospatial • Day 37 MoCA score 17/30 • Patient was treated with baclofen and improved; patient continued with outpatient rehabilitation therapy for 3 months
Butler et al. (2019)/ USA	Case report	1 (1)	Acute-onset anterograde amnesia (tachycardia, disorientation, memory impairment)	Brain MRI, CT scan, NP	None	Persistent impairments (Month 4)	• 21-year-old male presented with acute-onset anterograde amnesia after self-reported IV fentanyl use • Awoke hours after use and brought to ED 36 h after suspected overdose

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• MRI revealed restricted diffusion of the hippocampi • Comparison of pre-MRI imaging from 6 months before his overdose and after his overdose revealed 10 % volume loss • Neuropsychological testing 4 months later confirmed memory impairments (declarative, episodic, semantic)
Carroll et al. (2012)/ Switzerland	Case report	1 (1)	Delayed leukoencephalopathy (inappropriate behavior, apathy, incontinence, gait impairment, impaired executive functioning)	Brain MRI, CT scan, NP	Unavailable	Recovered (Month 6)	• 43-year-old opioid-naïve female experienced an overdose involving methadone and alprazolam (medication packaging found near her) • 26 days later patient had inappropriate and apathetic behavior • MRI on day 32 revealed increased signaling in the white matter • Day 46 patient was admitted to the hospital with impaired executive functioning, memory, speech and motor programming; patient also had incontinence and gait apraxia • Testing ruled out HIV, syphilis, Lyme disease, and hepatitis • Day 46 MRI revealed white matter changes in the corpus callosum, globus pallidus, and putamen nuclei • At 6 months, neuropsychological testing results were normal
Cerase et al. (2011)/ Italy	Case report	1 (1)	Leukoencephalopathy (comatose, severe physical & cognitive impairment)	Brain MRI, CT scan	Methadone (1)	Recovered (Month 3)	• 49-year-old male with intentional overdose involving methadone, alcohol & benzodiazepines; known 26 year history of OUD • MRI revealed bilateral signal intensities in the cerebral hemispheres • Intubated & required mechanical ventilation within 12 h of hospitalization • Persistent cognitive deficits (unspecified) noted 1 month after overdose • Month 3 follow-up MRI and clinical assessment concluded recovery; authors

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							note that full recovery is rare after a hypoxic-ischemic brain injury
Chang et al. (2009)/ Taiwan	Case report	1 (1)	Delayed leukoencephalopathy (comatose, delirium, bradykinesia, rigidity, incontinence, mutism, memory impairment)	Brain MRI, CT scan, NP	Unavailable	Partial recovery (Month 5)	• 42-year-old male, being treated with methadone for an OUD, was found unconscious; was intubated and ventilated in the ICU and transferred to inpatient bed on day 6; he was discharged after 3 weeks of hospitalization • Patient developed bradykinesia, rigidity, incontinence & mutism within 3 weeks of hospital discharge; readmitted to the hospital week 7 • Day 47 MRI revealed signal intensity in white matter & small lesions in bilateral corona radiata; patient required nasogastric feeding • Month 3 patient seen in neurology clinic; Cognitive Abilities Screening Instrument score was 67; Mini-Mental State Examination score was 18 • Month 5 Mini-Mental State Examination score 22; MRI revealed improvement in white matter noting mild cortical atrophy
Cheng et al. (2019)/ Taiwan	Case series	2 (2)	Delayed leukoencephalopathy (mutism, bradykinesia, bradyphrenia, odd behavior, incontinence, confusion)	Brain MRI, CT scan	Heroin (2)	1 partial recovery (Month 1), 1 partial recovery (Month 2),	• Report of 2 new cases and identified 48 cases based on literature search; literature search results were reviewed and reports meeting criteria of this systematic review were included separately • 33-year-old male presented to ED with altered mental state, overdose was unconfirmed, patient diagnosed with acute heroin intoxication; hospitalized for 1 week and 6 weeks after hospital discharge patient experienced mutism, bradykinesia, odd behavior and incontinence; baseline CT scan was normal whereas repeated CT scan at 7 weeks showed white matter hypodensities; MRI at week 8 confirmed abnormalities in the periventricular and subcortical regions; improvements demonstrated after one month of antioxidative combined therapy • 32-year-old male presented to ED with heroin overdose, CT scan revealed diffuse hypodensities in white matter; 1 month later patient experienced incontinence, mutism,

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							bradykinesia weakness; repeated CT scan revealed hypodensities in the bilateral hemispheres consistent with DPHL; short-term memory remained impaired at 2 months
Chute and Smialek (2002)/ USA	Case series Case report	10 (5) 1 (1)	Subarachnoid hemorrhage, encephalopathy, cerebral edema, cardiorespiratory arrest (comatose)	CT scan, brain autopsy	Opiates (5), Cocaine (1), Alcohol (1) Unavailable	Death (Day 1–6)	• Retrospective review of 10 postmortem cases of pseudo-subarachnoid hemorrhage on CT scans in Maryland from 1997 to 2000; 2 cases died due to narcotic intoxication & in 2 cases opiate use contributed to cause of death • 42-year-old female found unresponsive; UDS positive for opiates & cocaine; CT scan revealed subarachnoid hemorrhage & patient died within 8 h of hospitalization; brain autopsy revealed encephalopathy, severe cerebral edema • 40-year-old female was found unconscious; CT scan revealed bilateral basal ganglia infracts; toxicology was positive for opiates and alcohol; patient died 36 h after admission; brain autopsy noted changes in the cerebellum • 44-year-old female became unconscious after snorting heroin; CT revealed brain edema cause by an anoxic brain injury; hyperdensities noted; patient died within 12 h; brain autopsy revealed subarachnoid hemorrhage • 45-year-old female had cardio-respiratory arrest and toxicology positive for opiates; CT scan revealed diffuse cerebral infarction; patient died within 60 h; brain autopsy confirmed global hypoxic-ischemic injury • 45-year-old male became comatose after being arrested for driving while intoxicated; toxicology positive for opiates; patient died on day 6; brain autopsy confirmed hemorrhagic necrosis
Cohen and Hack (2019)/ USA			Brain abnormalities (unresponsive, rigidity)	CT scan & brain MRI		Recovery (Day 5)	• 54-year-old male was unresponsive; MRI 15 h after admission revealed lesions in the bilateral globus pallidus and an edema; patient self-disclosed heroin use

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							• Authors noted resolution of symptoms on day 5
Corliss et al. (2013)/ USA	Case report	1 (1)	Brain abnormalities, rhabdomyolysis (N/A)	Brain autopsy	Benzodiazepines (1) Cannabinoids (1) Methadone (1)	Death (24 h)	• 23-year-old male overdosed on methadone and alprazolam (after period of incarceration) which resulted in acute necrosis of the bilateral globus pallidi and systemic rhabdomyolysis • Airlifted to tertiary care facility; poor prognosis resulted in removal of life support and death within 24 h • Heroin use may cause remote pallidal injury, but authors conclude in this case that the acuity of the injury suggests that it resulted from an overdose
Corre et al. (2013)/France	Case report	1 (1)	Brain abnormalities (comatose)	CT Scan & brain MRI	Methadone (1), Cannabis (1), Alcohol (1), Benzodiazepines (1)	Recovered (Unknown)	• 29-year-old male was found comatose after using 60 milligrams of methadone (as reported by a witness) • Toxicology was negative for cocaine, opiates and amphetamines • CT scan revealed hypodense signal in right cerebellar hemisphere & MRI revealed hyperdensitites in the basal ganglia • Patient had persistent renal failure and kinetic cerebellar syndrome, but authors reported his status as recovered
Darke et al. (2000)/ Australia	Case-control	60 (30)	N/A	NP	Unavailable	Unknown	• 30 methadone patients (cases) were matched (age, gender, and education) with 30 non-heroin using controls • Premorbid abilities were the same for controls and cases • 73 % of cases had experienced a non-fatal overdose, 63 % had a co-occurring alcohol use disorder (AUD) and 67 % had a history of head injury • Overall worse cognitive performance was found in cases versus controls • Lifetime AUD and number of previous overdoses was associated with worse cognitive performance in cases

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
Dassanayake et al. (2012)/ Australia	Case-control	175 (25)	N/A	NP	Unavailable	Unknown	• Study of patients who presented at the hospital with intentional overdose; cases (n = 107) consisted of CNS-D-related overdoses (25 involved opioids) and controls (n = 68) had overdoses involved SSRIs or SNRIs • Cases demonstrated impairment on all measures, but not reported separately for opioids • Findings suggest that post-CNS-D overdose results in cognitive impairment that may affect functioning post-hospital discharge • Outcomes are reported in Oxley et al., 2015 (see below)
Fatovich et al. (2008)/ Australia	Prospective cohort	224 (224)	N/A	Clinical observation	Unavailable	Variable	• Secondary analysis of existing medical records for patients that presented to the ED from 1998 to 1999 with a heroin overdose (adults & adolescents reported at aggregate, could not differentiate those <18 years old) • Overdose was determined by Glasgow Coma Scale scores, meiosis, respiration rate <12, history of opiate use or disclosure by patient or bystander, or evidence of injection drug use at scene • 11.6 % required hospitalization & only 1 had hypoxic brain injury
Ferrari et al. (2020)/ Italy	Case report Case report	1 (1) 1 (1)	Overdose (unresponsive, liver failure, polyneuropathy)	CT scan	Tramadol (1) Methadone (1)	Unknown	• 49-year-old female found unconscious with empty Tramadol package nearby; CT scan revealed intracranial bleeding; toxicology positive for Tramadol • Rescue veno-arterial femoro-femoral extracorporeal life support (VA-ECLS) started and charcoal cartridge used to expediate clearance of Tramadol • Patient regained consciousness on day 10; tracheotomy performed on day 16 & discharged to pneumology ward on day 41
Gheuens et al. (2010)/ Belgium			Spongiform leukoencephalopathy (hypertonic quadriparesis,	Brain MRI, NP		Persistent impairments (Month 3)	• 49-year-old woman was admitted to the ICU following a methadone overdose, she was discharged to outpatient treatment after unspecified time period

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
			catatonia, mutism, unable to eat)				• 2 weeks after the overdose, the patient developed an akineticrigid syndrome; MRI revealed bilateral changes in the white matter; patient gradually worsened, developed hypertonic quadriparesis and was too impaired to complete cognitive assessment; within 2 weeks patient was completely catatonic, mute and required a feeding tube • Second MRI indicated progression of white matter abnormalities. Due to severity, a stereotactic brain biopsy was performed which confirmed spongiosis, possible exposure to toxic agent could not be identified. • At 3 months, patient showed some improvement and motor functioning improved after botox injections; however, neuropsychological tests confirmed persistent frontal impairments and MRI was unchanged
Ginsberg et al. (1976)/ USA	Case series	3 (1)	Leukoencephalopathy (N/A)	Brain autopsy	Unavailable	Death (Day 23)	• Case series of hypoxic-ischemic leukoencephalopathy, one case was associated with an opioid overdose • 23-year-old male was comatose due to suspected heroin-related overdose, toxicology was not performed but patient was responsive to naloxone and died on day 23 of hospitalization; postmortem brain autopsy found bilateral lesions in the frontal, parietal and occipital lobes; medial globus pallidus was necrotic bilaterally
Gottfried et al. (1997)/ USA	Case report	1 (1)	Anterograde and retrograde amnesia (odd behavior, confusion, incontinence, myoclonic jerks)	Brain MRI	Benzodiazepines (1) Amphetamines (1) Opiates (1)	Persistent Impairments (Month 6)	• 36-year-old male was found unresponsive following an overdose involving opiates, benzodiazepines, and amphetamines; was comatose for 48 h and discharged on day 8 • Day 24, patient exhibited odd behavior, confusion, incontinence and experienced myoclonic jerks • Day 26 patient was readmitted; drug toxicology was negative; MRI revealed bilateral hyperintensities in the white matter • By day 34 patient was comatose and transferred to the ICU; MRI revealed

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							decreased signal in the globus pallidus and right anterior temporal lobe biopsy revealed patchy demyelination • Patient showed improvement in functioning at 3 months; however, he was still disorientated at 6 months and had severe anterograde and retrograde amnesia
Grigorakos et al. (2010)/ Greece	Retrospective cohort	42 (42)	N/A	Clinical observation	Heroin (42)	Variable (ICU discharge)	• Study included patients admitted to the ICU from 1987 to 2006 for morbidity associated with a heroin overdose (n = 42) • 2 patients, who were unresponsive to naloxone in the pre-hospital setting, died in the ICU due to anoxemic encephalopathy; an additional 4 patients died due to severe sepsis • 88 % were admitted to ICU due to hypoxemia and 2 patients had persistent mental compromise
Gupta et al. (2009)/ Bahrain	Case report	1 (1)	Spongiform leukoencephalopathy (unresponsive, tachypnea, altered mental status, bradycardia, facial paresis)	CT scan, Brain MRI	Opioids (1), Benzodiazepines (1)	Partial (Month 6)	• 42-year-old male was found unconscious, toxicology positive for opioids and diazepam, unsuccessful naloxone reversal • CT scan & MRI revealed bilateral hypodensities, including in hippocampus • Patient was ventilated for 1 week and did not fully regain consciousness until month 6, patient unable to independently ambulate • MRI at month 6 revealedencephalomalacia & resolution of lesions in the hippocampus • Authors conclude that leukoencephalopathy was caused by heroin inhalation and it was not associated with hypoxia or ischemia; they noted that the lesions were spongiform
Haghighi-Morad et al. (2020)/ Iran	Case series	10 (6)	Encephalopathy (intoxication, confusion, neurological deficits)	Brain MRI	Methadone (6), Opiates (2)	Unknown	• Case series using hospital records of methadone intoxication (overdose) occurring between May 2016-March 2018, cases were included if they had an abnormal MRI finding & toxicology positive only for methadone; 4 cases were under the age of 18 • In 4 adult cases, imaging documented abnormalities between days 2–12 in the hospital and 2 cases had delayed (9- &

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First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							18- days later) onset occurring after hospital discharge • Imaging abnormalities discussed in aggregate, cannot differentiate the adult cases
Hill et al. (2000)/ Canada	Case report	1 (1)	Leukoencephalopathy (comatose)	CT Scan, Brain MRI	Opioid (1)	Death (Day 26)	• 33-year-old man was found comatose after heroin use; suspected heroin inhalation as track marks were not found • CT scan revealed bilateral intensities in pallidum; brain MRI found increased intensity in deep white matter in cerebellum and cerebral hemispheres • Laboratory testing ruled out carbon monoxide poisoning, HIV and pulmonary disease • Patient never regained consciousness
Holyoak et al. (2014)/ Australia	Case series	2 (1)	Toxic leukoencephalopathy (hypoxia, hypoglycemia)	CT scan, Brain MRI	Unavailable	Death (Day 60)	• 26-year-old male was found hypoxic & collateral reported that patient had ingested Oxycodone and Clonazepam; known history of PTSD, OUD, sedative use disorder and previous non-fatal overdoses • CT scan revealed bilateral hypodensities in globus pallidus • Patient was in the ICU & transferred to inpatient bed on day 12, patient died in hospital on day 60
Hsu et al. (2009)/ Taiwan	Case report	1 (1)	Rhabdomyolysis and stroke (cognitive impairments, aphasia, limb weakness)	Brain MRI	Opioids (1)	Persistent impairments (Week 2)	• 33-year-old male presented with rhabdomyolysis and stroke after overdose resulting from IV heroin use; patient was enrolled in a methadone clinic and known to have used methamphetamine • Overdose confirmed as patient responsive to naloxone administration; toxicology confirmed opioid use and testing confirmed Hepatitis C • Patient remained in ICU for 2 weeks and then transferred to standard hospital bed • MRI revealed hyperintensities in bilateral globus pallidi and left cerebral peduncle, believed to be related to pre-existing injury

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• At 2 weeks patient had cognitive impairments, aphasia and limb weakness
Huisa et al. (2013)/ USA	Case series	2 (2)	Delayed leukoencephalopathy (comatose, confusion, spasticity, myoclonus, insomnia, hallucinations)	Brain MRI, NP	Methadone (1)	1 Full recovery, 1 Persistent impairments (Year 1)	• Two patients with delayed post-anoxic leukoencephalopathy after use of diverted methadone • In both cases, MRI revealed bilateral lesions within the white matter and neuropsychological testing found impairments in executive functioning • One year later one patient had fully recovered while the second had persistent impairment
Jasne et al. (2019)/ USA	Case series	6 (4)	Encephalopathy, amnesia, acute cerebellar edema, Obstructive hydrocephalus (unconscious, hypoxic, cyanosis)	Brain MRI, CT scan	Unavailable	1 Death (Hospital), 1 Partial recovery (Month 1), 1 Persistent impairments (Month 6)	• Convenience sample of patients at two hospitals, between 2014 to 2017, that presented to neurocritical care units with cerebellar edema; 4 cases involved opioid use and presumed overdose • Unknown whether drug toxicology was conducted; authors just reported that patients had used opiates, heroin, fentanyl, cocaine and benzodiazepines • MRI revealed bilateral symmetric distribution in the gray matter of the cerebellar cortex and hippocampi, and asymmetrically in the basal nuclei • Patient presumed to have used fentanyl had profound antegrade amnesia & was unable to live independently, follow-up MRI at 9 months showed improvement
Jensen et al. (1990)/ Denmark	Case series	2 (2)	Ischemic stroke (comatose, cyanosis, paralysis, aphasia, hemianopia)	Brain scintigraphy, CT scan	Unavailable	1 Persistent impairment (Year 1), 1 Persistent impairment (Month 15)	• 30-year-old male found unconscious after injecting heroin and regained consciousness several days later; had aphasia, hemiparalysis & hemianopsia; brain scintigraphy on day 20 revealed infarct in left hemisphere; by month 15 patient had persistent aphasia and hemiparalysis • 35-year-old woman found comatose after injecting heroin; patient was aphasic and had paralysis; day 2 CT scan revealed edema but no hypodensities; CT scan on day 18 & day 72 revealed a declining

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							hypodensity in the left basal ganglia; Patient had persistent hemiparalysis at year 1
Khot et al. (2007)/ USA	Case report	1 (1)	Delayed post-hypoxic demyelination (bradyphrenia, memory deficits, abulia, akinetic, mutism, rigidity)	CT scan, Brain MRI, Brain autopsy	Morphine (1), Codeine (1)	Death (Day 66)	• 46-year-old male was found unconscious & toxicology was positive for morphine and codeine, although there was no evidence of injection drug use; patient reported unsuccessful attempt to snort heroin which he then rubbed on his gums • Patient rapidly declined after an international flight home & demonstrated memory deficits; readmitted to hospital on day 20; CT scan & MRI revealed bilateral hypodensities in the globi pallidi • Patient continued to decline & MRI on day 25 revealed new hypodensities; patient's Arylsulfatase-A activity was normal • Patient was transferred to home with hospice due to his vegetative state and he died on day 66 • Brain autopsy revealed bilateral necrosis in the globi pallidi & extensive demyelination in the cerebral white matter
King et al. (2015)/ USA	Case report	1 (1)	Delayed post hypoxic leukoencephalopathy (odd behavior, memory deficits incontinence, parkinsonism, bradyphrenia, apathy, mutism)	Brain MRI, CT scan	Unavailable	Persistent impairments (Week 10)	• 63-year-old male developed delayed post hypoxic leukoencephalopathy (DPHL) 10 days after an opioid overdose, patient was known to have an OUD and AUD • Patient had Hepatitis C which had been treated with interferon • Initial CT scan following overdose was normal • 10 days later patient exhibited odd behavior and MRI confirmed delayed post hypoxic leukoencephalopathy (DPHL) • Patient had severe impairments in attention and short-term memory, patient continued to decline and experienced incontinence, parkinsonism, bradyphrenia, apathy, and mutism • Clinical deterioration reversed with antioxidant therapy (Vitamins E, C, B-complex; coenzyme Q10)

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
Koch et al. (2018)/ German	Case report	1 (1)	Cerebral edema (Comatose, tachycardia, and hypothermia)	CT scan	U-47,700 (1) Benzodiazepines (1)	Death (Day 6)	• 24-year-old male overdosed on U-47,700 and benzodiazepine (flubromazepam) • CT scan revealed cerebral damage and severe brain edema • On day 6, ventilation removed and patient died
Koksel et al. (2019)/ USA	Case series	87 (20)	Leukoencephalopathy	Brain MRI	Unavailable	N/A	• Cases of suspected acute toxic leukoencephalopathy (ATL) over a 15 year period; included if patient was adult, excluded cases whether ATL resulted from metabolic or infection; ATL was confirmed by imaging; unclear which cases resulted from overdose • 20 patients' ATL was associated with use of opioids
Kuhlman and Gwathmey (2018)/ USA	Case series	26 (1)	Gluteal compartment syndrome (leg pain, numbness)	Brain MRI	Opiates (1)	No brain injury	• 2 case reports (only 1 reported Brain MRI) & 24 previously published case reports of gluteal compartment syndrome • 28-year-old female was found 6 h after a heroin overdose & sought medical care 4 days later due to leg pain; was diagnosed with gluteal compartment syndrome, brain MRI was normal & cognitive deficits were not reported
Landais (2014)/ France	Case report	1 (1)	Memory impairment (Hypoxemia, partial consciousness & memory deficits)	Brain MRI, NP	Unavailable	Partial recovery (Month 10)	• 40-year-old male with intentional morphine overdose was found partially conscious; drug toxicology not reported • MRI on day 9 revealed bilateral lesions in the hippocampus & month 10 MRI revealed resolution of lesions • Neuropsychological exam (Free and Cued Selective Reminder Test (FCSRT), BEM & DO 80) occurred on day 20 due to patient's memory deficits which found impairment in verbal and visual memory • NP repeated at month 4 and revealed some improvement noting persistent long-term memory deficits
Lefaucheur et al. (2017)/ France	Case report	1 (1)	Leukoencephalopathy (cognitive impairments,	Brain MRI, NP	Unavailable	Recovery (Month 4)	• 29-year-old male presented with acute cognitive impairments three weeks after a coma caused by an overdose

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			anosognosia, apraxia, memory impairment)				• Opioid overdose confirmed by response to naloxone, no signs of hypoxia • Patient known to use heroin and alcohol, history of suicide attempts, & depression • Brain MRI revealed bilateral hyperintensities in white matter, discharged home after one month with no improvements noted at that time • At 4 month follow-up, patient had dramatic improvements in cognitive functioning
Loftsgard et al. (2017)/ USA	Case report	1 (1)	Hypoxic-ischemic brain injury (multiorgan failure, respiratory failure)	CT scan, brain autopsy	Opioids (1) Benzodiazepines (1)	Death (Day 4)	• 19-year-old male overdosed involved opioids and benzodiazepines, drugs confirmed by toxicology; patient had multiorgan failure & acute hypoxia; CT scan revealed diffuse anoxic brain injury; patient had neurogenic pulmonary edema; On day 4, patient died after life support was withdrawn • Autopsy confirmed that global hypoxic-ischemic brain injury was the cause of death
Long et al. (2013)/ China	Case report	1 (1)	Leukoencephalopathy (comatose, hydrocephalus)	Brain MRI, CT scan	Opiates (1)	Recovered (Month 1)	• 34-year-old male presented to hospital after 24 h of being unconscious following a heroin overdose • MRI on day 1 revealed bilateral cerebellar abnormalities, repeat MRI on day 5 revealed enlarged lesions in the bilateral cerebellar hemispheres • On day 5, patient became comatose and had developed acute hydrocephalus • Within 1 month, patient recovered and the lesions were absorbed
McDonald et al. (2013)/ Australia	Case-control	225 (148)	N/A	NP	Unavailable	Unknown	• Cases were 125 patients receiving medications for OUD (94 on methadone and 31 on buprenorphine), 50 abstinent opioids users in a residential treatment program and 50 matched controls • Social cognition was measured using The Awareness of Social Inference Test (TASIT) • After controlling for cognitive performance and other characteristics, number of

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							previous overdoses predicted TASIT I scores (emotional perception) • Authors conclude that the areas of the brain damaged by overdose-related hypoxic injuries may impact emotional functioning
Meyer (2013)/ USA	Case report	1 (1)	Delayed leukoencephalopathy (incontinence, lethargic, socially withdrawn)	CT scan, Brain MRI	Unavailable	Recovered (Year 1)	• 39-year-old female intentionally overdosed on methadone and diazepam (toxicology not reported); 1 week in hospital and 2 days in psychiatric hospital; clinical assessment did not find any cognitive impairments • 3 weeks after discharge she became socially withdrawn, incontinent, lethargic and returned to hospital; CT scan and MRI revealed hypodensities in subcortical white matter; neurological exam found slowed gait, disorientation and poor short-term memory • Clinical and radiographic exam at year 1 follow-up confirmed recovery
Molloy et al. (2006)/ England	Case report	1 (1)	Delayed leukoencephalopathy (confusion, inattention)	Brain MRI, NP	Unavailable	Recovered (Month 9)	• 40-year-old female presented with confusion and decreased attention 17 days after acute treatment and hospitalization due to morphine overdose • Brain imaging consistent with acute disseminated encephalomyelitis • Neuropsychological examination at 24 months prior confirmed no pre-existing cognitive impairments • Addenbrooke' s Cognitive Examination score 40/100 (suggesting severe global cognitive impairment – memory and verbal fluency)
Morales Odia et al. (2010)/ USA	Case report	1 (1)	Encephalopathy, severe cerebellitis, hydrocephalus (confusion, gait impairment, delirium, agitation, disorientation)	Brain MRI, CT scan	Morphine (1) Benzodiazepines (1)	Persistent impairments (Month 3)	• 46-year-old male presented with multifocal encephalopathy and severe cerebellitis after an overdose involving oxycodone and OxyContin • Initially he presented with confusion; on day 2 he had gait impairment, delirium, agitation, and disorientation; treated for acute opiate withdrawal • CT scan on day 3 confirmed severe obstructive hydrocephalus

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• Brain MRI revealed bilateral lesions in the cerebellum and globus pallidi, day 6 MRI revealed abnormalities in the basal ganglia had resolved • Patient had rehabilitative therapy and cognitive improvements, while speech impairments and ataxia remained
Morrow et al. (2019)/ Canada	Retrospective cohort	14,011 (14,011)	Encephalopathy (N/A)	Clinical observation	Unavailable	Variable (During hospitalization)	• Two cohorts included patients admitted to the hospital from 2000 to 2015 for accidental opioid overdose and investigated risk of neurological, respiratory, cardiac and other adverse events • First cohort (n = 2433) included patients hospitalized for an accidental opioid overdose and excluded individuals who had an overdose in the past year • Second cohort included long-term prescription opioid users, among those who had been hospitalized for an accidental opioid overdose (n = 538) – 20 matched controls were identified for each case (n = 11,040) • 3% of opioid-related overdose hospitalizations had encephalopathy and 25 % had an adverse outcome (composite measure) • 3% died in the hospital and 5.5 % had respiratory failure; number of hospitalizations with respiratory failure increased during the study period • Risk of encephalopathy or other adverse outcomes did not increase with subsequent overdose admissions
Muller et al. (2018)/ Germany	Case control	26 (14)	Brain abnormalities (N/A)	Brain autopsy	Unavailable	N/A	• Brain autopsy data compared between cases (n = 14) whose cause of death was a heroin overdose and controls (n = 12) • While cases were on average 10 years younger compared to controls, the relative volume of their pallidus externus was smaller

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• Authors conclude that there is evidence of structural and cognitive deficits in individuals with heroin use
Mumma et al. (2009)/ USA	Case report	1 (1)	Cardiac arrest (comatose, mild dysarthria, cognitive impairment, rhabdomyolysis, slurred speech)	CT Scan, Brain MRI, NP	Opiates (1), Benzodiazepines (1)	Recovered (Month 8)	• 28-year-old male was comatose; CT scan and brain MRI revealed bilateral hypodensities in the globus pallidum • Patient regained consciousness on day 6, had slurred speech and had mild cognitive impairment; was transferred from hospital to rehabilitation facility • Month 8 follow-up patient was functioning well and had a Cerebral Performance Category score of 1
O'Brien et al. (2009)/ Ireland	Retrospective cohort	43 (21)	N/A	NP	Unavailable	Variable (Months 20–37)	• Prospective outcomes at 31 months were assessed for patients treated in the ICU for drug overdose between 2004–2006; 21 cases involved opioids • Karnofsky Index, a measure of functional impairment, at baseline the median score was 60 (range = 0–80) and at follow-up 80 (70–90) suggesting that all of those survived had functional improvements • 11 patients died in the hospital and at follow-up, an additional 8 patients had died • At follow-up, 54 % of those who survived were unemployed
O'Brien and Todd (2009)/ Australia	Case series	10 (10)	Brain injury (N/A)	CT scans, Brain MRI, NP	Unavailable	Variable (Year 2–4)	• Case series of patients presenting to a brain injury rehabilitation facility with hypoxic brain injuries following heroin overdose between July 1997–June 1999 • 5 patients had normal CT scans & 3 had abnormal findings (1 global hypoxia, 1 bilateral watershed changes, 1 changes in left globus pallidus & basal ganglia) • NP included Functional Independence Measure (FIM) and Community Integration Questionnaire (CIQ) • Prior to brain injury, all patients were living independently & 9 self-reported a history of heroin use

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First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• Mean length of inpatient stay at brain injury rehab center was 83 days (range: 15–437); results of NP documented improvements in cognition during rehab • Follow-up conducted over the telephone with 9/10 patients; 2 had died; 3 were unable to work & only 3 were living independently
Oehmichen et al. (1996)/ Germany	Retrospective cohort	180 (168)	N/A	Brain autopsy	Unavailable	N/A	• Brain autopsies from IV drug users from 1990 to 1993, cases with HIV were excluded • Urine or blood was used to confirm presence of illegal drugs, including heroin • The case of death in 64 % of cases was acute heroin intoxication (not involving other substances), 19 % had polysubstance intoxication, and 18 % had a delayed drug overdose death • Brain edema identified in 90 % of cases of heroin overdose
Ormseth et al. (2019)/ USA	Retrospective cohort	300 (15)	N/A	Brain MRI, CT scan	Opioids (15) Polysubstance (10) Cocaine (3)	Variable (During hospitalization)	• Cohort study including patients who presented at a single hospital with cardiac arrest between 2012–2017, who were initially unconscious, following return of spontaneous circulation (ROSC) • 9% had an overdose-related cardiac arrest and among those, 86 % involved opioids and 73 % died by hospital discharge • Patients with an overdose-related cardiac arrest were more likely to have signs of hypoxic-ischemic brain injury and more likely to have withdrawal of life-sustaining therapy
Oxley et al. (2015)/ Australia	Case-control	36 (21)	N/A	NP	Unavailable	Variable (During hospitalization)	• Prospective case-control study that compared cognition among patients hospitalized for an intentional overdose between 2013–2014 for Central Nervous System Depressants (CNS-D) (21 cases) and Central Nervous System non-depressant (antide-pressant, acetaminophen) drugs (CNS-ND) (15 controls); follow-up at 7- and 28-days; baseline data reported in Dassanayake et al., 2012 (see above)

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• Cases had greater impairment in cognitive flexibility, cognitive efficiency, and working memory; cases were more likely to be in the 10th percentile on the TMT-B at both follow-up periods – which correlates with driving impairment • Authors conclude that additional research is needed to determine whether patients who have CNS-D related overdoses should not drive after hospital discharge
Pearson et al. (1975)/ USA	Case-control	11 (11)	N/A	Brain autopsy	Morphine (8) Methadone (3)	N/A	• Random sample of 96 brains among 1140 drug-related deaths (492 specified narcotics); study included a subset of 11 brains of decedents had known OUD compared to 11 controls • All subjects were male and controls ranged in age from 15 to 63 years old (1 adolescent case); all cases included because outcomes reported in aggregate • OUD brains had significant decrease of neurons within the globus pallidus • Only 2 of 11 cases had evidence of acute hypoxic neuronal necrosis; observed damage appears to be progressive • Authors conclude that permanent brain damage results from repeat hypoxia
Pfister et al. (2016)/ USA	Retrospective cohort	178 (178)	N/A	Clinical observation	Opioids (178)	Deaths - 18 (During hospitalization)	• The study included patients admitted to the ICU for opioid overdose between 2001 – 2014, which was confirmed by toxicology or self-report • The opioids most commonly used were oxycodone (41 %) and hydrocodone (28 %), only 16 % had used heroin • Mean ICU length of stay was 3 days and 89 % required mechanical ventilation • 18 patients died in hospital (9 due to hypoxic brain injury) and 6 were discharged to a nursing home
Pirompanich and Chankrachang	Case report	1 (1)	Spongiform leukoencephalopathy (confusion, mutism,	Brain MRI	Heroin (1) Morphine (1)	Persistent impairments (Month 6)	• 41-year-old male presented with opioid overdose; non-responsive to naloxone; discharged home and mild cognitive impairment noted

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(2015)/ Thailand			akinetic, spastic, hyperreflexive)				• 5 days later patient developed confusion and was unable to complete activities of daily living • Upon hospital readmission, patient was mute, akinetic, spastic and hyperreflexive; MRI at 1 week after readmission revealed bilateral brain abnormalities (lesions and involvement in white matter)
Quinn and Abbott (2014)/ USA	Case report	1 (1)	Delayed leukoencephalopathy (incontinence, nausea, confusion, odd behavior)	Brain MRI	Opioids (1)	Persistent impairments (Year 1)	• 56-year-old female, with schizoaffective disorder and Hepatitis C-related cirrhosis, had an unintentional overdose involving prescription opioids and she had hypoxic respiratory failure; she was treated in the ICU and hospitalized for 1 week • Patient experienced increased symptoms post-discharge including incontinence, nausea, confusion and odd behavior; patient was taking several psychiatric and pain medications • Patient was given ECT for catatonia/ neuroleptic malignant syndrome; repeated MRI revealed bilateral white matter changes • At 1 year, patient continued to be mute and have stupor
Ramirez-Zamora et al. (2015)/ USA	Case report	1 (1)	Brain abnormalities (confusion, apathy, inattention, memory deficits)	Brain MRI	Opioids (1) Cannabinoids (1)	Persistent impairments (Week 1)	• Patient called ambulance after taking a high dose of Oxycodone, patient did not lose consciousness • Brain MRI conducted within 24 h revealed bilateral abnormalities in the globus pallidus and hippocampi • Over 1 week in the hospital, patient demonstrated inattention, apathy, and memory impairment
Revesz and Geddes (1988)/ England	Case report	1 (1)	Encephalopathy (cardiac arrest, hypothermia, pulmonary edema)	CT scan, brain autopsy	Methadone (1), Amphetamines (1)	Death (Day 6)	• 35-year-old male was found unconscious 12 h after release from prison, due to an overdose; patient had a known history of OUD; patient had cardiac arrest lasting 30–40 minutes; CT scan on day 6 revealed extensive infarction in thalami and brain stem; life support was removed and patient died

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• Brain autopsy revealed inflammation and symmetrical lesions in the grey structures
Richter et al. (1973)/ USA	Case series	42 (Undetermined)	Delayed encephalopathy, dementia, Parkinsonian syndrome (hemiballistic movements)	Unknown	Unavailable	Unknown	• Loosely reported case series of 42 patients with a history of being treated in a hospital for heroin overdose • Authors observed 3 cases of dementia & 2 cases of delayed encephalopathy following a heroin overdose • 31-year-old had unilateral Parkinsonian syndrome • 28-year-old male had hemiballistic movements • 3 of 21 had bilateral lesions in the globi pallidi (presumably identified post-mortem)
Rizzuto et al. (1997)/ Italy	Case report	1 (1)	Delayed spongiform encephalopathy (comatose, heart failure, rhabdomyolysis, renal failure)	Brain MRI, brain autopsy	Unavailable	Death (Week 6)	• 30-year-old male presented with a heroin overdose, was found unconscious 18 h after injecting heroin, he was responsive to naloxone • On day 2 of hospitalization, patient received dialysis due to acute renal failure • MRI revealed brain abnormalities in the white matter of the cerebellum, pallidum and centrum ovale; 3 weeks later onset of delayed spongiform encephalopathy and patient died 20 days later • Brain autopsy revealed an edema and sponginess of white matter, no evidence of lesions or necrosis
Salazar and Dubow (2012)/ USA	Case report	1 (1)	Delayed leukoencephalopathy (confusion, lethargy, akinetic mutism)	CT scan, Brain MRI	Morphine (1)	Partial recovery (Day 40)	• 54-year-old man accidentality overdosed on morphine pills, CT scan & MRI revealed bilateral hypodensities in the globi pallidi; discharged from hospital after unknown duration & patient still had mild confusion • Day 20 patient readmitted to the hospital due to confusion, lethargy & akinetic mutism • Testing ruled out Lyme disease, West Nile virus, HIV, herpes & other viruses • Brain MRI revealed diffuse hyperintensity in the white matter & in the corpus callosum

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• Day 40 patient was discharged to a nursing home
Shprecher et al. (2008)/ USA	Case series	3 (3)	Delayed leukoencephalopathy, pneumonia (hypotension, memory deficits, disorientation, gait impairment, delusional, catatonia, automatisms, incontinence, mutism, loss of interest, fatigue, inattention, catatonia, imbalance)	Brain MRI, NP	Unavailable	1 Partial recovery (Year 1), 1 Partial recovery (Week 38), 1 Persistent impairments (Week 8)	• 39-year-old woman overdosed on methadone and cocaine (toxicology not reported); patient was readmitted to the hospital at week 4 due to memory deficits, disorientation & unsteady gait; MRI revealed increased signal in the white matter; bilateral gegenhalten noted at week 32; at year 1 patient was unable to work or drive due to emotional lability, attention deficits & fatigue; MRI revealed volume loss & persistent signal abnormalities in white matter; comparison of WAIS-III pre-overdose and 1 year after overdose documented declines in verbal IQ and memory
							• 51-year-old was found unconscious after methadone overdose (toxicology not reported); recovered after 2 days; day 21 patient was reported to have loss of interest, declined mental status & paranoid delusions; day 28 patient was catatonic, incontinent, had mutism & automatisms; MRI revealed bilateral hyperintensity in white matter; week 16 Mini-Mental State Examination (MMSE) score of 27 /30; week 38 patient had partial recovery with persistent memory deficits, imbalance & needed help with self-care; MRI documented persistence of signal abnormalities in the white matter
							• 56-year-old woman intentionally overdosed on methadone, fentanyl & benzodiazepines (toxicology not reported) and patient was discharged day 11; day 15 patient had significant cognitive decline confirmed by MMSE score of 15/30; day 14 MRI revealed hyperintensities in white matter; week 8 patient had persistent memory and attention deficits, as well as inability to live independently
Shu et al. (2016)/ Australia	Case report	1 (1)	Dystonia-Parkinsonism (involuntary movements, gait impairment, jaw spasms, dystonia, bradykinesia)	Brain MRI	Unavailable	Persistent declines (Year 3)	• 20-year-old male presented to the hospital 2 days after a presumed overdose due to involuntary movements on right side; patient could not recall the first 36 h after injecting heroin (had also used quetiapine & alprazolam)

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• MRI revealed bilateral hyperintensities in the golbus pallidus and caudate nuclei; patient experienced worsening symptoms and MRI at week 1 revealed new hyperintensities • Year 3 he presented with persistent declines in gait & ability to ambulate
Singh and Saini (2015)/ Singapore	Case report	1 (1)	Leukoencephalopathy (inattention, stiffness, mutism, developed bradykinesia, tremors)	Brain MRI	None	Persistent impairments (Week 6)	• 58-year-old male presented with inattention and stiffness; he became mute within a few days and developed bradykinesia, tremors; toxicology positive for morphine • 30 days prior patient had presented for suspected heroin overdose, but toxicology was not performed and CT scan was normal • MRI scan at hospital readmission revealed bilateral abnormalities in the white matter • At week 2 of hospitalization, minimal improvements were noted and the patient was transferred to long-term care facility
Switzer et al. (2020)/ Canada	Case report	1 (1)	Delayed leukoencephalopathy, amnesia (rigidity, tremor, gait impairments, inattention, unconscious, memory deficits)	Brain MRI, NP	Fentanyl (1)	Partial recovery (Month 5)	• 52-year-old male had acute amnesia after being unconscious for 12 h following a fentanyl overdose; MRI confirmed hippocampal injuries & MMSE score of 18/30; within 24 h patient was stable with only memory deficits • By month 1 patient developed Parkinsonism symptoms (e.g., rigidity, tremor, slow gait) which partially improved with treatment by month 5 • Partial recovery at month 5 based on repeated MRI; NP exam found persistent inattention, poor recognition memory & poor violation; notably patient was not able to live independently
Taheri et al. (2011)/ Iran	Retrospective cohort	403 (108)	Brain abnormalities (comatose)	Clinical observation, CT scan	Unavailable	Variable (During hospitalization)	• Sample included patients who were unconscious due to drug overdose; overdose was determined by bystander report, evidence at the scene, suicide note or toxicology • Mean age was 38 years old and most (79 %) were male

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							• 40 % had used opium and 5% involved Tramadol • Among those who had used opium: 12 % were determined to be suicides, 29 % were comatose, 15 % had abnormal CT scans and 1 case found evidence of changes in the basal ganglia
Taylor et al. (2019)/ Canada	Case report	1 (1)	Amnesia (unconscious, confusion)	Brain MRI, NP	Opiates (1)	Persistent deficits (Month 4)	• 63-year-old pain patient found unconscious after using 3 fentanyl pain patches; regained consciousness after naloxone infusion and toxicology positive for opiates; patient had profound anterograde amnesia • Testing ruled out herpes simplex virus, arbovirus & syphilis • MoCA score was 19/30 & MRI on day 7 revealed bilateral hyperintensities in hippocampus • Day 12 MRI showed resolution of hyperintensities and NP results suggested mild executive impairment • Follow-up telephone interview with patient's husband confirmed persist amnesia
Torralba-Moron et al. (2017)/ Spain	Case series	3 (2)	Delayed leukoencephalopathy (unresponsive, amnesia, bradypnea, muscle spasm, inattention, fever)	Brain MRI, CT scan	Methadone (2), Alprazolam (1), Alcohol (1)	1 Persistent deficits (Discharge), 1 Death (Day 40)	• Two males in their mid-forties overdosed after using methadone (toxicology not reported); patients known to have a 5 year history of heroin use • One patient initially had non-specific neuroimaging, but on day 13 experienced fluctuating consciousness & MRI revealed bilateral globus pallidus injury; at discharge patient was amnestic, lack of attention & dysexecutive abnormalities • Second patient had been treated for HIV and his initial CT scan revealed decreased density in globus pallidus; then after a few days he deteriorated & MRI revealed bilateral lesions in the globus palldus; patient did not regain consciousness
Vendrame and Azizi (2007) /USA	Case report	1 (1)	Brain abnormalities (comatose, cyanosis, gait impairment)	Brain MRI	Opiates (1) Cocaine (1) Cannabis (1)	Partial improvements (Month 3)	• 23-year-old male had a drug overdosed & became comatose • Brain MRI on day 2 revealed bilateral abnormalities in the cerebellum, globis

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First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
							pallidus, and motor cortex; brain MRI at week 2 found that the lesions were reduced • Patient discharged on day 24, overall improvement • At 3 months, patient still had ambulation problems and was unable to walk independently
Vila and Chamorro (1997)/ Spain	Case series	2 (2)	Stroke (comatose, ballistic movements)	Brain MRI, CT scan	Unavailable	Recovered (Day 3 & Month 9)	• 19 and 34-year-old males developed ballistic movements after heroin overdose • Case 1 left hospital AMA and returned 1 week later due to involuntary movement in his extremities; CT and MRI scans revealed bilateral globus pallidus hypodensities; patient treated with haloperidol and symptoms resolved at 9 months • Case 2 MRI revealed ischemic infarcts right lenticulostriate vascular territory and inferior branch right middle cerebral artery; patient treated with haloperidol and symptoms resolved on day 3
Villella et al. (2010)/ Italy	Case report	1 (1)	Spongiform leukoencephalopathy (comatose)	Brain MRI	None	Partial improvements (Year 2)	• 32-year-old male was unconscious following a suspected overdose after injecting heroin; testing ruled out Hepatitis C and HIV • Patient discharged from hospital after unspecified number of weeks in the hospital, started outpatient neurological rehabilitation program; continued improvement noted at 2 years
Voigt (2013)/ Germany	Case report	1 (1)	Brain damage (hypoventilation, bradycardia, hypotension, miosis)	CT scan, Brain MRI	None	No improvements (Day 30)	• 58-year-old male was found unconscious; drug toxicology was negative; CT scan revealed edema after which physician found 75 mcg fentanyl patch on patient • Wife reported that patient had pain after biking & may have applied fentanyl patch obtained from a deceased relative; wife reported that patient thought it was a heat releasing patch • CT scan at hour 72 revealed hypoxic brain damage • Day 30 patient transferred to rehabilitation center and remained in a vegetative state

First author (Pub. year)/ Country	Methods	Overall sample (Sample with opioids & OD)	Diagnosis (Symptoms)	Measure (s) impairment	Drugs confirmed by toxicology (Num. of subjects)	Outcomes (Time frame)	Key findings/Summary
Wijdicks (2005)/ USA	Case report	1 (1)	Encephalopathy (comatose, apathy, memory deficits, rigidity, monotonic, gait impairment)	Brain MRI, CT scan	Opioids (1) Benzodiazepines (1)	No improvements (Month 3)	• 24-year-old male overdosed and was found comatose • CT scan and MRI confirmed bilateral globus pallidus lesions and white matter lesions • Known history of mandibular fracture one month earlier resulting from blow to face • Within 3 days he regained consciousness, at 4 weeks patient had limited ability to ambulate and no change at 3 months
Yarid and Harruff (2015)/ USA	Retrospective cohort	27 (10)	N/A	Brain autopsy	Opiates (8) Benzodiazepines (2) Methadone (2) Cocaine (2) Methamphetamines (1)	N/A	• Cases defined as brain autopsies, from 1994 to 2013, with bilateral basal ganglia lesions • 10 deaths attributed to drug overdose involving heroin; 3 of which lived long enough to be diagnosed with anoxic encephalopathy • Bilateral injuries are suggestive of global insult • Deaths attributed to carbon monoxide had no evidence of globus pallidus or basal ganglia necrosis
Zamora et al. (2015)/ USA	Case series	5 (4)	Delayed leukoencephalopathy (incontinence, mutism, ataxia, odd behaviors, executive functioning impairment)	Brain MRI	Unavailable	Death -1 Recovery -2, Persistent impairments 1 (Week 2-Week 5)	• Cases had a hypoxic event characterized by neurological impairments, recovery, and relapse; 4 of 5 had opioid-related overdose; however, toxicological results were not reported • Median time to relapse was 23 days, all cases had brain abnormalities confirmed by MRI, which were bilateral, symmetric and involved white matter

NOTES: AMA = against medical advice; ATL = acute toxic leukoencephalopathy; CNS-D = Central Nervous System Depressants; CNS-ND = Central Nervous System non-depressant; DPHL = delayed post hypoxic leukoencephalopathy; ECT = electroconvulsive therapy; ED = emergency department; ICU = intensive care unit; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; OUD = opioid use disorder; NP = neuropsychological testing; ROSC = return of spontaneous circulation (ROSC); SSRI = selective serotonin reuptake inhibitor; TMT-B = Trail making test, part B; WASI-III = Wechsler Abbreviated Scale of Intelligence 3rd Edition.

Table 2

Study quality assessment.

First author (Pub. year)	Study design (Sample size)	Selection bias[a]	Performance bias[b]	Attrition bias[c]	Detection bias (overdose)[d]	Detection bias (brain abnormalities/CF)[d]	Reporting bias[e]
Achamallah et al. (2019)	Case series (N = 3)	High risk	High risk	High risk	Low risk	Low risk	Unclear
Adrish et al. (2014)	Case report (N = 1)	High risk	High risk	High risk	Low risk	Unclear	High risk
Alquist et al. (2012)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	Unclear
Alturkustani et al. (2017)	Retrospective cohort (N = 5)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Andersen and Skullerud (1999)	Retrospective cohort (N = 100)	High risk	High risk	Low risk	High risk	Low risk	High risk
Arciniegas et al. (2004)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Barash and Kofke (2018)	Case series (N = 22)	High risk	High risk	High risk	Low risk	Low risk	Unclear
Barnett et al. (2001)	Case report (N = 1)	High risk	Low risk	Low risk	High risk	Low risk	High risk
Beeskow et al. (2018)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Bileviciute-Ljungar et al. (2014)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Butler et al. (2019)	Case report (N = 1)	Low risk	High risk	Low risk	High risk	Low risk	Unclear
Carroll et al. (2012)	Case report (N = 1)	High risk	Low risk	Low risk	High risk	Low risk	High risk
Cerase et al. (2011)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Chang et al. (2009)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Cheng et al. (2019)	Case series (N = 2)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Chute and Smialek (2002)	Case series (N = 5)	High risk	High risk	Low risk	High risk	High risk	High risk
Cohen and Hack (2019)	Case report (N = 1)	High risk	High risk	High risk	High risk	Low risk	High risk
Corliss et al. (2013)	Case report (N = 1)	High risk	Unclear	Low risk	Low risk	Low risk	High risk
Corre et al. (2013)	Case report (N = 1)	High risk	High risk	High risk	Low risk	Low risk	High risk
Darke et al. (2000)	Case-control (N = 60)	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Dassanayake et al. (2012)	Case-control (N = 175)	Low risk	Low risk	Low risk	Unclear	Low risk	High risk
Fatovich et al. (2008)	Prospective observational (N = 224)	Unclear	High risk	Low risk	High risk	High risk	High risk
Ferrari et al. (2020)	Case report (N = 1)	High risk	High risk	High risk	Low risk	High risk	High risk
Gheuens et al. (2010)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Ginsberg et al. (1976)	Case series (N = 3)	High risk	High risk	Low risk	High risk	Low risk	High risk
Gottfried et al. (1997)	Case report (N = 1)	High risk	High risk	Low Risk	Low risk	Low risk	High risk

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First author (Pub. year)	Study design (Sample size)	Selection bias[a]	Performance bias[b]	Attrition bias[c]	Detection bias (overdose)[d]	Detection bias (brain abnormalities/CF)[d]	Reporting bias[e]
Grigorakos et al. (2010)	Retrospective cohort (N = 42)	High risk	High risk	Low risk	Low risk	High risk	High risk
Gupta et al. (2009)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Haghighi-Morad et al. (2020)	Case series (N = 10)	High risk	High risk	High risk	Low risk	Low risk	High risk
Hill et al. (2000)	Case report (N = 1)	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Holyoak et al. (2014)	Case series (N = 2)	High risk	High risk	Low risk	High risk	Low risk	High risk
Hsu et al. (2009)	Case report (N = 1)	High risk	Low risk	High risk	Low risk	Low risk	High risk
Huisa et al. (2013)	Case series (N = 2)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Jasne et al. (2019)	Case series (N = 6)	High risk	High risk	High risk	High risk	Low risk	High risk
Jensen et al. (1990)	Case series (N = 2)	High risk	High risk	High risk	High risk	High risk	High risk
Khot et al. (2007)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
King et al. (2015)	Case report (N = 1)	High risk	Low risk	Low risk	High risk	Low risk	High risk
Koch et al. (2018)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Koksel et al. (2019)	Case series (N = 87)	High risk	High risk	High risk	High risk	Low risk	High risk
Kuhlman and Gwathmey (2018)	Case series (N = 26)	High risk	High risk	High risk	High risk	Low risk	High risk
Landais (2014)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Lefaucheur et al. (2017)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Loftsgard et al. (2017)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Long et al. (2013)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
McDonald et al. (2013)	Case-control (N = 225)	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Meyer (2013)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Molloy et al. (2006)	Case report (N = 1)	High risk	Low risk	Low risk	High risk	Low risk	High risk
Morales Odia et al. (2010)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Morrow et al. (2019)	Retrospective cohort (N = 14,011)	High risk	High risk	Low risk	High risk	High risk	High risk
Muller et al. (2018)	Case control (N = 25)	High risk	High risk	Low risk	High risk	Low risk	High risk
Mumma et al. (2009)	Case Report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
O'Brien et al. (2009)	Retrospective cohort (N = 43)	High risk	High risk	Low risk	Unclear	Low risk	High risk
O'Brien and Todd (2009)	Case series (N = 10)	High risk	High risk	Low risk	High risk	Low risk	High risk
Oehmichen et al. (1996)	Cohort (N = 180)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Ormseth et al. (2019)	Retrospective cohort (N = 300)	High risk	High risk	Low risk	High risk	High risk	High risk
Oxley et al. (2015)	Prospective case-control (N = 36)	Low risk	High risk	High risk	Unclear	Low risk	Unclear

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First author (Pub. year)	Study design (Sample size)	Selection bias[a]	Performance bias[b]	Attrition bias[c]	Detection bias (overdose)[d]	Detection bias (brain abnormalities/CF)[d]	Reporting bias[e]
Pearson et al. (1975)	Case-control (N = 11)	Low risk	High risk	Low risk	High risk	Low risk	Unclear
Pfister et al. (2016)	Retrospective cohort (N = 178)	High risk	High risk	Low risk	Low risk	High risk	High risk
Pirompanich and Chankrachang (2015)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Quinn and Abbott (2014)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Ramirez-Zamora et al. (2015)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Revesz and Geddes (1988)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Richter et al. (1973)	Case series (N = 42)	High risk	High risk	High risk	High risk	High risk	High risk
Rizzuto et al. (1997)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Salazar and Dubow (2012)	Case report (N = 1)	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Shprecher et al. (2008)	Case series (N = 3)	High risk	High risk	Low risk	High risk	Low risk	High risk
Shu et al. (2016)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Singh and Saini (2015)	Case report (N = 1)	High risk	High risk	Low risk	High risk	Low risk	High risk
Switzer et al. (2020)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Taheri et al. (2011)	Cohort (N = 403)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Taylor et al. (2019)	Case report (N = 1)	High risk	Low risk	High risk	Low risk	Low risk	High risk
Torralba-Moron et al. (2017)	Case series (N = 3)	High risk	High risk	High risk	High risk	Low risk	High risk
Vendrame and Azizi (2007)	Case report (N = 1)	High risk	High risk	Low risk	Low risk	Low risk	High risk
Vila and Chamorro (1997)	Case series (N = 2)	High risk	High risk	High risk	High risk	Low risk	High risk
Villella et al. (2010)	Case report (N = 1)	High risk	Low risk	Low risk	High risk	Low risk	High risk
Voigt (2013)	Case report (N = 1)	High risk	High risk	High risk	Low risk	Low risk	High risk
Wijdicks (2005)	Case report (N = 1)	High risk	Unclear	Low risk	Low risk	Low risk	High risk
Yarid and Harruff (2015)	Retrospective cohort (N = 27)	High risk	High risk	Low risk	Unclear	Low risk	Low risk
Zamora et al. (2015)	Retrospective case series (N = 5)	High risk	High risk	High risk	Low risk	Low risk	Low risk

[a]Selection bias: does the design or analysis control for confounding factors.

[b]Performance bias: did the researchers rule out concurrent intervention or unintended exposure that could bias results.

[c]Attrition bias: was there differential nonresponse, dropout, or loss to follow-up.

[d]Detection bias: was toxicological confirmation of opioid-related overdose reported and was neuroimaging, psychological testing or autopsy used to confirm brain abnormalities/ cognitive impairments.

[e]Reporting bias: conclusion supported by study design & objective measures CF = cognitive functioning.