Review Article on Opioid Utility the Other Half of Equianalgesia

Combining opioids and benzodiazepines: effects on mortality and severe adverse respiratory events

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Opioids and benzodiazepines are increasingly used alone or in combination. However, the combined use of these agents increases the risk for potentially lethal respiratory depression. This review summarizes current evidence on the effects of the combined use of opioids and benzodiazepines on mortality and severe respiratory adverse events. The results of 29 included manuscripts showed that concomitant use of opioids and benzodiazepines increased the risk for these outcomes in most of clinical and non-clinical settings. However, the risk for harm and benefit of the drug combination strongly correlates to its context and there are situations, such as in the hospice setting, where benefits may outweigh the risks.

Keywords: Opioids; benzodiazepines; mortality

Submitted Nov 29, 2019. Accepted for publication Dec 30, 2019.
doi: 10.21037/apm.2019.12.09
View this article at: http://dx.doi.org/10.21037/apm.2019.12.09

Introduction

Currently, the USA and many other western countries are experiencing not only increased use and abuse of opioids, but also of other drugs that affect central nervous system activity (1,2). Particularly the use of benzodiazepines, the most commonly prescribed sedative, has seen a sharp increase over the last decades (3), and it is estimated that 3% of the general population receives long-term prescriptions of these drugs (4). Benzodiazepines are approved for a variety of conditions, most notably anxiety and sleep disorders. In addition, they are generally considered to have a good overall safety profile. However, like opioids, benzodiazepines have a potential for dependence and intoxication during prolonged use and when used in high doses (5). Unbeknownst to many patients and prescribers, when benzodiazepines are prescribed in combination with opioids, there is a much greater danger of harm compared to either taken in isolation. Benzodiazepines and opioids both depress respiration, thereby increasing the risk for potentially lethal apnoea (6). Accumulating data indeed suggest that drugs like benzodiazepines, contribute significantly to opioid related fatalities (7). Having recognized this threat, a U.S. Centres for Disease Control and Prevention (CDC) 2016 guideline urged clinicians to avoid concurrent prescription of opioids and benzodiazepines whenever possible (8). In addition, the drug combination received a black box label by the U.S. Food and Drug Administration (FDA) highlighting the dangers of concomitant prescribing. Nevertheless, concurrent prescribing continues to be common practice among physicians (3). However, it is known that the risk for harm (or benefit) when using opioids or benzodiazepines is critically dependent on the context. For example, was the drug combination prescribed for treatment of anxiety and chronic pain or during palliative care, or was the harm from intentional or unintentional misuse or abuse? These differences affect the risk and incidence of severe adverse

events. This review summarizes currently available evidence on the concomitant use of opioids and benzodiazepines on serious patient harm and categorizes the results according to various clinical and ambulatory settings.

Methods

The goal of this review was to evaluate and summarize current clinical evidence of the combined use of opioids and benzodiazepines on mortality and adverse respiratory outcomes. Secondary aims were to evaluate whether outcomes of such practice would differ among various clinical and non-clinical settings. To this end, a search query was composed using the following Mesh terms: "Analgesics, Opioid", "Hypnotics and Sedatives", "Benzodiazepine", "Mortality", "Apnoea", "Respiratory insufficiency" and "Heart arrest". With this query, PubMed data base was searched on 11 October 2019 without date range limits.

Title and abstracts were screened for inclusion in the review. Only original research manuscripts written in English language that investigated the interaction between opioids and benzodiazepines on major adverse events including death and (cardio-)pulmonary arrest were eligible. We chose to focus on manuscripts that primarily reported on the opioid-benzodiazepine interaction, as this interaction is the most common and clinically relevant interaction. Interaction of opioids and other classes of sedatives were not specifically searched but results of manuscripts that reported on these interactions are displayed for included manuscripts. Abstracts were independently screened by MB, FJO and ED; inconsistencies were resolved by consensus. Full text of eligible articles was obtained and included manuscripts were sorted based on the clinical setting: "abuse and addiction"; "palliative healthcare"; "inpatient healthcare"; "ambulatory healthcare".

Pooled data analyses

To quantify the risk for mortality, we performed analyses of combined data when available and if appropriate. These analyses were conducted using statistical package R (version 3.5.0) with the metafor package (9,10). Data were analyzed using random effects models, assuming two sources of variance, within-study error and between-study error. Separate analyses were performed for hazard ratios and incidence risk ratios. Heterogeneity was assessed by measuring the degree of inconsistency in the studies' results (I^2).

Results

The flow chart of the PubMed search is shown in *Figure 1*. The search yielded 1,862 unique manuscripts. Five potentially eligible manuscripts were identified through reference searching (i.e., snowball method). After careful screening of 1,867 titles and abstracts, full text of 133 papers were assessed for eligibility. The majority of the manuscripts studied only the effect of opioids or benzodiazepines alone and did not specifically investigate the interaction. These manuscripts were excluded. Finally, 29 manuscripts met the inclusion criteria and were included in this review (see *Figure 1*). The characteristics and main findings of these studies are presented in *Tables 1-4*. Thirteen manuscripts were assigned to the "abuse and addiction" category, one to "palliative healthcare" category, three to the "inpatient healthcare" category and twelve to the "ambulatory healthcare" category. The majority of studies were retrospective cohort studies, followed by post-mortem studies and 2 prospective studies. Outcomes reporting varied accordingly: most studies reported incidences or incidence risk ratios or odds- or hazard ratios for mortality, post-mortem studies reported proportional mortality or death ratios. Data of 10 retrospective studies originating from the "abuse and addiction" or "ambulatory healthcare" subcategories were suitable for the pooled analyses of hazard ratios (HR) and/or incidence risk ratio (IRR). Both analyses indicate that the risk for mortality is increased when opioids are concomitantly used with benzodiazepines [pooled HR 1.72 (1.18–2.52); I^2=97% and pooled IRR 2.51 (1.44–4.36); I^2=95%; see *Figure 2*]. We will now discuss evidence for each category separately.

Abuse and addiction

In total, 13 manuscripts that reported on abuse or intentional misuse of opioids and sedatives, mostly benzodiazepines, were included in this review (see *Table 1*) (11-23). Besides the interaction between opioids and benzodiazepines, interactions between opioids and other centrally acting substances, such as cocaine, antidepressants and alcohol were also commonly reported (12,13,15-18,20,23). The data came from post-mortem analyses of deceased subjects (n=3) (14,17,21), retrospective cohort studies (n=9) (11-13,15,16,18-20,22), and one prospective study (23). All studied the risk of death or severe adverse events when using opioids, benzodiazepines or both. Post-mortem studies indicate that poly substance abuse

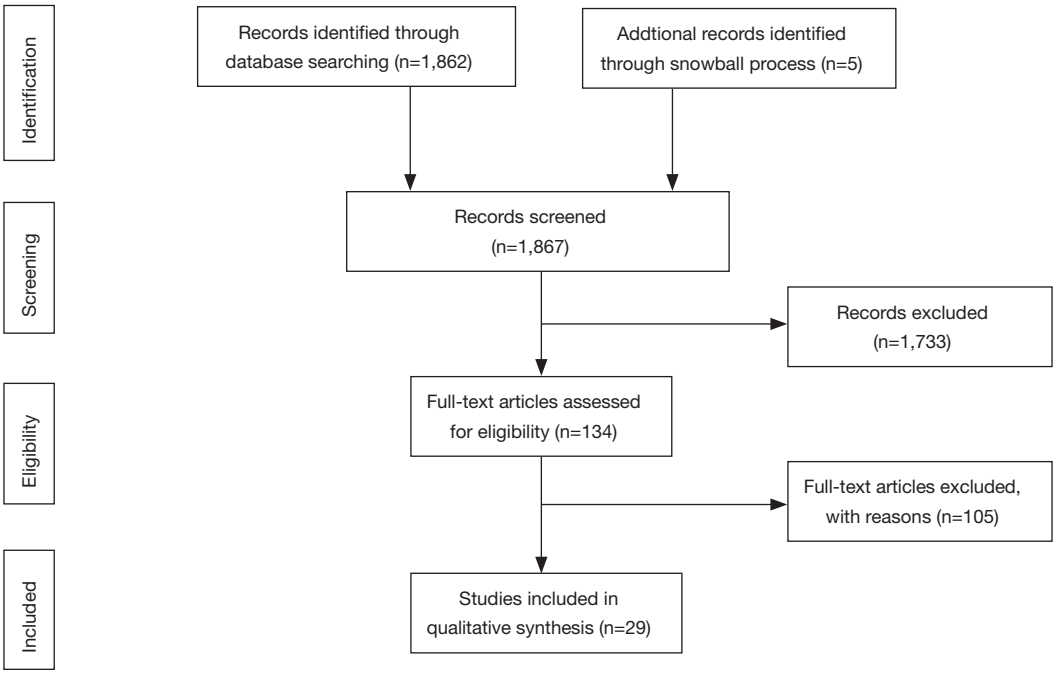

Figure 1 Consort flow-chart.

was common in deceased subjects, with incidences ranging from 20% to 80% (14,17,21). Overall, the majority of data show that the use of opioids with benzodiazepines or other centrally acting drugs has increased over the years, and that this drug combination increases the risk for mortality. Data of four studies were suitable for pooled analyses. These analyses also indicated a higher risk for mortality for combined use [pooled HR 1.36 (1.07–1.72), I^2=0%; pooled IRR 1.77 (0.32–9.75), I^2=0%; see part A in *Figure 3* and part A in *Figure 4*]. The results of two studies diverge from the trending findings. Abrahamsson *et al.* did find a positive correlation between concomitant use with non-overdose death, but not with overdose death and all-cause mortality (12). All-cause mortality however was significant in the unadjusted- and sensitivity analyses of this study. Second, Mirakbari *et al.* found no increased risk on adverse outcomes for intoxicated patients admitted to the emergency department (23). However, the methodology of this study was prone to inclusion and follow up bias In contrast, a study that reported on the treatment and outcomes after ICU admission for opioid intoxication found that patients who had also ingested benzodiazepines or amphetamines had a higher risk for mechanical ventilation and an increased length of stay (13).

A specific subgroup in this section consists of patients that are on opioid replacement therapy with buprenorphine or methadone (12,18,19,22). Data from these studies indicate that benzodiazepines are involved in a significant part of fatalities in this subgroup. Interestingly, patients on methadone replacement therapy may be at higher risk for mortality and severe adverse respiratory events when concomitantly using benzodiazepines, than patients on buprenorphine replacement therapy (12,19).

Finally, the manuscripts that reported on the effect of opioid combination with other CNS active substances, show an increased the risk for mortality, albeit the risks differed substantially between manuscripts and drug combination (12,13,15-18,20,23).

In conclusion, concomitant use of benzodiazepines or other CNS active drugs by active opioid abusers and those on opioid replacement therapy substantially increases the risk for mortality.

Palliative healthcare

One manuscript was identified that reported on the use of opioids combined with benzodiazepines or antipsychotics such as haloperidol in terminally ill patients admitted to a hospice service (24). This study found that survival in terminally ill patients was not reduced by concomitant use

Table 1 Manuscripts appointed to "misuse and addiction" category

Author	Year	Type	Interaction	Population	Outcome	Result	Comment
Calcaterra[†] (11)	2018	Retrospective cohort study	Opioid – BDZ	Cases of intentional misuse or abuse registered in national poison database system (USA) 2001–2014	Mortality	Adjusted OR for mortality was 1.55 for concomitant abuse or misuse compared to single use (adjusted for age and gender)	Concomitant abuse or misuse of both drugs increased by 2.90 to 3.11-fold in study period
Abrahamsson[†] (12)	2017	Retrospective cohort study	Opioid – BDZ, pregabalin and Z-drug	Swedish adults on opioid replacement therapy for opioid dependence 2005–2012	Opioid- and all cause mortality	Concomitant opioid - BDZ use increased the risk for non-overdose death (AHR 1.74) and concomitant use of opioid with Z-drug (HR 1.60) and pregabalin (HR2.82) also increased risk for mortality	There was no statistically significant correlation between concomitant use to overdose death (HR 1.05, NS) or all-cause mortality (AHR 1.44, NS)
Pfister (13)	2016	Retrospective cohort	Opioid – BDZ, amphetamines and other CNS agents	Adult patients admitted to ICU for opioid overdosis treatment	Admission characteristics and outcomes	Co-intoxication was most prevalent with BDZ (39.3%) followed by amphetamines (13.5%); co-intoxication increased the risk for mechanical ventilation (91% *vs.* 77%) and had longer length of stay (median 3 *vs.* 2 days)	Oxycodone was the most abused opioid (31%)
Petrushevska (14)	2015	Proportional mortality study	Opioid - BDZ	Postmortem toxicologic data from deceased subjects in Macedonia	Proportion of mortality attributable to opioids and co-intoxicating substances	Mortality was primarily caused by heroin overdose (51.2%) or the combination of methadone with BDZ (11.7%). 30.3% of cases were related to polydrug use	
Visconti (15)	2015	Proportional mortality study	Opioids – BDZ, alcohol, cocaine, antidepressants	Database on opioid overdose decedents from 2010–2012 in SF	Proportion of mortality attributable to opioids and co-intoxicating substances	93.7% of deaths involved prescribed opioids *vs.* 9.4% involved heroin; other involved substances (% of cases) were: none: 25.1%; alcohol: 19.6%; BDZ: 27.5%; cocaine: 25.3%; antidepressants: 22.7%	
Pavarin (16)	2015	Retrospective cohort	Heroin – BDZ, cocaine, alcohol	Subjects involved in healthcare due to heroin abuse in Bologna between 2004-2009	Mortality	Mortality in the cohort was determined by opioid overdose for 17% of deceased; IRR for mortality for concomitant use of opioids with: alcohol: 1.48; BDZ: 2.78; cocaine: 3.16	
Nielsen (17)	2015	Proportional mortality study	Methadone – BDZ, alcohol, illicit opioids, antidepressants	Postmortem methadone related fatalities registered between 2008-2011 in Denmark	Proportion of mortality attributable to co-intoxicating substances with methadone	97% of deceased had concomitantly used an active substance: 40% had co-ingested (multiple) BDZ; 23% alcohol	

Table 1 (*continued*)

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Author	Year	Type	Interaction	Population	Outcome	Result	Comment
Leece† (18)	2015	Retrospective case control	Methadone – BDZ, antidepressants, antipsychotics and alcohol	Opioid prescription registered Ontario Drug Benefit database	Mortality	AOR for mortality of methadone with BDZ: 1.6; antipsychotics: 2.3; alcohol: 1.9	
Lee (19)	2014	Retrospective cohort	Methadone – BDZ and buprenorphine – BDZ	Overdoses registered at national poison data system between 2002 and 2010	Mortality and severe respiratory adverse events	Incidence of mortality was higher in patients in that concomitantly used methadone with BDZ group (2.3%) compared to BUP – BDZ users (0%); methadone – BDZ users were also more likely to experience severe respiratory depression compared to BUP-BDZ users	
Calcaterra (20)	2013	Proportional mortality study	Opioid – BDZ, cocaine, alcohol and anti-depressants	Deaths between 1999 and 2009 due to overdose or poisoning related to pharmaceutical drugs	Death ratio for opioids and co-intoxicating substances	From 2005–2009 opioids alone had the highest ADR (5.47), followed by opioid- BDZ co use (ADR 1.27) and opioid-cocaine (ADR 0.74), alcohol (ADR 0.63) and antidepressants (ADR 0.61)	ADR for opioid sedative co-intoxication excluding BDZ had the lowest ADR (0.12)
Häkkinen (21)	2012	Proportional mortality study	Buprenorphine – BDZ	Opioid related fatalities registered at Finnish postmortem toxicology database between 2000-8	Proportion of mortality attributable to buprenorphine and co-intoxicating substances	BUP was found in 29% of case fatalities; co-use of BDZs or alcohol was found in 82% and 58% of these cases	
Cousins† (22)	2011	Retrospective cohort	Methadone – BDZ	Subjects on methadone replacement therapy between 1993 - 2004	Drug related mortality when off-treatment	Number of co-prescriptions of BDZ in this population was positively related to increased risk for mortality (AHR 1.39)	Risk of death was greatest in first week off-treatment; co-prescription of methadone with BDZ occurred in 64.3% of all subjects
Mirakbari (23)	2003	Prospective cohort	Opioid – alcohol, cocaine and other CNS depressants	Patients admitted at ED post overdose resuscitation	Major AE, including death	Concomitant use was common (80% of cases); concomitant use did not increase adverse event rate in the first 24 h	Inclusion bias: fatalities before ED arrival were not included; telephone follow up may have been incomplete

†, study included in pooled analysis. BDZ, benzodiazepine; BUP: buprenorphine; CNS, central nervous system; AE, adverse event; ED, emergency department; (A)OR, (adjusted) odds-ratio; (A)HR, (adjusted) hazard-ratio; ADR, adjusted death-ratio (per 100,000 person-years); IRR, incidence risk-ratio; NS, not statistically significant.

Table 2 Manuscript appointed to "palliative healthcare" category

Author	Year	Type	Interaction	Population/setting	Outcome	Result	Comment
Golčić (24)	2018	Retrospective cohort	Opioids – BDZ, antipsychotics	Patients admitted to Hospice between 2013 and 2014	Survival and nighttime death percentage	The combination of opioids with BDZ did not shorten survival (HR 0.85, NS) and did not increase incidence of nighttime death; the combined use of an opioid, BDZ and antipsychotic was associated with longer survival (HR 0.61)	Single center, Hospice; higher opioid doses (>300 OME) were associated with longer survival (HR 0.61)

BDZ, benzodiazepine; HR, hazard-ratio; OME, oral morphine equivalents; NS, not statistically significant.

Table 3 Manuscripts appointed to "inpatient healthcare" category

Author	Year	Type	Interaction	Population	Outcome	Result	Comment
Sigurdsson (25)	2019	Retrospective, cohort study; propensity matched	Opioid – BDZ	>18 years, non-cardiac surgery, Iceland	Mortality; persistent postoperative opioid use	30D mortality for combined use vs single use: 3.2% *vs.* 1.8%; long-term mortality for concomitant users was HR 1.41 compared to controls; preoperative single and concurrent users persisted more frequently in opioid use	Preoperative single users did not have a higher mortality risk compared to controls; concomitant users had higher co morbidity index
Izrailtyan (26)	2018	Retrospective cohort study	Opioid – sedative	>18 years; in hospital CPRA, RA or CPR in surgical and non-surgical patients	Risk for CPRA	Opioids and sedatives independently and additively increased risk for CPRA; AOR for opioid BDZ in medical patients 3.83 and 2.34 in surgical patients	Hispanic origin, surgery for malignancy, liver disease, obesity and COPD further increased the risk for CPRA
Overdyk (27)	2016	Retrospective cohort study	Opioid – sedative	Adult inpatient discharges reported in premier database	Risk and outcome of in hospital CPRA	Opioids and sedatives independently (AOR 1.81) and additively (AOR 3.47) increase the risk for in hospital CPRA	

BDZ, benzodiazepine; CPRA, cardiopulmonary and respiratory arrest; (A)OR, (adjusted) odds-ratio; (A)HR, (adjusted) hazard-ratio; ADR, adjusted death-ratio (per 100,000 person-years); IRR, incidence risk-ratio; NS, not statistically significant.

of an opioid with a benzodiazepine or antipsychotic. In fact, the chance of surviving longer in this setting was higher for patients that used all three classes of medication. In addition, night-time death percentage was not increased in patients taking a drug combination. Finally, it was found that patients receiving opioid doses of more than 300 mg oral morphine equivalents survived longer compared to patients on receiving lower doses. In conclusion, data from one study suggests that concomitant use of opioids with benzodiazepines or antipsychotics in the hospice setting may be safe. Additional research is needed to corroborate these results.

Inpatient healthcare

The search yielded three manuscripts that reported on the effect of opioid and sedative use in hospitalized patients (25-27). The studies by Overdyk *et al.* and Izrailtyan *et al.*

Table 4 Manuscripts appointed to "ambulatory healthcare" category

Author	Year	Type	Interaction	Population	Outcome	Result	Comment
Hawkins† (28)	2019	Retrospective cohort study, propensity matched	Opioid – BDZ	Posttraumatic disorder; within Veterans affairs healthcare; patients with cancer diagnosis were excluded	1-yr mortality	All-cause mortality (AHR 1.52), lethal overdose (AHR 2.59) or circulatory related mortality (AHR 1.81) was higher for concomitant users *vs.* single or non-users	
Hernandez† (29)	2018	Retrospective cohort study	Opioid – BDZ	Adult patients without cancer diagnosis with prescribed opioids; registered at Medicare part D claims database	Risk for fatal and non-fatal opioid overdose	Within first 90 and 180 days, concomitant opioid-BDZ use is associated an increased risk of opioid overdose (HR 5.01 and 1.87 for 90- and 180-day period respectively)	
Gressler (30)	2018	Retrospective database, propensity matched	Opioid – BDZ	Subjects without cancer diagnosis on opioids and or BDZs registered at Veterans Health administration datasets from 2008 to 2012	All-cause mortality and opioid related adverse outcomes (e.g., accidents injuries and overdoses)	Risk for mortality (OR 1.34) or any adverse outcome (OR 1.36) was increased for concomitant opioid-BDZ use	
Sun (31)	2017	Retrospective cohort study	Opioid – BDZ	Privately insured patients in USA on opioids without a diagnosis of cancer between 2001 and 2013	ED visit or hospital admission related to opioid overdose	Risk for ED visit or overdose related admission was highest for concomitant users (OR 2.14) compared to intermitted and chronic single opioid users (OR 1.4 and 1.8 respectively)	Proportion of patients on opioid – BDZ treatment had risen from 9% in 2001 to 17% in 2013; co-intoxication accounted for 15% of ED visits and hospital admissions related to opioid overdose
Gomes (32)	2017	Retrospective case control	Opioid – gabapentin	Patients without a diagnosis of cancer that received opioids under Ontario public drug programme Ontario Canada	Opioid related mortality	Concomitant users had a (gabapentin) dose depended higher OR (overall OR 1.99) for mortality compared to opioid use alone	
Garg† (33)	2017	Retrospective cohort	Opioid – BDZ and muscle relaxant	Medicaid patients with noncancer pain on opioids	Opioid related mortality	Risk for opioid related mortality was elevated for concomitant use of opioids with BDZ (AHR 6.4) and muscle relaxants (AHR 12.6), even at low daily opioid dose	

Table 4 (*continued*)

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Author	Year	Type	Interaction	Population	Outcome	Result	Comment
Gaither† (34)	2016	Retrospective cohort	Opioid BDZ and psychotherapeutic cointerventions	Patients with substance disorder (i.e., alcohol or drug use) on long-term opioid treatment for chronic pain enrolled in Veterans aging cohort study	All-cause mortality	Opioid-BDZ co-prescription was associated with higher mortality (AHR 1.41); psychotherapeutic cointerventions appeared protective (AHR 0.43), especially in subgroup of patients with substance use disorder	Psychotherapeutic cointerventions and substance disorder treatment appeared protective in general but did not modify AHR for co-prescription
Dasgupta (35)	2016	Prospective cohort study	Opioid – BDZ, alcohol, cocaine and heroin	Subjects on prescribed opioids registered in North Carolina controlled substances reporting system in 2010	Proportion of mortality attributable to opioids and co-intoxicating substances	80% of opioid recipients were also prescribed a BDZ; BDZ were involved in 61.4% of lethal opioid overdoses	22.8% of residents received at least one opioid prescription; 1 year follow up
Weisberg† (36)	2015	Retrospective cohort Propensity matched	Opioid – BDZ	Subjects with HIV infection on long-term opioid therapy enrolled in Veterans aging cohort study	Opioid related Mortality	Concomitant use increased the risk for mortality (HR 1.56); long-term opioid and BDZ receipt alone were associated with increased risk for mortality (HR 1.4 and 1.26 respectively)	There was a significant interaction between long term opioid receipt and HIV status with mortality
Park† (37)	2015	Retrospective case cohort study	Opioid – BDZ	Subjects with acute, chronic and non- cancer pain on opioids or died while receiving opioids between 2004 and 2009 registered in Veterans healthcare system	All-cause mortality	Nearly 50% of lethal drug overdoses were attributable to co-intoxication; mortality risk was increased in subjects with history of BDZ prescription (HR 2.33) or with current prescription (HR 3.86), dose dependently	Co-prescription was common: 27%
Chang (38)	2015	Retrospective cohort	Opioid sedative	Patients treated for cancer; national health insurance research database Taiwan	Survival	Odds for survival were lowest for concomitant users (OR 0.06), followed by opioid use alone (OR 0.08) and sleeping medication (OR 0.87, NS)	
Ekström† (39)	2014	Retrospective cohort	Opioid – BDZ	Patients with advanced COPD on oxygen therapy registered in national Swedish Swedevox registry between 2005 and 2009	All-cause mortality	Concurrent use of opioids with benzodiazepines did not increase mortality (HR 1.25, NS)	Benzodiazepines and opioids alone were dose dependently associated with increased mortality, however, opioid dosed <30 mg OME/day did not increase mortality (HR 1.03, NS)

†, study included in pooled analysis. BDZ, benzodiazepine; ED, emergency department; OR, odds-ratio; (A)HR, (adjusted) hazard-ratio; NS, not statistically significant.

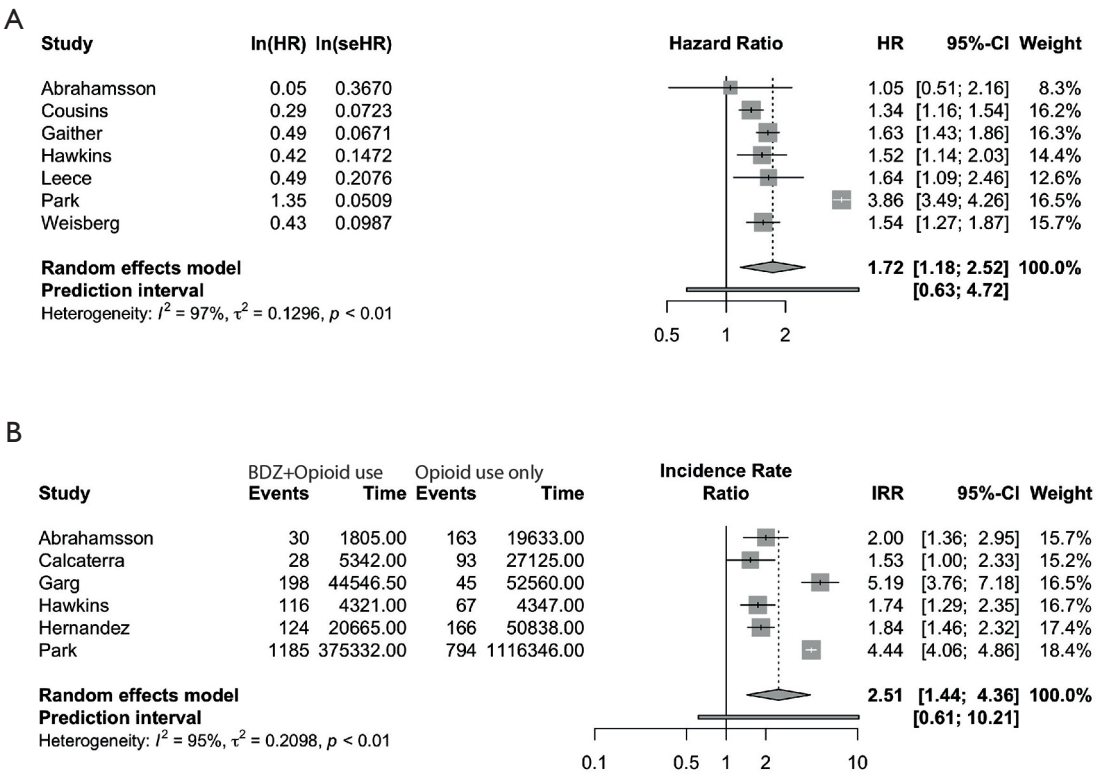

Figure 2 Forrest plots displaying (A) hazard ratio and (B) incidence risk ratio for all available data.

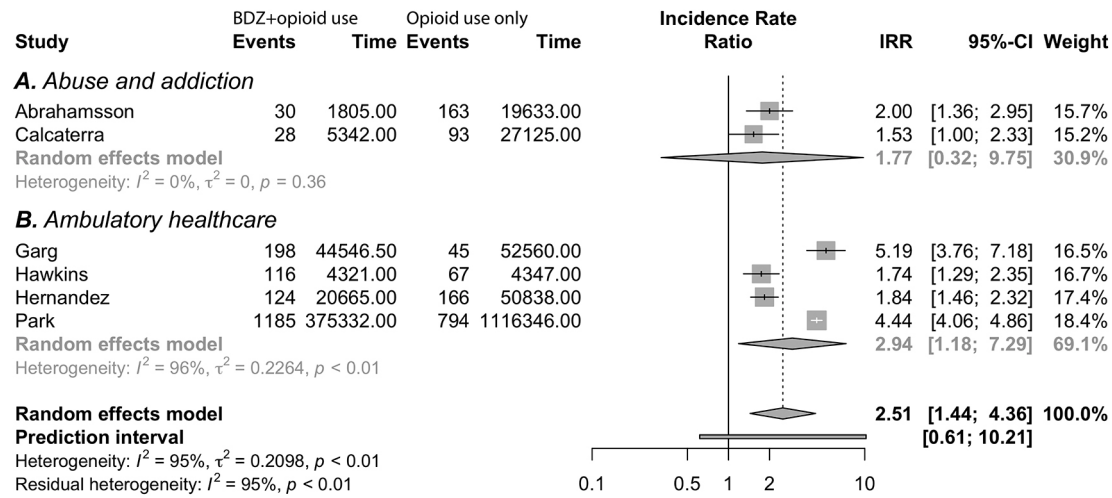

Figure 3 Forrest plot displaying incidence risk ratio for data from (A) abuse and addiction category and (B) ambulatory healthcare.

retrospectively investigated in-hospital cardiopulmonary or respiratory arrest (CPRA) on surgical and medical wards by analysing more than 21 million inpatient discharge records available from Premier database between 2008 and 2013. They found that opioids and sedatives independently and additively increased the risk for CPRA (26,27). Sigurdsson

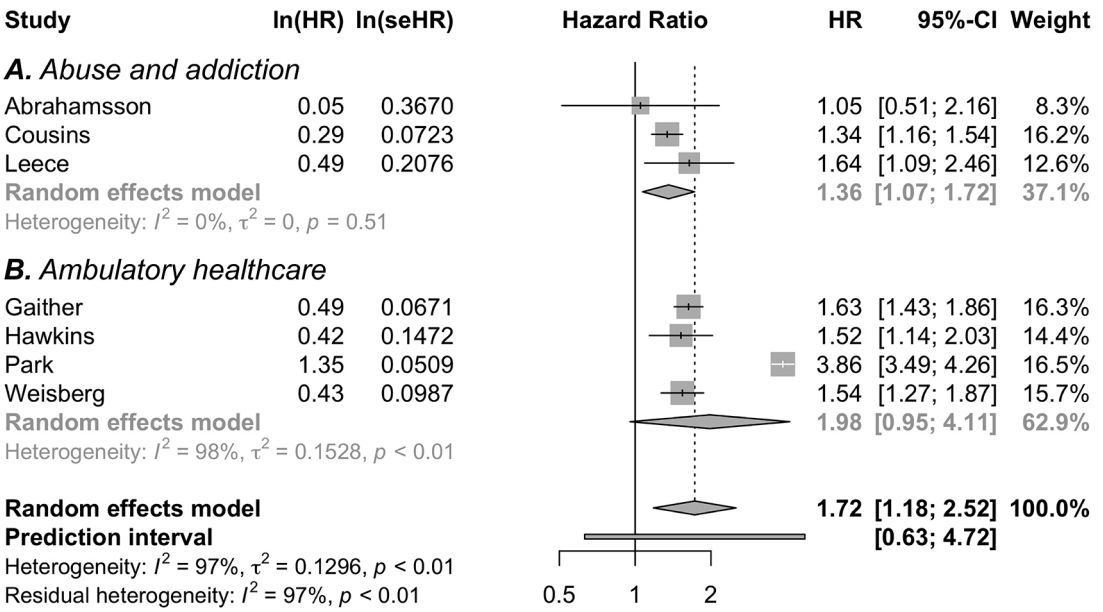

Figure 4 Forrest plot displaying hazard ratio for data from (A) abuse and addiction category and (B) ambulatory healthcare.

et al. investigated the effect of preoperative opioid and/or benzodiazepine use on postoperative mortality and persistent opioid use after surgery. This study found that single prescriptions for opioids or benzodiazepines filed within 6 months before surgery did not increase the risk for mortality, whereas combined prescription was associated with increased risk for both short-term (<30 days) and long-term mortality (25). An additional finding of this study was that both single and combined preoperative use of opioids and benzodiazepines increased the risk for persistent postoperative opioid use. Unfortunately, the data from the studies in this category were not suitable for pooled analysis.

In conclusion, combined use of opioids and sedatives are likely to increase the risk for in hospital cardiopulmonary and respiratory adverse events and postoperative mortality.

Ambulatory healthcare

Twelve studies described various populations on chronic opioid therapy from large US healthcare or insurance databases (28-39). Manuscripts in this section entailed a wide range of subpopulations including patients receiving opioids and benzodiazepines for chronic non cancer pain (n=7) (29-33,35,37), cancer pain (n=1) (38), psychiatric disorders (n=2) (28,34), HIV positive patients (n=1) (36) and patients with end stage chronic obstructive pulmonary disease (n=1) (39). Most manuscripts reported about the interaction of opioids with benzodiazepines, but interactions between opioids and gabapentin, alcohol, cocaine and muscle relaxants were also reported. Pooled analyses were performed on suitable data from four studies in this category (28,29,33,34,36,37,39). This showed that the risk for death was higher for combined use of opioids with benzodiazepines [pooled HR 1.98 (0.95–4.11); I^2=98%; pooled IRR 2.94 (1.18–7.29); I^2=94%; see part B in *Figure 3* and part B in *Figure 4*]. These results are in line with the overall picture of the data; however, heterogeneity was large and the pooled hazard ratio did not reach statistical significance. In addition, the risk for other serious adverse outcomes was also increased in patients receiving opioids and benzodiazepines.

One study reported on the use of long-term opioid therapy for chronic pain enrolled in the veterans aging cohort study (34). This study found an elevated risk for mortality for co-users, but a protective effect when used in psychotherapeutic interventions. In US veterans with post-traumatic stress disorder, opioids and benzodiazepines elevated the risk of death when compared to single drug and non-users (28). Finally, one manuscript evaluated the use of opioids and benzodiazepines in patients having end stage obstructive lung disease on oxygen therapy (39). Both opioids and benzodiazepines dose dependently increased

the risk for mortality when used alone or in combination. However, low doses of either agent alone or combined to alleviate dyspnoea appeared safe.

In conclusion, the data in this category suggest that the combined use of opioids and benzodiazepines increases the risk for mortality among a variety of subpopulations.

Discussion

This manuscript reviewed the effects of concomitant use of opioids and benzodiazepines and found that in most situations this combination results in an elevated risk of death or serious harm. Most manuscripts reported on the drug interaction in patients of the abuse and addiction and the ambulatory healthcare settings. For these settings, we were able to conduct pooled analyses of suitable data from 10 studies to provide a quantification of the increased risk for mortality (11,12,18,22,28,29,33,34,36,37). These analyses indicated a significant effect of combined opioid benzodiazepine use on mortality. However, in terminal patients no negative effects of the combination were found (24). Before we separately discuss each category, we will first discuss the main actions of opioids and benzodiazepines on the central nervous system.

Opioids are derivatives of the naturally occurring opium peptide morphine that act on opioid receptors at cellular level. The most prominent of these receptors, the μ-opioid receptor, is associated with the analgesic, respiratory depressant and rewarding effects of opioids. Benzodiazepines entail a class of sedative drugs that share the same core chemical structure of a fused benzene and diazepine ring. Benzodiazepines are allosteric agonists of the GABAa receptor and predominantly bind the a1 and a2 subunits of this receptor, inhibiting neuronal signal transmission. The affinity of the various types of benzodiazepines to the alpha units on the GABAa receptor determines their predominant clinical effect (i.e., sedation or anxiolysis). Apart from their beneficial effects, both opioids and benzodiazepines negatively interfere with respiratory control. The drive to breathe is controlled by neurons of the respiratory centres in the brainstem. Since both opioid and GABAa receptors are expressed on respiratory neurons, opioids and benzodiazepines profoundly disrupt physiologic control of breathing. Opioids' main effect is a reduction in respiratory rate which is caused by its direct inhibitory effects on mu receptors in the brainstem (40). In contrast, benzodiazepine respiratory depression is primarily characterized by a reduction in tidal volume. This is demonstrated by a decreased slope of the ventilatory response curve to carbon dioxide rather than the rightward shift of the curve that is seen with opioids (41,42). In addition to these effects on respiratory drive, both benzodiazepines and opioids reduce upper airway patency and cause obstructive apneas and hypopneas (43). A pharmacokinetic interaction between these agents may also play a role in their effect on respiration. For instance, some opioids are metabolized via CYP3A4, an enzyme that is inhibited by alprazolam. Combined use of these agents would result in elevated opioid serum concentrations causing a prolonged effect.

Thus, it is clear that opioids and benzodiazepines both negatively interfere with respiration. Indeed, both animal and human studies have shown that the combination of opioids with benzodiazepines lead to more hypoxia and hypercapnia when compared with single use of these agents (44-47). Since we anticipated that risk and benefits of combined opioid-sedative use would be dependent on the clinical use case, eligible manuscripts were categorized as follows: abuse and addition, palliative care, inpatient and outpatient settings.

Abuse and addition

The literature suggests that polypharmacy with benzodiazepines, cocaine, antidepressants, pregabalin and alcohol is commonly encountered when analyzing lethal overdoses by patients abusing opioids or on opioid replacement therapy. The data unequivocally suggests combining these drugs with opioids increases the risk for fatal overdose. There may be various reasons why drug abusers use a combination of drugs. Many drug abusers suffer from concomitant psychiatric disorders, rendering them at risk for (poly-)drug abuse in the first place. Second, benzodiazepines amplify the pleasurable effects of opioids (48). For instance, heroin users report a more intense and prolonged effect when concomitantly using a benzodiazepine. These effects are known to heroin users, but also noted by subjects on methadone or buprenorphine replacement therapy, who report a "heroin-like" profound drug effect when these agents are concomitantly used with a benzodiazepine (49,50). Nevertheless, subjects on opioid replacement therapy are often co-prescribed benzodiazepines to treat underlying psychiatric disorders and to facilitate treatment compliance. Part of the hazard of combined use is that the tolerance to respiratory depression by chronic opioid users does not imply tolerance

to respiratory depression for benzodiazepines. This causes a high risk of overdose even among experienced opioid abusers (6). In addition, clinicians may erroneously expect their patients on opioid replacement therapy to require larger doses of sedatives to obtain an adequate treatment effect.

The combination of benzodiazepines with buprenorphine or methadone deserves special attention. Although buprenorphine is known for its ceiling effect on respiratory depression, this effect is only observed without the concurrent use of other central nervous system depressing agents (51). Indeed, post-mortem data from Hakkinen *et al.* show that benzodiazepines and alcohol were found in 82 and 58% of deceased subjects using buprenorphine (21). Nevertheless, there are indications that the risk for lethal adverse events caused by concomitant (mis-)use is lower with buprenorphine compared to methadone (12,19). This observation warrants further research as the choice between buprenorphine and methadone may have significant consequences for the risk of adverse events.

Palliative healthcare

One manuscript reported on the effect of the combined use of opioids, benzodiazepines and antipsychotics in the hospice setting (24). In this study, the combined use of opioids with benzodiazepines and antipsychotics, appeared not to negatively affect survival time or increase the risk of night-time death. It is known that opioids and benzodiazepines alone do not significantly compromise respiratory function or affect survival time in terminally ill patients (52-54). This is consistent with Clemens *et al.*, who showed that in terminally ill patients suffering from anxiety and dyspnoea the combination of lorazepam and morphine was both effective and safe. Mean oxygen saturation did not change significantly after initiation of therapy, whereas dyspnoea and respiratory rate diminished notably (55). Although these investigators did not study survival length, data from our review support these findings and indicate that the combined use of these agents may be safe in this population.

Counterintuitively, the data from Golčić *et al.* also show that patients on high dose opioid therapy survived longer compared to patients receiving lower doses (24). A caveat here is that patients receiving more than 300 oral morphine equivalents (OME) per day were on average younger. Nevertheless, the trend points in the same direction when looking at all dose ranges; even in the lower dose ranges, in which age did not differ so much, a dose dependent decrease in the hazard ratio was observed, albeit not statistically significant. We speculate that high pain levels that are often encountered in terminally ill patients warrant higher opioid doses to achieve optimal nociception-anti nociception (i.e., pain – analgesic) balance.

Inpatient healthcare

The data from our review show that concomitant opioid benzodiazepine use in hospitalized patients increase the risk for adverse events on both surgical and medical wards (25-27). These results add to the results of a recent meta-analysis that investigated risk factors associated with opioid induced respiratory depression (OIRD) after surgery (56). It was found that concurrent prescription of sedatives was present in 56% of patients with OIRD. In addition, it appeared that OIRD occurred most frequently in the first 24 hours after surgery and that patients with coexisting cardiac disease, pulmonary disease and sleep disordered breathing were at highest risk (56). These findings largely correspond with the data from this review. Evidently, recognition of patients who are at risk for respiratory complications is essential to optimize postoperative care in order to minimize adverse events. The results of this review and the meta-analysis suggest that opioids and sedatives should be avoided in high risk patients whenever possible. If not possible to avoid, these patients should have their respiration monitored electronically and continuously for early detection of OIRD.

Ambulatory healthcare settings

The data from this group entailed the biggest proportion of studies included in this review. On average, these were large database studies conducted in various subpopulations, which shared the setting of representing out-of-hospital or ambulatory healthcare (28-39). The data uniformly indicated that combined use of opioids and sedatives (mostly benzodiazepines, but also gabapentin, alcohol, muscle relaxants, cocaine, etc.) increased the risk for mortality among all subpopulations. Exposure-response evaluations showed that the risk for mortality was highest in patients that had recently commenced treatment (29) or had a history of benzodiazepine use (37). These risk factors add to other known risk factors for adverse outcomes such as older age, high opioid daily dose, and long duration of opioid use (57). In addition, two manuscripts in this review evaluated

the effect of co-prescription of opioids and benzodiazepines to patients with post-traumatic stress disorder or substance abuse disorders (28,34). Concurrent use of opioids with benzodiazepines was associated with increased risk for mortality, whereas psychological interventions aimed to treat underlying psychiatric illness appeared to be protective. Minimizing concurrency and close follow up with psychological interventions should therefore be considered in these patients. Finally, Ekström *et al.* evaluated concurrent use of opioids and benzodiazepines in patients with severe obstructive lung disease (39). They found that benzodiazepines and opioids dose dependently increased mortality, although low doses appeared to be safe and did not increase the risk for mortality during hospital admission. These results are in line with previous data showing that low dose opioids or benzodiazepines do not increase the risk for severe adverse events or significantly alter blood gas results in these patients (58-60).

Our review has several limitations. First, although we identified a considerable number of manuscripts, we only searched the PubMed database for manuscripts written in English language and, as such, we may have missed valuable manuscripts. Most data came from retrospective and post-mortem studies whose results may be confounded by unknown variables. We performed analyses of pooled data when available and separately for hazard ratios and incidence risk ratios. Since only ten studies could be included in these analyses and because of the high degree of heterogeneity, the results should be regarded as indicative rather than absolute measures of the risk for mortality.

We focused on interactions between opioids and benzodiazepines and did not give extensive attention to other CNS active agents, such as alcohol and antidepressants. Thus, our conclusions for interactions between opioids and sedatives other than benzodiazepines are exploratory.

Lastly, this review focused on the impact of opioids and benzodiazepines on patient harm (i.e., mortality and severe respiratory adverse events) and we did not specifically review the benefits of the drug combination. This is important, as the chance of benefit versus the chance of harm [i.e., risk/benefit ratio or the utility, see review of Van Dam *et al.* (61)] is always a consideration when prescribing a drug or drug combination for a patient. Our conclusion is that the utility of the opioid-benzodiazepine combination is negative (i.e., the chance of harm is greater than the chance of benefit) for the majority of clinical uses. However, utility critically depends on the clinical context and the dose and type of opioid and sedative and we identified a possible positive utility in patients suffering from terminal illness.

In conclusion, this review indicates that the combined use of opioids with benzodiazepines increases the risk for severe adverse respiratory events and the risk for mortality over a broad line of clinical and non-clinical settings. However, there are situations, such as in the hospice setting, where benefits may outweigh the risks.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Mellar P. Davis) for the series "Opioid Utility the Other Half of Equianalgesia" published in *Annals of Palliative Medicine*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

Conflicts of Interest: The series "Opioid Utility the Other Half of Equianalgesia" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Boon M, van Dorp E, Broens S, Overdyk F. Combining opioids and benzodiazepines: effects on mortality and severe adverse respiratory events. Ann Palliat Med 2020;9(2):542-557. doi: 10.21037/apm.2019.12.09

