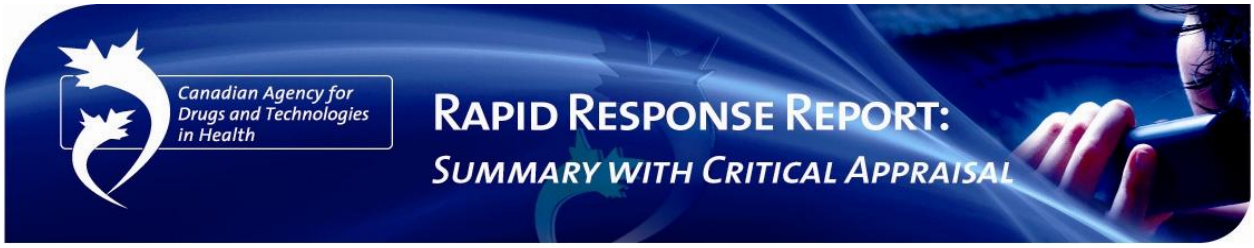

TITLE: Combination Benzodiazepine-Opioid Use: A Review of the Evidence on Safety

DATE: 16 September 2011

CONTEXT AND POLICY ISSUES:

Benzodiazepines are most commonly prescribed for the management of anxiety and insomnia.[1] They can also be used for sedation or amnesia before medical or surgical procedures, treatment of seizure, treatment of alcohol or sedative withdrawal, or acute agitation.[1] They are known to have dose-dependent adverse central nervous system effects, including drowsiness, ataxia, fatigue, and somnolence.[2] Additive effects may occur when benzodiazepines are administered concomitantly with other central nervous system (CNS) depressants.[2] Benzodiazepines are linked to causing respiratory insufficiency, characterized by snoring with flow limitation and obstructive apnea, and increase in upper airway resistance and work of breathing.[3] Another adverse effect not directly related to CNS depression includes dependence.[1]

Opioids are used most commonly for treatment of pain. Like benzodiazepines, they also have the potential to cause CNS depression, resulting in sedation and decreased mental alertness.[4] The use of opioids can result in respiratory depression and side effects include well known disturbances in ventilator pattern.[3]

The 2010 Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain recommends that for patients taking benzodiazepines, tapering should be considered prior to opioid initiation.[5] If tapering is not indicated or is unsuccessful, it is recommended that opioids be titrated more slowly and at lower doses. The rationale the guideline provides for this recommendation is that the combination increases the risk of sedation, overdose, and diminished function. The evidence referenced found serum concentration of opioids is lower in mixed overdoses than in pure overdoses, suggesting that other drugs significantly lower the lethal opioid dose.[5] The National Institute for Health and Clinical Excellence clinical guideline on methadone and buprenorphine for the management of opioid dependence outlines that the initiation of treatment with methadone presents a potential risk of respiratory depression, and that interactions with benzodiazepines may also increase this risk.[6]

The interaction between benzodiazepines and opioids including buprenorphine and methadone has resulted in respiratory depression in both animal models and humans.[3] Opioids and benzodiazepines act in combination with different classes of the opioid and gamma-aminobutyric acid (GABA) receptors.[3] Both GABA and opioid systems play an important role in the activity of the neurons that control ventilation. Regarding opioid receptors, however, only limited interactions of benzodiazepines have been reported, especially at very high concentrations such as those observed after intrathecal administration.[3]

Unlike methadone and other commonly prescribed opioids, buprenorphine is a partial opioid agonist. Even higher than normal therapeutic doses rarely result in clinically significant respiratory depression.[6] Buprenorphine replacement therapy for heroin addiction has been used in France since 1996.[7] A review of its use indicated that deaths among addicts who had taken buprenorphine often involved concurrent benzodiazepine use.[7] It should be noted that the review also outlined high rates of injection of tablets during the first few months of treatment. The mechanism of buprenorphine/benzodiazepine interaction, either pharmacokinetic or pharmacodynamic, remains to be clarified.[3] The main hypothesis is derived from the majority of studies analyzing opioid benzodiazepine interactions which reported synergistic, or at least additive hypnotic, analgesic, and ventilator depressant effects based on pharmacodynamic interactions.[3] Regarding the respiratory effects of the buprenorphine/benzodiazepine combination, a potential pharmacokinetic mechanism cannot be excluded, though in vitro studies have failed to demonstrated any significant P450 cytochrome-mediated metabolic interactions.[3]

The purpose of this report is to review the evidence on the risk of serious adverse events related to combination benzodiazepine-opioid use.

RESEARCH QUESTION:

1. What is the clinical evidence on the risk of serious adverse events associated with combination benzodiazepine-opioid use?

KEY MESSAGE:

Limited evidence from non-randomized studies suggested a positive association with the use of benzodiazepines in combination with methadone and mortality risk. There is less evidence on the risk of adverse events associated with the combination of buprenorphine and benzodiazepines.

METHODS:

Literature search strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and August 17, 2011.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. The selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Adults using benzodiazepines and opioids (including methadone and suboxone) concurrently
Intervention	Benzodiazepines and opioids [including methadone and buprenorphine/ naloxone (Suboxone)] in combination
Comparator	Any
Outcomes	Death, respiratory depression, other adverse events
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies (safety only)

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1, were published prior to 2006, did not include safety outcomes, the population studied was treated with the interventions of interest as inpatients, or the interventions of interested were considered part of the procedural sedation.

Critical Appraisal of Individual Studies

The quality of randomized controlled trials (RCTs) and non-randomized studies were evaluated using the Downs and Black instrument.[8] A quality score for each study was not calculated, instead, strengths and limitations were highlighted according to criteria from the instrument. A formal quality assessment of non-comparative studies or case reports was not conducted since they provide limited information.

SUMMARY OF EVIDENCE:

Quantity of Research Available

The literature search yielded 436 relevant citations. Upon screening titles and abstracts, 403 citations were excluded and 33 potentially relevant articles were retrieved for full-text review. An additional four potentially relevant reports were identified through grey literature searching. Of the 37 potentially relevant reports, 24 did not meet the inclusion criteria. A total of 13 publications were included in the review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). A total of two randomized controlled trials and 11 non-randomized studies were identified. No relevant health technology assessments, meta-analysis, or systematic reviews were identified.

The details on the study characteristics, critical appraisal and findings can be found in Appendices 2, 3, and 4, respectively.

Summary of Study Characteristics

Country of Origin

Both RCTs were performed in the UK.[9,10] The non-randomized studies were primarily from the US (six studies),[11,12,12-15] with one from the UK,[16] and one each from Finland,[17] Australia,[18] Israel,[19] and Singapore.[20]

Year of Publication

One non-randomized study was published most recently in 2011,[11] two were published in 2010,[18,19] two in 2009,[12,17] two in 2008,[12,15] two in 2007,[13,16] and two in 2006.[14,20] The RCTs were published in 2007 and 2006.[9,10]

Study setting

Both RCTs were conducted under controlled conditions in an ambulatory setting. [9,10] Three non-randomized studies were performed on patients in an ambulatory setting.[12,15,19] One was performed in both inpatient and outpatient settings.[17] Five studies were retrospective reviews of cases of deaths related to methadone, heroin, or buprenorphine [13,14,16,18,20], one of these was a matched case-control study[16]. One case study described a patient admitted to the emergency department,[11] another case series included one case of a patient admitted to hospital.[12]

Patient population

RCTs included adults maintained on methadone or buprenorphine treatment or maintenance therapy.[9,10]

The study population in two non-randomized studies were patients treated with methadone or buprenorphine/naloxone (as opioid substitution therapy) for opioid dependence,[17,19] including concomitant benzodiazepine abuse.[17] Two studies included adults on stable doses of opioids, which included methadone.[12,15]

Two studies reviewed cases of methadone-related deaths,[13,14]and one study reviewed cases of buprenorphine-related deaths.[20] Two studies reviewed cases of death due to methadone and compared them with cases of heroin-related deaths.[16,18]

The two case studies were based on adult patients, one maintained on buprenorphine/naloxone at the time of admission for pneumonia,[11] and another admitted after an opioid and benzodiazepine overdose.[12]

Intervention and comparators

Two RCTs compared the effects of different doses of diazepam with placebo.[9,10]

Two non-randomized studies assessed the use of benzodiazepines in combination with ongoing opioid substitution therapy (methadone or buprenorphine),[17,19] one more generally on stable

opioid therapy,[15] one compared use of opioids alone, to opioids with or without benzodiazepines, antidepressants, or both.[12]

Five retrospective studies examined the effect of recent benzodiazepine use based on autopsy toxicology,[13,14,18,20] or benzodiazepine and cocaine use based on post-mortem blood and urine toxicology.[16]

One case report described an interaction between lorazepam and buprenorphine/naloxone,[11] the other study was a case of fentanyl, methadone, and a benzodiazepine overdose.[12]

Outcomes reported

Outcomes of the included RCTs measured physiological parameters, performance measures, and subjective measures in patients.[9,10]

One non-randomized study reported changes in memory tests,[17] one evaluated general side effects reported by patients.[12] One study reported on predictive factors of survival,[19] another on the apnea-hypopnea index and central sleep apnea index.[15]

Three studies reported the relative risk of overdose death.[14,16,18] Two studies reported the prevalence of benzodiazepine use in methadone or buprenorphine related deaths.[13,20]

Outcomes of the two case reports were respiratory depression requiring intubation[11] and delayed hypoxic leukoencephalopathy.[12]

Summary of Critical Appraisal

The RCTs were identified with high study quality; however, they had limited external validity.[9,10] They demonstrated significant decreases in selected performance scores and subjective psychological ratings after single dose benzodiazepine administration in combination with methadone or buprenorphine maintenance dosing. Although there is the potential for safety concerns, the endpoints selected, controlled conditions, and testing of a single benzodiazepine dose provided limited information regarding the safety of regular use of benzodiazepines in combination with methadone or buprenorphine.

Two non-randomized studies were formally appraised.[16,17] One matched case-control study was of high quality.[16] Since this study was retrospective, it was limited to conclusions of association. Additionally, the study was unable to describe patterns of benzodiazepine use, with only urinalysis at a specific time point available. The non-randomized study which reported inferior working memory tests in patients on opioid substitution therapy with concomitant benzodiazepine abuse used a comparison group of healthy, normal patients.[17] Because of the significant differences between the comparison groups, it cannot be concluded that effects of the combination therapy would be significantly more than either therapy alone.

Non-randomized, non-controlled studies were not formally appraised. Studies that outlined the prevalence of benzodiazepines use found in cases of methadone and buprenorphine deaths were descriptive and were unable to provide conclusions about risk.[13,20]

One observational study sought to describe the prevalence of side effects associated with low or moderate dose opioids with or without benzodiazepines, antidepressants or both.[12] Though it

reflected current practice in a large population of chronic pain patients using opioids, it was limited by the likely heterogeneity within the different groups compared, though not well described, and the subjective self-reported endpoints. The study was able to provide some information that at low or moderate doses, self-reported side effects were generally mild for all groups.

The case report that described respiratory depression as a possible result of buprenorphine/naloxone administration with lorazepam is complicated by the fact that the patient was admitted for pneumonia.[11] Although there was a temporal relationship with administration of lorazepam, the possibility of worsening of her underlying clinical condition cannot be excluded.

The case review, which included one case of delayed hypoxic leukoencephalopathy secondary to benzodiazepine/opioid overdose, was limited because the other cases included in the series were secondary to opioids alone.[12] There was no indication from this report that the addition of the benzodiazepine in this case increased the risk for this outcome.

Summary of Findings

Risk of death

The matched case control study that evaluated the association between benzodiazepine use on the risk of fatal heroin and methadone deaths found significant increases in risk for both groups, supporting the status of benzodiazepine use as a risk factor for methadone and heroin overdose.[16] Another non-randomized study found similar significant odds ratios for increased risk of methadone-related death with benzodiazepine use.[14] One study found that cases of methadone related deaths were significantly more likely to have toxicology positive for benzodiazepine use compared with heroin-related deaths, suggesting that the combination of methadone and benzodiazepines may be a particularly high risk combination.[18] Another study of patients maintained on methadone as part of a hospital affiliated treatment clinic, found that factors significantly related to longer survival included no benzodiazepine abuse on admission, and no benzodiazepine abuse after one year of treatment.[19] Two different studies reported prevelance of benzodiazepine positive toxicology in 176 methadone,[13] and abuse in 21 buprenorphinerelated mortalities,[20] rates of 32.4% and 90%, respectively.

Physiological parameters, performance measures, subjective ratings of drug effects

Two RCTs compared different strengths of a single dose of diazepam with placebo when administered to methadone and buprenorphine patients.[9,10] No significant effects were found on the physiological parameters from the different doses examined. Significant effects were noted in the performance measures in all trials. Subjective ratings of sedation (VAS) and strength of drug effect in two studies were significantly affected by diazepam administration.

Sleep disordered breathing

One study assessed the relationship between chronic, stable opioid therapy, with or without benzodiazepine or other medications and sleep-disordered breathing.[15] A significant decrease of central apnea index with benzodiazepine use was found. A dose response relation was also found between the central apnea index and diazepam equivalents in these patients.

Other Adverse Effects

One study evaluated the prevalence of side effects in patients on opioids, with and without benzodiazepines, antidepressants, or both, but was unable to find a significant difference with respect to incidence of side effects between groups.[12]

One case study outlined the case of a woman admitted to hospital for pneumonia and started on antibiotics.[11] She was administered several doses of her own buprenorphine/naloxone, and additionally a dose of lorazepam to help her anxiety. Temporally related to her dose of lorazepam, her respiratory status deteriorated. Another case study outlined a patient with delayed hypoxic leukoencephalopathy, a rare complication of hypoxic-ischemic encephalopathy, as a result of polysubstance overdose of methadone, fentanyl and benzodiazepines.

Limitations

Based on the available evidence, there are no RCTs that reliably assess the risk of ongoing benzodiazepine use in combinations with opioids. The RCTs identified provide limited information regarding the potential harm caused by a single dose of diazepam in patients maintained on methadone and buprenorphine.[9,10] The retrospective studies were able to associate increased risk of overdose death with methadone and benzodiazepine use; however, the use of benzodiazepines in these cases could not be characterized.[13,14,16,18] Another study found an association between increased survival in the absence of benzodiazepine abuse at a methadone maintenance treatment clinic.[19] It is unknown if the risks of benzodiazepine abuse or use would be similar. One retrospective review reported a high prevalence (90%) of concurrent benzodiazepine and bupreprenorphine abuse in a small number of cases of buprenorphine related deaths.[20] Though several studies were generally well conducted and sought to evaluate the risk of the combination of benzodiazepines and opioids, it is difficult to draw conclusions based on retrospective studies which are able to only determine association or RCTs with limited external validity. The consistency of results across studies was fair, indicating possible harm across a range of outcomes when benzodiazepine use or abuse was combined with opioids, with a stronger signal for methadone. On the other hand, the generalizability of study results is difficult, given the heterogeneity in the populations studied and the different definitions specified for benzodiazepine use or abuse.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

According to the evidence, there is a positive association between the risk of death and the use of benzodiazepines in combination with methadone. Though limited, there is an indication that opioids, including buprenorphine, have the potential for increased risk in combination with benzodiazepines. Clinical mechanisms are hypothesized. As a result, it seems reasonable that use of opioids with benzodiazepines should be limited until this risk is further clarified, with each patient case assessed on its own merits. Further research that will examine the effect of combination benzodiazepines use and opioid therapy, especially buprenorphine, may demonstrate lower risk with this combination.

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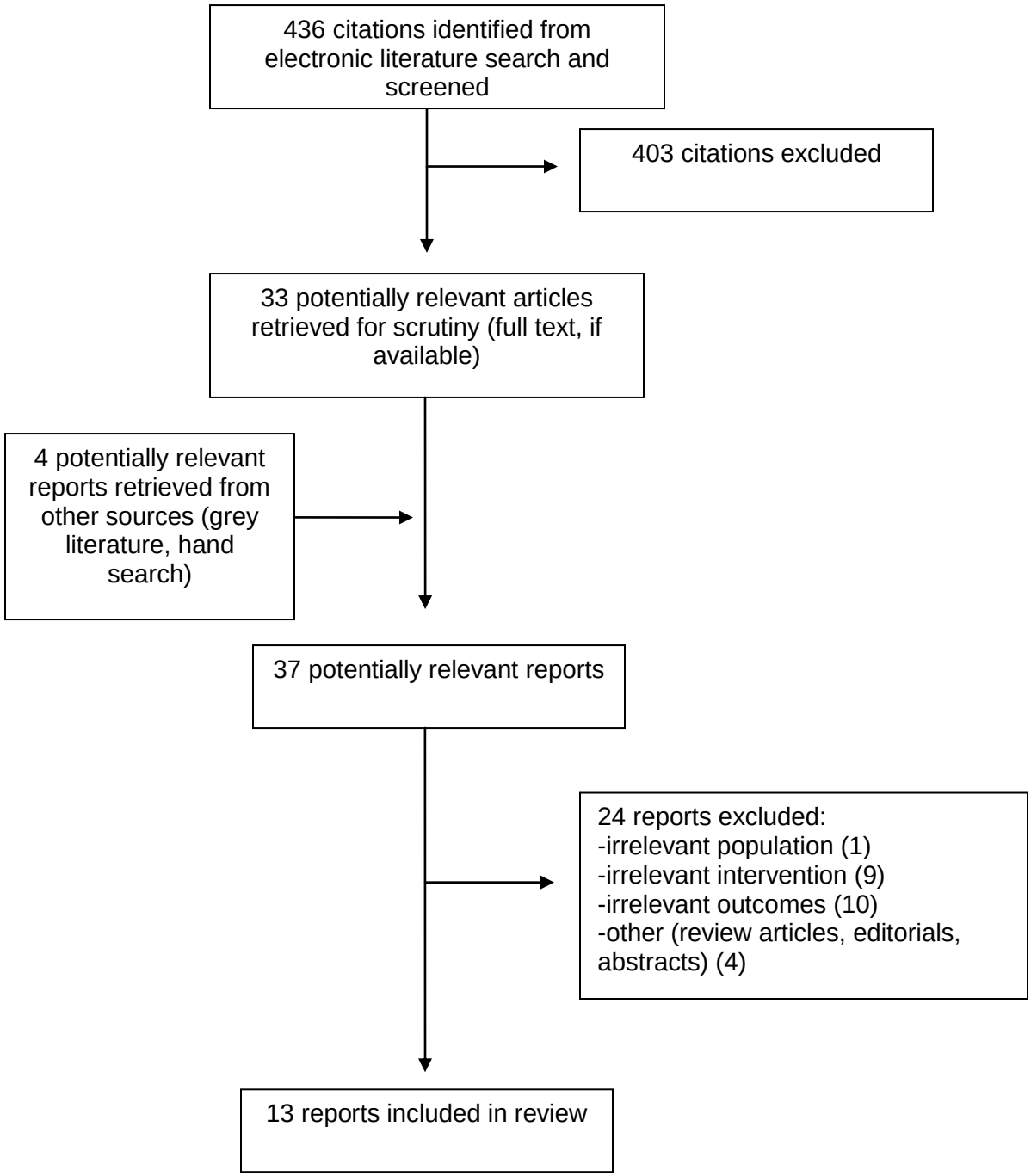
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size	Intervention	Comparators	Outcome
Randomized Controlled Trials					
Lintzeris, 2007, UK [9]	Prospective, DB, randomly ordered, 2 x 2 within-subject design	11 adults in METH or BUP treatment, history of BZD use but no recent use within 2 weeks	Diazepam 40mg, 150% dose of maintenance opioid	Placebo, 100% dose of maintenance opioid	Physiological measures, subjective measures of drug effects, performance measures
Lintzeris, 2006, UK [10]	DB, randomized, prospective, within-subject design	16 adults in METH or BUP treatment, a history of BZD use but no recent use within 2 weeks	Diazepam 10mg, 20mg	Placebo	Physiological measures, subjective measures of drug effects, performance measures
Non-randomized studies					
Rapeli, 2009, Finland [17]	Prospective, observational	28 adults treated with OST for OD (13 with METH, 15 with BUP/NAL), concomitant BDZ dependence or abuse	OST and ongoing BZD use in 24 hour prior to testing	15 normal comparison adults	Memory tests including immediate verbal memory, working memory, memory consolidation, subjective memory
Oliver, 2007, UK [16]	Retrospective, matched case-control	1000 heroin related deaths, 300 methadone related deaths	Recent BZD or cocaine use, (post mortem blood and urine toxicology)	No recent BZD or cocaine use	Relative risk of fatal opioid overdose
Non randomized, non-comparative studies, case reports					
Martin, 2011,	Case report	1 patient admitted to ED for	NA	NA	Respiratory depression

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size	Intervention	Comparators	Outcome
USA [11]		pneumonia, BUP/lorazepam co-ingestion occured			
Darke, 2010, Australia [18]	Case review of opioid toxicity deaths	1193 patient deaths, 1000 due to heroin toxicity, 193 due to METH toxicity	NA	NA	Toxicology, systemic disease on autopsy
Peles, 2009, Israel [19]	Retrospective review	613 adults admitted to a MMT clinic	NA	NA	Mortality rate and survival since first admission to MMT
Manchikanti, 2009, USA [12]	Prospective observational	1000 patients on stable doses of opioids (morphine equivalency <90mg daily) in a pain management program using opioids with and without BZD, antidepressants, or both	NA	NA	Side effects (patient self-report)
Shprecher, 2008, USA [12]	Case reports	1 patient admitted to hospital secondary to Fentanyl/ methadone/ BZD overdose	NA	NA	DHL
Webster, 2008, USA [15]	Prospective observational	140 patients on stable ATC opioid therapy with/without other medication(36% also used BZD)	NA	NA	Apnea-hypopnea index, central apnea index
Shields, 2007, USA [13]	Retrospective review	176 methadone related deaths	NA	NA	Post-mortem examination, blood and urine toxicology
Chan, 2006, USA [14]	Retrospective review	493 methadone-positive decedents	NA	NA	Risk factors for accidental overdose death

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size	Intervention	Comparators	Outcome
Lai, 2006, Singapore [20]	Retrospective review	21 buprenorphine related deaths	NA	NA	Autopsy results, postmortem toxicological analysis

ATC=around-the-clock; BUP=buprenorphine; BZD= benzodiazepine; DHL=delayed hypoxic leukoencephalopahy; DB= double blind; ED=emergency department; METH=methadone; MMT=methadone maintenance clinic; NA=not applicable; NAL=naloxone; OD= opioid dependence; OST=opioid substitution therapy; RCT= randomized controlled trial

APPENDIX 3: Critical Appraisal of Included Studies

First Author, Publication Year	Strengths	Limitations
Randomized Controlled Trials		
Lintzeris, 2007 [9]	• Study was of high quality; objectives, randomization, main outcomes, characteristics of patients, interventions of interest, main findings were clearly described. • Internal validity was appropriate. • Actual probability values were reported .	• Distributions of confounders were not clearly described. • Confidence intervals were not presented in the results. • External validity is limited; sample size was small (4 METH patients, 7 BUP patients), conducted under controlled conditions, single doses only evaluated. • Main outcome measures were reliable, but are surrogate measures of harm of use. • No direct statistical comparisons of METH and BUP groups (unmatched subjects). • Lacked statistical power for selected outcomes.
Lintzeris, 2006 [10]	• Study was of high quality; objectives, randomization, main outcomes, characteristics of patients, interventions of interest, main findings were clearly described. • Internal validity was appropriate. • Actual probability values were reported	• External validity is limited; sample size included 8 METH patients and 8 BUP patients, conducted under controlled conditions, single doses only evaluated. • Main outcome measures were reliable, but are surrogate measures of harm of use. • Though inferences were drawn, not designed to perform direct statistical comparisons between the METH and BUP groups.
Non-randomized studies		
Rapeli, 2009[17]	• Clinically relevant hypothesis • Main outcomes, characteristics of patients, interventions of interest, main findings were clearly described.	• Patients from cases and comparison groups were unmatched. • Sample size was small, 13 METH, 15 BUP/NAL or BUP patients and 15 normal comparison patients studied twice. • Patients in the intervention group were not from the same population as patients from the healthy normal controls, study was unable to control for confounders between groups or identify all

First Author, Publication Year	Strengths	Limitations
	• Selected potential confounders described. • Standard deviation, actual probability values reported.	potential confounders. Significant differences identified included years of education, use of other substances of abuse, personality disorder diagnosis, and of course, opioid abuse. • Unable to control for dose changes and time. • Other adverse effects not monitored or reported. • Characteristics of patients lost to follow-up not described. • Blinding was not performed.
Oliver, 2007 [16]	• Study was of high quality; objectives, main outcomes, characteristics of case series and control series patients, interventions of interest, main findings were clearly described. • Matching process was clearly described. • Potential confounders were identified.	• Retrospective, limited to conclusions of association. • Unclear if cases and controls were recruited over the same timeframe. • Unable to describe patterns of benzodiazepine use, based on positive urinalysis. • Case groups of METH and BUP fatalities were more heterogenous than control groups.

BUP = buprenorphine; BZD= benzodiazepine; METH=methadone; NAL=naloxone

APPENDIX 4: Study Findings and Author's Conclusions

First Author, Publication Year	Study Findings of Safety Outcomes	Author's Conclusions
Randomized Controlled Trials		
Lintzeris, 2007 [9]	No significant effects on physiological measures. Significant effect on VAS score for sedation in both METH (p=0.006) and BUP groups. (p=0.04) Significant effects for diazepam condition x time for reaction time in the METH group. (p=0.01) Significant effect for diazepam condition on reaction time and diazepam condition x time (p=0.03). Significant effect for diazepam condition for cancellation task (p=0.03) and for diazepam condition x time (p=0.001).	"BZD significantly influence response to METH and BUP, impacting upon subjective effects such as sedation, and performance such as attention and psychomotor skills." (p.193)
Lintzeris, 2006 [10]	No significant effects on physiological measures. Significant effects on: VAS ratings of sedation, VAS strength of drug effect for both METH and BUP groups. (p=0.02) Significant effects for diazepam and diazepam condition x time for reaction time in the METH group (p=0.04,p=0.02), and for cancellation time (p=0.002) Significant effect for diazepam condition on reaction time (p=0.02). Significant effect for diazepam condition x time for cancellation time (p=0.02).	"The extent of the deterioration in these performance measures is somewhat concerning. For example in methadone-treated patients [the increase in mean peak reaction time] could be associated with considerable impairment in function. This raises concerns regarding the safety of using even therapeutic BZD dose s in circumstances where patients may be performing tasks, such as manual labor, driving, or operating machinery." p. 281 "Diazepam may significantly alter the response to opioid substitution treatment with

First Author, Publication Year	Study Findings of Safety Outcomes	Author's Conclusions
		METH or BUP." p.274
Non-randomized studies		
Rapeli, 2009 [17]	Both patient groups were significantly inferior to normal comparison group in working memory tests at 2 months and 6-9 months. Both patient groups reported significantly more subjective memory problems than normal comparison participants.	"OD patients taking opioid agonist drugs and BZDs score worse than normal comparison persons in tests of memory during the firths six months of their OST." p. 13
Oliver, 2007 [16]	Risk of fatal heroin overdose in patients with evidence of recent BZD use OR=2.4 (95% CI=1.64 to 3.60; p<0.001). Risk of fatal methadone overdose associated with recent use of BZD and increased, OR=9.16, (95%CI=5.05 to 16.63; p<0.001)	"Findings support the status of BZD use as a significant risk factor for opioid overdose, especially for METH-related death in which a near ten times increase in risk of fatal overdose was observed." p. 5
Non randomized, non-comparative studies, case reports		
Martin, 2011 [11]	Baseline O_2 saturation was 100% on RA. BUP/NAL + lorazepam 1mg administered, within 1 hour severe respiratory depression (RR 10 breaths/min, BP 90/40 mmHG, O_2 saturation was 78% on a non-rebreather mask) and eventual intubation	"BZDs should be avoided when treating anxiety in patients taking BUP/NAL." p. 201
Darke, 2010 [18]	METH cases were significantly more likely to have positive toxicology for BZD compared to heroin cases (OR =3.64, 95% CI 2.63-5.11)	"There were notable differences in the toxicology and disease patterns of these groups. Great caution would appear warranted in prescribing BZD to METH users, and thorough physical examinations of treatment patients would appear

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		clinically warranted." p. 5
Manchikanti, 2009 [12]	No significant differences with respect to incidence of side effects between groups. Severe side effects accounted for only 14/137 instances, and were all constipation.	"Long-term low or medium dose opioid therapy with BZD and/or antidepressants provided in conjunction with interventional techniques is associated with minimal side effects and these side effects are minor." p.266
Peles, 2009 [19]	Factors significantly related to longer survival included no BZD abuse on admission (p=0.02), and no BZD abuse after 1 year (for those who stayed in MMT for at least 4 months) (p=0.03)	"BZD abuse reduced both retention and survival, emphasizing the high priority that should be given to stopping it." p. 141
Shprecher, 2008 [12]	Intentional overdose of METH, fentanyl and BZD developed severe progressive cognitive decline and DHL 11 days later.	"Characteristics of DHL outlined, regardless of initial cause of cerebral hypo-oxygenation, prognosis is incomplete recovery with lasting cognitive deficits." p.477
Webster, 2008 [15]	Direct relation between central apnea index and methadone (p=0.004) and BZD use (p=0.042). Dose response relation between the apnea-hypopnea index and methadone morphine equivalents (p=0.002). A dose response relation was found between the central apnea index and methadone morphine equivalents (p=0.008) and with diazepam equivalents (p=0.004).	"Sleep-disordered breathing was common in chronic pain patients on opioids. The dose-response relation of sleep apnea to METH and BZDs calls for increased vigilance." p. 425
Shields, 2007 [13]	Of 176 methadone related fatalities, combination of only	"The high number of deaths, which not only occurred

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	METH and BZD in 4.25% of cases detected in blood and urine, 32.4% detected in blood.	during the induction phase of methadone use but also involved various combinations of psychoactive drugs (polypharmacy) with METH, strongly suggests an additive effect between METH and other drugs during a vulnerable period of consumption." p. 1395
Chan, 2006 [14]	Of the 493 methadone positive deaths, 32% were BZD positive. Odds of having an AOD death in methadone-positive decedents testing BZD positive was 1.66 (95% CI= 1.12 to 2.45; p< 0.02 for BZDs)	"In our study, we observed an association between a fatal AOD in decedents who test positive for methadone and the detection of a TCA, a BZD, and both." p. 547
Lai, 2006 [20]	19/ 21 (90%) of BUP related deaths were of concurrent abuse of BUP and BZD.	"This study highlighted that concurrent administration of BUP and BZD was potentially fatal. The diversion of sublingual BUP preparations for IV use presented and additional danger." p. 85

AOD=acccidental overdose death; BP=blood pressure; BUP=buprenorphine; BZD= benzodiazepine; CI=confidence interval; DHL=delayed hypoxic leukoencephalopahy; METH=methadone; NAL=naloxone; OD=opioid dependence; OST=opioid substitution therapy; RA=room air; TCA=tricyclic antidepressant