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Substitution treatment for opioid dependence with slow-release oral morphine: Retention rate, health status, and substance use after switching to morphine

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Background

- OAT has been long lasting in Germany
- Options for treatment include racemic methadone (38.1%) or levomethadone (35.9%).
- Buprenorphine is used in almost a quarter (23.2%) of patients.
- Intravenous diamorphine for 1.1% of OAT patients
- SROM 1.5 % after Beck's non inferiority trial
- Randomized RTC between methadone and SROM shows comparative effects in reducing illegal substance use, comparable retention rates, and increased benefits in reducing cravings, anxiety and depression, and physical complaints
- Improvements in SROM vs methadone in regards to drug to drug interactions.

CENTRAL AIM:

- Investigate SROM's long term effects in routine clinical practice.

Methods

- Prospective, non interventional, observational study between 2016 and 2017 examining individuals 18 years of age or older on OAT from 23 addiction clinics who have switched to SROM.

Program description:

- Individuals were originally on racemic methadone, levomethadone, buprenorphine or diamorphine.
- Eligibility for study included individuals who had an “unsatisfactory course on OAT including continued cravings or adverse drug effects.
- Info collected: baseline demographic characteristics, age, sex, and social circumstances , clinical findings, and prior treatment experiences.
- Data collected at 1,3, 6, and 12 months.

Methods

Primary Outcome:

- Change in mental health symptoms using the Brief Symptom Inventory-18 and Global Severity Index.

Secondary Outcomes:

- Retention rates after 1, 3, 6, and 12 months.

Other outcomes:

- Self reported alcohol and drug use:
- Physical Health using the Opioid Treatment Index Health Symptom Scale (OTI-HSS)
- Any withdrawal symptoms were evaluated using the SOWS tool
- Cravings were measured using a visual analogue scale (VAS)

Methods

Sample Size Calculation:

- Sample size calculated from a previous cross over study finding 5% improvement in mental health when switching from methadone to morphine.
- They chose 10% instead due to length of study and comparing baseline to T12.
- Standard deviation chosen to be 0.30, alpha 0.05, and power of 80%.
- N=147, with expected drop out rates of 25% it was adjusted to 196 patients.
- AE were evaluated comparing intensity, frequency, duration, and relation to SROM.

Analysis:

- GSI values between baseline and 12 months were calculated using paired sample t-test.
- Study done as intention to treat and per protocol patients.
- ITT replaced the last value of t12 with last available data.
- Retention rates analyzed descriptively.
- SPSS used.

Results

- Study enrolled 180 participants.
- ¾ male, and average age was 44 .
- On average clients were on OAT for 7 years.
- 77% were on levomethadone prior to the switch
- Overall there were 12 past and 7 on going comorbidities
- 2/3 had at least one prior psychiatric diagnosis.
- Average initial dose 781.4 (±309.6) mg for all patients
- Average final dose 764.3 (±289.1) mg
- If clients dropped out they were switched to their original racemic mixture.
- Most frequent reasons for dropping out: insufficient satisfaction with the way SROM worked for the patients (28.8%), followed by side effects (15.3%), patient's absenteeism from treatment without further information (15.3%), or hospitalization (10.2%)

Table 1
Characteristics, living conditions, and health status of patients at baseline t0 (before switching to SROM) ($N = 180$).

Characteristic	N (%)
Sex (N = 180)	
Male	134 (74.4%)
Female	46 (25.5%)
Age in years (mean, SD) (N = 180)	44,4 (8.8)
Duration of opioid dependence in years (mean, SD) ($N = 177$)	23.0 (9.9)
Duration of OAT in years (mean, SD) ($N = 172$)	6.9 (6.9)
Previous medication before switching (mean dose) (N = 180)	
Levomethadone	105 (58.3%, 48.4 mg)
Buprenorphine	35 (19.4%, 11.9 mg)
Racemic methadone	34 (18.9%, 94.9 mg)
Other (e.g. dihydrocodeine, diamorphine, tramadol)	6 (3.3%)
Nationality (N = 180)	
German	170 (94.4%)
Other	10 (5.6%)
Migrant background ($N = 179$)	
No	156 (87.2%)
Born in Germany as a child of migrants	13 (7.3%)
Self-immigrated	10 (5.6%)
Partnership (N = 179)	
Single	113 (63.1%)
In relationship, living apart	15 (8.4%)
In relationship, living together	51 (28.5%)
Number of own children ($N = 175$)	
No children	108 (61.7%)
1–5 children	67 (38.3%)
Professional situation (N = 180)	
Full-time	33 (18.3%)
Part-time	24 (13.3%)
Jobbing	12 (6.7%)
School, apprenticeship, studying	5 (2.8%)
Pension, early retirement	17 (9.4%)
Unemployed	66 (36.7%)
Homemaker	7 (3.9%)
Other	16 (8.9%)
Housing situation (N = 180)	
In own apartment/partners flat	150 (83.3%)
At relatives	11 (6.1%)
Temporarily with friends/acquaintances	5 (2.8%)
Assisted living (health care facilities, care home, women's center)	8 (4.4%)
Hotel/boardinghouse/residential home	6 (3.3%)
Homeless, living on the street	0
Health anamnesis (N = 180)	
Number of previous comorbidities (mean, SD)	2.2 (1.9)
Number of persistent comorbidities (mean, SD)	1.3 (1.5)
Number of preexisting psychiatric diagnoses (mean, SD)	1.0 (1.0)
Number of preexisting physical findings (mean, SD)	1.4 (2.4)
Human Immunodeficiency Virus (HIV)-positive	4 (2.2%)
Hepatitis C antibodies positive	104 (59.4%)
Hepatitis C RNA positive	40 (23.3%)
Hepatitis B antibodies positive	54 (31.2%)
Tuberculosis	2 (1.1%)

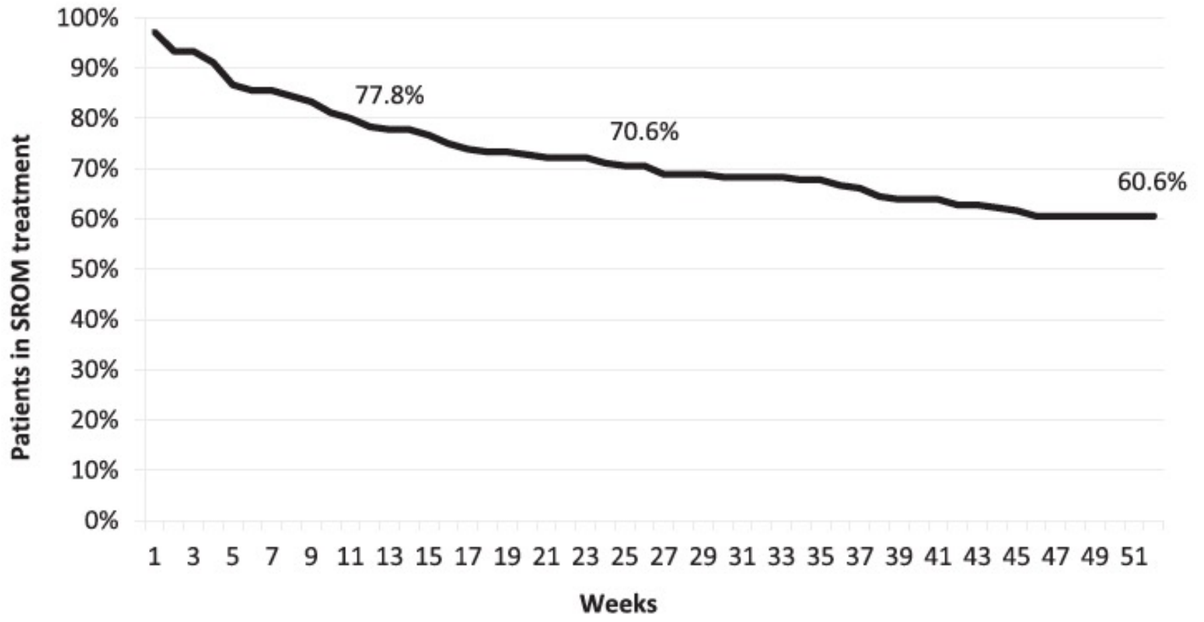

Fig. 1. Treatment retention after 3, 6 and 12 months of medication with SROM ($N = 180$).

Table 2
Mean Global-Severity-Index (GSI) and mean values for depression, anxiety and somatization of BSI-18 at baseline and after 12 months (ITT and PP analysis).

Patients self-declaration	Baseline Mean (SD)	12 month Mean (SD)	Statistics *t*-Test	Effect size Cohen's dz[a]
ITT analysis				
Mental health (GSI) $N = 178$	0.86 (0.71)	0.69 (0.70)	$t = 4.20$ $p < 0.001$	d = 0.315
Depression $N = 175$	1.14 (1.04)	0.88 (0.95)	$t = 4.93$ $p < 0.001$	d = 0.373
Anxiety $N = 174$	0.79 (0.77)	0.62 (0.78)	$t = 3.39$ $p = 0.001$	d = 0.257
Somatization N = 174	0.63 (0.61)	0.54 (0.59)	$t = 2.45$ $p = 0.015$	d = 0.186
PP analysis				
Mental health (GSI) N = 103	0.75 (0.63)	0.57 (0.64)	$t = 3.42$ p = 0.001	d = 0.337
Depression $N = 97$	1.03 (0.98)	0.70 (0.79)	$t = 4.66$ $p < 0.001$	d = 0.473
Anxiety N = 97	0.69 (0.70)	0.51 (0.73)	$t = 2.40$ p = 0.018	d = 0.244
Somatization $N = 96$	0.52 (0.54)	0.44 (0.55)	$t = 1.39$ $p = 0.169$	d = 0.142

[a] Cohen's dz is a type of Cohen's d for determining the effect size, which is an essential indicator when evaluating the strength of a statistical claim and the practical significance of identified differences. Cohen suggested d = 0.2 to be considered a 'small' effect size, 0.5 a 'medium' effect size.

Table 3
Physical (OTI-HSS) and mental (BSI-18) health during 12 months treatment with SROM.

Patients self-declaration	Baseline Mean (SD)	3 month Mean (SD)	6 month Mean (SD)	12 month Mean (SD)	Statistics P-S[a]
Mental health ($N = 95$) (Total mean value GSI)	0.74 (0.64)	0.52 (0.65)	0.56 (0.61)	0.57 (0.67)	P-S = 0.16 p = 0.001
Depression (mean score) $N = 88$	0.97 (0.97)	0.68 (0.82)	0.76 (0.84)	0.66 (0.79)	P-S = 0.21 p < 0.001
Anxiety (mean score) $N = 87$	0.66 (0.70)	0.46 (0.69)	0.47 (0.62)	0.50 (0.76)	P-S = 0.12 $p = 0.013$
Somatization (mean score) $N = 86$	0.49 (0.51)	0.42 (0.62)	0.48 (0.61)	0.45 (0.56)	P-S = 0.03 $p = 0.42$
Physical Health $N = 93$ (Score OTI-HSS)	7.6 (5.1)	4.9 (4.7)	5.3 (4.9)	5.3 (5.2)	P-S = 0.31 p < 0.001
Number of physically abnormal findings $N = 112$	1.1 (1.6)	1.0 (1.5)	1.0 (1.5)	0.9 (1.5)	P-S = 0.02 $p = 0.62$

[a] P-S = Pillai's trace (general linear model).

Table 4
Average number of days of alcohol and illegal drug use during past 30 days under SROM treatment.

Patient self-reports $N = 113$	Baseline Mean (SD)	1 month Mean (SD)	3 month Mean (SD)	6 month Mean (SD)	12 month Mean (SD)	Statistics P-S[a]
Heroin	4.9 (8.6)	1.6 (3.8)	1.6 (3.8)	1.5 (4.7)	1.4 (4.7)	P-S = 0.17 $p < 0.001$
Intravenous consumption	2.7 (6.7)	0.6 (2.2)	0.4 (1.4)	0.2 (0.9)	0.2 (0.9)	P-S = 0.14 $p = 0.002$
Cocaine	1.3 (3.9)	0.5 (1.6)	0.8 (3.2)	0.4 (1.5)	0.5 (2.0)	P-S = 0.07 $p = 0.119$
Amphetamines, methamphetamine, speed	0.5 (2.5)	0.3 (1.5)	0.2 (1.1)	0.2 (1.1)	0.2 (1.4)	P-S = 0.02 $p = 0.772$
Tranquillizers	3.3 (7.5)	1.7 (4.7)	1.6 (5.1)	1.4 (4.2)	2.1 (6.1)	P-S = 0.07 $p = 0.092$
Cannabis	5.9 (9.7)	5.4 (9.1)	5.4 (9.6)	6.1 (9.9)	5.7 (10.3)	P-S = 0.01 $p = 0.857$
Alcohol	6.4 (9.8)	4.9 (8.3)	5.0 (7.8)	4.8 (8.4)	4.0 (7.5)	P-S = 0.09 $p = 0.044$

[a] P-S = Pillai's trace (general linear model).

Results

Cravings:

- VAS scale reported : 34.8 (SD 34.5) at baseline to 13.6 (SD 23.9) after 12 months of SROM treatment (N = 94, Pillai's trace = 0.35, $p < 0.001$).
- Reduction of craving was most pronounced during the first three months (t3 = 19.0; SD 24.5) but fell a further 5.4 points during the following nine months
- Withdrawal symptoms, according to SOWS, also improved significantly from 5.7 (SD 5.7) at baseline to 2.4 (SD 3.6) at t12 (N = 110, Pillai's trace = 0.29, $p < 0.001$).

Adverse effects:

- 84 AE in 43 patients (23.9%). 2/5ths of all AEs occurred in first 2 months. 35.7% of AEs had no relationship to SROM
- Most frequent AEs were within the domain of psychiatric disorders.
- Second most frequent Aes were gastrointestinal issues like nausea and diarrhea.
- Only twelve cases of ADRs usually within the first 4 weeks of swiching.

Discussion

- Demonstrated that SROM as an OAT option is beneficial.
- SROM can be used as a substitute for levomethadone and buprenorphine as well.
- Previous SROMOS study had 1/3 of people in full or part time employment
- Some concerns around adherence as individuals were stable for the most part with 7 years of OAT treatment but required a switch due to physical or metal health concerns.
- Retention rates for SROM comparable to other OAT options, which typically are above 50%.
- Using the BSI-18, while the study did not achieve standard sample size there were positive mental health changes 20% in ITT, and 24% in PP .
- Observed improvements in mental and physical health, as well as improvements in alcohol consumption and illegal drug use, may be attributable primarily to the substitution medication as no study related intervention except SROM was one (ie. No counselling)

Limitations

LIMITATIONS:

- Observational study only as opposed to a controlled clinical study..
- Selection bias concerns present with overall results and comparable sub-groups
- Difficult to recruit patients and sample size population was not reached.

QUESTIONS:

- Treatment effects on therapy naïve people remains unknown.

Our Discussion

Association Between Benzodiazepine or Z-Drug Prescriptions and Drug-Related Poisonings Among Patients Receiving Buprenorphine Maintenance: A Case-Crossover Analysis

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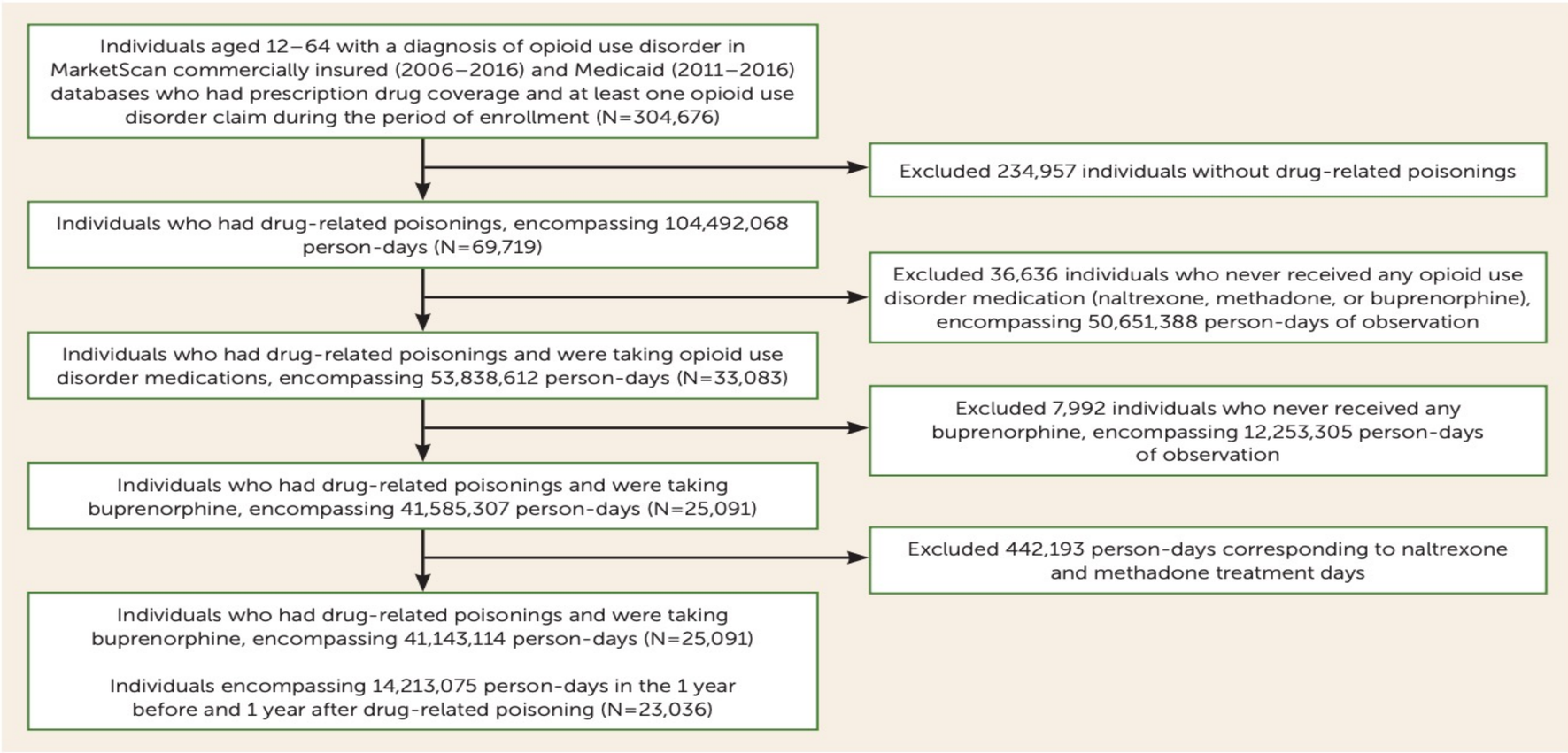
Background

- Buprenorphine is used to treat OUD
- Up to 30% of this population may be using concurrent Benzos which put them at high risk of overdose.
- Some findings suggest that benzodiazepines may enhance retention in buprenorphine maintenance treatment
- Benzodiazepines have also been associated with:
  - Increases in drug-related poisonings
  - All-cause mortality
  - Non-overdose deaths
  - Decreased retention in treatment
  - Accidental injury-related emergency department visit
  - Limited studies on the interaction between benzos and buprenorphine.

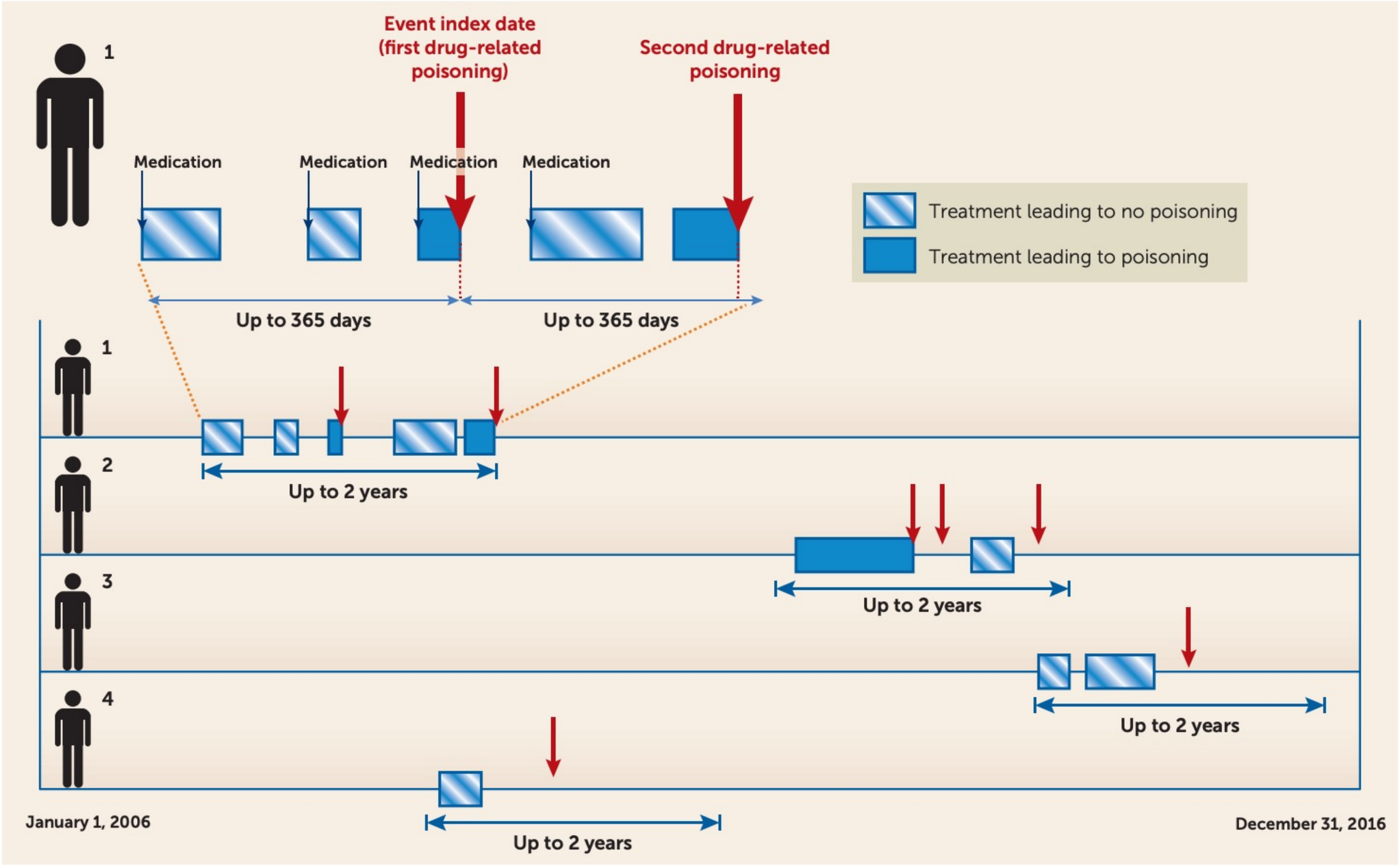
Methods

FIGURE 1. Derivation of the analytic sample during follow-up of patients with opioid use disorder with a drug-related poisoning



Methods Continued

- Individuals ages 12 to 64 with insurance claims indicating an opioid use disorder diagnosis, at least one buprenorphine prescription, and at least one nonfatal drug-related poisoning were included for analysis.
- Buprenorphine use was characterized in terms of strength, quantity, and days of supply in order to calculate a daily milligram dose.
- Stratified into daily buprenorphine doses >12 mg and <12mg
- Case crossover study design was used.
- Units of observation were person-days, denoting days during which patients were enrolled in a health insurance plan.
- Case periods were days when a patient experienced nonfatal drug related poisonings
- Control periods were nearby days without poisoning events
- Person-day of observation by the presence or absence of benzodiazepine or Z-drug treatment and the presence or absence of buprenorphine treatment
- Individuals with fewer observation days on either side of the index event were included with missing days treated as censored.
- selective serotonin reuptake inhibitors (SSRIs) (sertraline, fluoxetine, escitalopram, and citalopram) were included in our conditional logistic models as an active comparator analysis


1
Event index date
(first drug-related
poisoning)
Second drug-related
poisoning
Medication
Medication
Medication
Medication
Treatment leading to no poisoning
Treatment leading to poisoning
Up to 365 days
Up to 365 days
1
2
Up to 2 years
3
Up to 2 years
4
Up to 2 years
January 1, 2006
December 31, 2016

Methods Continued

- Ascertainment of Outcomes and Exposures:
  benzodiazepine, Z-drug, and buprenorphine prescriptions were evaluated on strength, quantity dispensed, and days of supply
- Strength of each benzodiazepine or Z-drug in terms of total diazepam-equivalent milligrams
- Daily diazepam-equivalent dose by multiplying the number supplied by strength (in diazepam-equivalent milligrams) and dividing by days of supply
- Benzodiazepine and Z-drug dosage was stratified into high-dose (diazepam-equivalent-mg dose .30 mg) and lowdose (#30 mg)
- Benzodiazepine exposure was categorized by the duration of action, namely, short-acting (half-life #24 hours) or longacting (half-life .24 hours)

Methods Continued

Statistical Analysis:

- SAS
- logistic regression models stratified by subject and modeled the risk of poisoning as a function of drug exposure by days with or without treatment.
- additive or interactive effects of benzodiazepines or Z-drugs and buprenorphine in association with drug-related poisonings.
- SSRIs were included in our models as an active comparator analysis
- Subgroup analyses were conducted to assess the effect of buprenorphine treatment days, compared with days without treatment, on drug-related poisoning among patients who received benzodiazepine or Z-drug prescriptions and those who did not

Characteristic		
	N	%
Buprenorphine use	16,451	71.41
Low-dose (≤12 mg daily)	9,469	41.11
High-dose (>12 mg daily)	11,690	50.75
Benzodiazepine or Z-drug use	12,890	55.96
Benzodiazepine use excluding Z-drugs	11,839	51.39
Low-dose (≤30 diazepam-equivalent mg daily)	10,356	44.96
High-dose (>30 diazepam-equivalent mg daily)	5,227	22.69
Short-acting benzodiazepine use	9,292	40.34
Alprazolam	6,210	26.96
Lorazepam	4,433	19.24
Oxazepam	130	0.56
Triazolam	248	1.08
Estazolam	19	0.08
Temazepam	1,127	4.89
Midazolam	47	0.2
Long-acting benzodiazepine use	6,660	28.91
Clonazepam	3,885	16.86
Diazepam	3,612	15.68
Chlordiazepoxide	206	0.89
Clobazam	1	0
Flurazepam	33	0.14
Quazepam	2	0.01
Z-drug use	5,068	22
Zolpidem	4,640	20.14
Eszopiclone	1,025	4.45
Zaleplon	216	0.94
Methadone use	420	1.82
Naltrexone use	1,449	6.29
Naltrexone extended-release use	746	3.24
Selective serotonin reuptake inhibitor use	10,286	44.65

	Mean	SD
Age (years)	30.05	12.15
Year of birth	1980	
Days of observation	298.73	107.88
	N	%
Male	11,713	50.85
Relationship of patient to primary beneficiary		
Employee	4,345	28.30
Spouse	3,746	24.40
Child or other	7,263	47.30
Medicaid	7,682	33.35

TABLE 2. Opioid use disorder treatment characteristics at the person-days level among individuals with a drug-related poisoning (N=23,036)[a]

Characteristic	N	%
Treatment days marked by drug-related poisoning	26,243	0.18
Days treated with buprenorphine	2,210,927	15.56
Dose (mean±SD)	15.44	7.31
Low-dose (≤12 mg daily)	758,261	5.33
High-dose (>12 mg daily)	1,367,893	9.62
Days treated with selective serotonin reuptake inhibitors	1,715,489	12.07
Days treated with benzodiazepines or Z-drugs	2,493,800	17.55
Dose (diazepam-equivalent mg daily) (mean±SD)	23.39	25.88
Days treated with benzodiazepines excluding Z-drugs	1,968,944	13.85
Dose (diazepam-equivalent mg daily) (mean±SD)	27.58	26.98
Low-dose (≤30 diazepam-equivalent mg daily)	1,453,110	10.22
High-dose (>30 diazepam-equivalent mg daily)	515,834	3.63
Days treated with short-acting benzodiazepines	1,584,424	11.15
Dose (diazepam-equivalent mg daily)	25.33	20.53
Days treated with long-acting benzodiazepines	452,820	3.19
Dose (diazepam-equivalent mg daily)	31.28	38.10
Days treated with Z-drugs	825,610	5.81
Dose (diazepam-equivalent mg daily) (mean±SD)	4.88	1.24
Concurrent use of buprenorphine or benzodiazepines or Z-drugs		
Days without buprenorphine or benzodiazepine or Z-drug treatment	9,982,529	70.23
Days treated with benzodiazepines or Z-drugs only	2,019,619	14.21
Days treated with buprenorphine only	1,736,746	12.22
Days treated with concurrent buprenorphine and benzodiazepines or Z-drugs	474,181	3.34

[a] Data are presented as Ns and percentages except as otherwise noted. Among all individuals with a history of drug-related poisoning during the study's observation window (1 year before and 1 year after the index poisoning event), the number of person-days for which insurance claims were filed for medication treatment was calculated. Because the data in this table do not represent the individual subject level, it was possible for an individual subject to contribute multiple person-days.

Results

- Excluded individuals without drug-related poisonings, individuals who never received medication for opioid use disorder, and individuals without days of naltrexone and methadone treatment and days of observation outside a maximum of a 1-year period before and after the index poisoning

- 1,968,944 person-days (13.9%) entailed claims for benzodiazepines or Z-drugs, of which 474,181 person-days entailed concurrent buprenorphine treatment

- mean daily dose of any benzodiazepine or Z-drug to be 23.4 diazepam-milligram equivalents and the mean daily dose for short-acting benzodiazepines, long-acting benzodiazepines, and Z-drugs to be 25.3, 31.3, and 4.9 diazepam-milligram equivalents

- Buprenorphine and Benzo-Z drug poisonings:

- Buprenorphine treatment days were associated with 37% lower odds of drug-related poisoning (95% CI=0.60, 0.66) compared with nontreatment days
- Odds of poisoning increased 81% on days when patients were treated with benzodiazepines or Z-drugs (95% CI=1.73, 1.91; model 1)

- Z-drug treatment days were associated with increased odds of poisoning events (odds ratio=1.29, 95% CI=1.19, 1.39), but this was notably lower than the odds associated with benzodiazepine treatment days (odds ratio=1.88, 95% CI=1.78, 1.98; model 2)
- No association between SSRI treatment days and drug-related poisonings (odds ratio=0.95, 95% CI=0.90, 1.00; model 3)
- No difference in magnitude of protective effect against poisoning conferred by buprenorphine treatment days when conducting stratified analyses of patients who used benzodiazepines or Z-drugs (odds ratio=0.64, 95% CI=0.60, 0.69, model 4) and those who never used benzodiazepines or Z-drugs during the study's observation period (odds ratio=0.64, 95% CI=0.59, 0.69; model 5).

Results

- Similarly elevated odds of drug-related poisoning for short acting benzodiazepine treatment days (odds ratio=1.86, 95% CI=1.75, 1.97; model 6) and long-acting benzodiazepine treatment days (odds ratio=1.68, 95% CI=1.54, 1.83; model 6)

- Similar patterns to overdose were noted between z-drugs and benzos stratified into low dose and high dose.

TABLE 3. Odds of drug-related poisoning associated with benzodiazepine use among individuals with opioid use disorder[a]

Variable	Odds Ratio	95% CI
Model 1		
Buprenorphine	0.63	0.60, 0.66
Any benzodiazepine or Z-drug	1.81	1.73, 1.91
Model 2		
Buprenorphine	0.63	0.60, 0.67
Benzodiazepines, excluding Z-drugs	1.88	1.78, 1.98
Z-drugs	1.29	1.19, 1.39
Model 3		
Buprenorphine	0.63	0.60, 0.67
Benzodiazepines, excluding Z-drugs	1.88	1.79, 1.99
Z-drugs	1.29	1.19, 1.40
Selective serotonin reuptake inhibitors	0.95	0.90, 1.00
Model 4		
Buprenorphine (among benzodiazepine or Z-drug users)	0.64	0.60, 0.69
Model 5		
Buprenorphine (among benzodiazepine or Z-drug nonusers)	0.64	0.59, 0.69
Model 6		
Buprenorphine	0.63	0.60, 0.66
Short-acting benzodiazepines	1.86	1.75, 1.97
Long-acting benzodiazepines	1.68	1.54, 1.83
Z-drugs	1.29	1.19, 1.39
Model 7		
Buprenorphine	0.63	0.60, 0.66
Low-dose benzodiazepines	1.78	1.67, 1.88
High-dose benzodiazepines	2.22	2.03, 2.43
Z-drugs	1.29	1.19, 1.39
Model 8		
Buprenorphine	0.64	0.62, 0.67
Any benzodiazepine or Z-drug, low-dose	1.86	1.77, 1.95
Any benzodiazepine or Z-drug, high-dose	2.53	2.35, 2.73
Model 9		
Low-dose buprenorphine	0.62	0.57, 0.67
High-dose buprenorphine	0.63	0.59, 0.67
Low-dose benzodiazepines	1.78	1.68, 1.88
High-dose benzodiazepines	2.22	2.03, 2.43
Z-drugs	1.29	1.19, 1.39
Model 10		
Buprenorphine only	0.61	0.58, 0.65
Benzodiazepine or Z-drug, low-dose (plus buprenorphine)	1.11	1.00, 1.23
Benzodiazepine or Z-drug, high-dose (plus buprenorphine)	1.64	1.39, 1.93
Benzodiazepine or Z-drug, low-dose (no buprenorphine)	1.69	1.60, 1.79
Benzodiazepine or Z-drug, high-dose (no buprenorphine)	2.23	2.04, 2.45

[a] Low-dose benzodiazepines are ≤30 diazepam-equivalent milligrams daily; high-dose benzodiazepines are >30 diazepam-equivalent milligrams daily; low-dose Z-drugs are ≤30 diazepam-equivalent milligrams daily; high-dose Z-drugs are >30 diazepam-equivalent milligrams daily; low-dose buprenorphine is ≤12 mg/day; and high-dose buprenorphine is >12 mg/day.

Discussion

- Buprenorphine treatment days conferred a nearly 40% reduction in poisonings, benzodiazepine or Z-drug treatment days corresponded to a near-doubling in poisoning risk
- Individuals taking both buprenorphine and benzodiazepines or Z-drugs were at elevated risk of poisoning, they still had a lower net risk than those taking benzodiazepines or Z-drugs without buprenorphine
- Patients with opioid use disorder for whom benzodiazepine or Z-drug cessation is risky, lower doses and shorter treatment duration of sedative/hypnotics may reduce risk
- Lower risk of poisonings with long-acting benzodiazepines compared with short-acting benzodiazepines and substantially lower risk associated with Z-drugs compared with either long- or short-acting benzodiazepines
- Switching benzodiazepine users from short-acting to long-acting agents or to Z-drugs may hold promise in lowering overdose risk

Discussion

- Even though benzodiazepines and Z-drugs may increase drug-related poisonings, buprenorphine's protective effect is not eliminated by benzodiazepine or Z-drug treatment
- Dose reduction in benzos and z-drugs while maintaining buprenorphine treatment can be advantageous.

Limitations

LIMITATIONS:

- Despite active comparator and case-crossover design, we cannot exclude the possibility of residual confounding by indication.
- Unmeasured exposures, such as illicit substances and nonprescribed benzodiazepines, have commonly been noted in the opioid user population (37) and warrant further investigation
- Secular time trends in exposure and outcome may introduce confounding into case-crossover designs
- Efforts to control for temporal variation and reduce heterogeneity in observation time per person using calendar time and time from event as a covariate and restricting study subjects to a maximum of 2-year periods of observation
- limited by its focus on nonfatal drug-related poisonings as opposed to poisoning deaths

Our Discussion

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