






Better Treatments for Breathlessness in Palliative and End of Life Care

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SAFETY OF BENZODIAZEPINES AND OPIOIDS IN INTERSTITIAL LUNG DISEASE: A NATIONAL PROSPECTIVE STUDY

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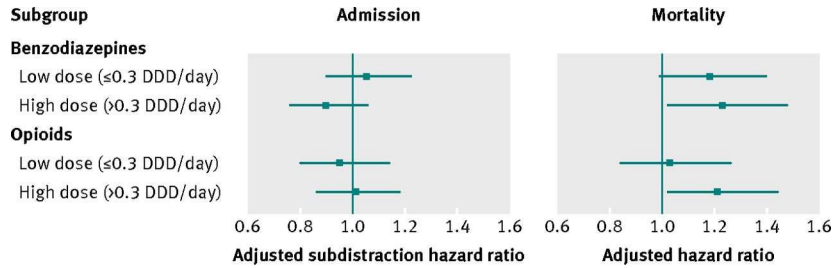
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BACKGROUND

- Chronic breathlessness is experienced by almost all patients with advanced fibrotic ILD
- High health, social and informal care costs
- National Institute Clinical Excellence IPF guidelines recommend the use of BDZ and opioids

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Adjusted hazard ratios with 95% confidence intervals.



Magnus P Ekström et al. BMJ 2014;348:bmj.g445



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Aim

To estimate the association of BDZ and opioids on the risk of admission to hospital and death in patients with respiratory failure attributable to fibrotic ILD

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Methods

- **Study Design**

- Nationwide, prospective, population-based study of patients in the Swedish National Registry of Respiratory Failure (Swedevox)

- **Subjects**

- Inclusion:

- Physician diagnosed pulmonary fibrosis patients aged 45 years old starting LTOT between Oct 2005 and Dec 2014

- All causes of pulmonary fibrosis

- Exclusion:

- Lung transplantation

- **DATABASES USED**

- National Patient Register for inpatient and outpatient care- data on co-morbidities and hospital admissions

- Swedish Prescribed Drug Register- data on all dispensed prescriptions during outpatient care

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Analysis

- Exposure during follow-up classified as unexposed and exposed at baseline

- Exposure to BDZ and opioids were coded:

- dichotomously (treated vs. non-treated),

- continuously as the baseline dose

- categorised into lower and higher dose (<30mg morphine, <15mg oxazepam)

- Effects of BDZ and opioids on rates of admission to hospital and mortality analysed using Fine-Gray and Cox regression

- Hospitalisation- First non-hospitalised day on LTOT until first hospitalisation of all causes (censoring at withdrawal of LTOT/death/study end)

- Mortality- Date of starting LTOT until date of death from all causes (censoring at withdrawal of LTOT or study end)

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Analysis

- Co-variates

Age, sex, WHO performance status, Lung function, comorbidities, number of hospitalisations prior to start of study

- Missing data imputed using chained multiple imputation with complete case sensitivity analysis

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RESULTS

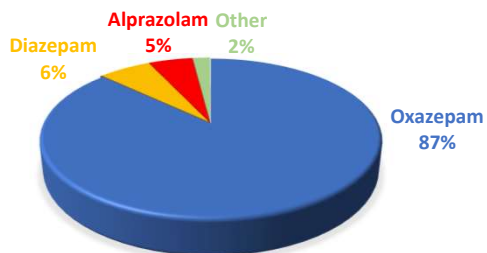
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Exposure to benzodiazepines and opioids in 1,603 patients with fibrotic ILD

	Benzodiazepine	Opioid
Benzodiazepine, n (%)		
Higher (>15mg oral oxazepam equiv/day)	65 (33.2)	27 (10.7)
Low (\leq 15mg oral oxazepam equiv/day)	131 (66.8)	32 (12.7)
Opioid, n (%)		
Higher (>30mg oral morphine equiv/day)	32 (16.8)	122 (48.4)
Low (\leq 30 mg oral morphine equiv/day)	27 (13.8)	130 (51.6)

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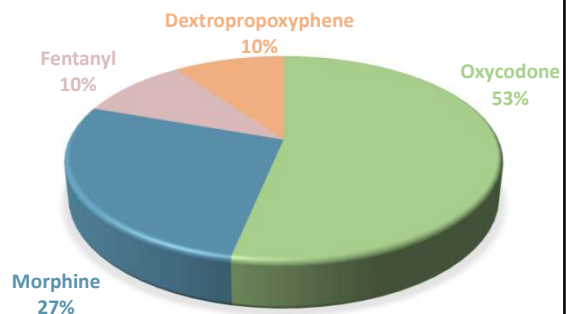
1. BDZ - 453 dispensed prescriptions included:



2. OPIOIDS - included the weak opioids (281 dispensed prescriptions)



3. STRONG OPIOIDS - (351 prescriptions dispensed)

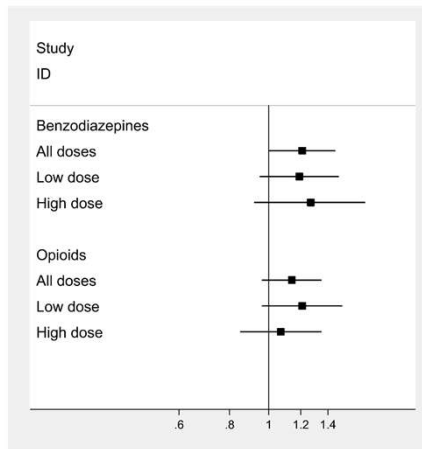


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	Benzodiazepine (n=196)	Opioid (n=252)	Unexposed (n=1,214)	P value
Age at starting LTOT, years	77.5 (8.2)	76.1 (8.9)	76.5 (8.8)	0.186
Women, n (%)	89 (45.4)	123 (48.8)	415 (34.2)	<0.001
FEV ₁ % of predicted*	66.3 (37.3)	67.0 (30.7)	71.6 (40.3)	0.106
VC % of predicted*	54.7 (32.2)	56.2 (36.6)	60.4 (34.7)	0.052
FEV ₁ /VC*	0.9 (0.3)	0.9 (0.3)	0.8 (0.4)	0.427
PaO ₂ breathing air*, kPa	6.5 (1.0)	6.6 (1.0)	6.6 (1.0)	0.441
PaCO ₂ breathing air*, kPa	5.3 (1.0)	5.3 (1.0)	5.1 (0.9)	<0.001
PaO ₂ breathing oxygen*, kPa	5.7 (0.9)	5.7 (1.0)	5.4 (1.0)	0.001
Smoking status, n (%)				
Never	61 (31.1)	66 (26.2)	338 (27.8)	0.797
Former	1 (1.0)	3 (1.2)	9 (0.797)	
Former/current	105 (53.6)	149 (59.1)	698 (57.5)	
Missing	30 (15.31)	37 (14.7)	178 (14.7)	
Body mass index (BMI)**, kg/m ²				
<18.5	10 (5.1)	12 (4.8)	35 (2.9)	0.579
18.5-24.9	107 (54.6)	143 (56.8)	707 (58.2)	
25-29.9	53 (27.0)	67 (26.6)	314 (25.9)	
≥30	26 (13.3)	30 (11.9)	158 (13.0)	
No (%) WHO performance status				
0-1	76 (38.8)	93 (36.9)	566 (46.6)	<0.001
2	54 (27.6)	70 (27.8)	350 (28.8)	
3-4	49 (25.0)	60 (23.8)	161 (13.3)	
Missing	17 (8.7)	29 (11.5)	137 (11.3)	
No (%) Cardiovascular diseases				
0	45 (23.0)	59 (23.4)	416 (34.3)	<0.001
1	3 (1.5)	3 (1.2)	58 (4.8)	
2	65 (33.2)	68 (27.0)	300 (24.7)	
≥3	83 (42.4)	122 (48.4)	440 (36.2)	
Comorbidity, n (%)				
COPD	50 (25.5)	67 (26.4)	234 (19.3)	0.010
Cancer	81 (41.3)	107 (42.5)	417 (34.4)	0.016
Depression/anxiety	43 (21.9)	33 (13.1)	37 (3.1)	<0.001
Osteoporosis	11 (5.6)	35(13.9)	47 (3.9)	<0.001
Pulmonary hypertension				
GERD	12 (6.1)	18 (7.1)	37 (3.1)	0.003

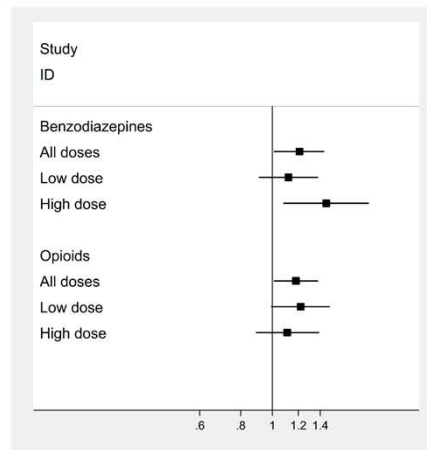
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Forest plot of BDZs and opioids admissions-adjusted hazard ratio (95%CI)



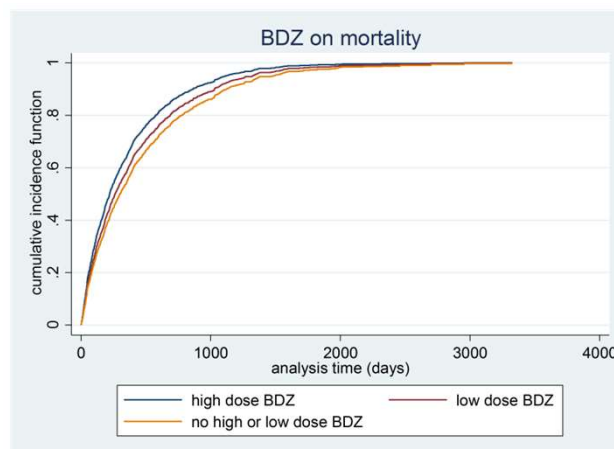
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Forest plot of BDZs, opioids and mortality-adjusted hazard ratios (95% CI)



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CIF plot of high or low dose BDZs and mortality



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	Adjusted hazard ratio (95%CI)*	
	Admission	Mortality
Covariates		
Age (years)	0.98 (0.98 to 0.99)	1.02 (1.01 to 1.03)
Male	1.05 (0.93 to 1.19)	1.41 (1.24 to 1.60)
VC % of predicted	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
FEV ₁ /VC	1.07 (0.94 to 1.22)	0.99 (0.89 to 1.11)
PaO ₂ breathing air	1.00 (0.93 to 1.07)	1.00 (0.94 to 1.07)
PaCO ₂ breathing air	0.95 (0.84 to 1.07)	0.89 (0.79 to 1.00)
PaO ₂ breathing oxygen	0.99 (0.88 to 1.10)	0.99 (0.89 to 1.11)
BMI		
<18.5	1	1
18.5-24.9	1.26 (0.86 to 1.85)	0.72 (0.52 to 0.99)
25-29.9	1.30 (0.87 to 1.92)	0.70 (0.50 to 0.97)
≥30	1.28 (0.85 to 1.93)	0.54 (0.38 to 0.77)
WHO performance status		
0-1	1	1
2	1.09 (0.95 to 1.26)	1.48 (1.29 to 1.70)
3-4	0.78 (0.65 to 0.96)	2.00 (1.67 to 2.38)
Missing	1.04 (0.86 to 1.26)	1.49 (1.22 to 1.81)
N of cardiovascular diseases		
0	1	1
1	1.11 (0.85 to 1.47)	1.03 (0.76 to 1.41)
2	1.05 (0.90 to 1.22)	0.99 (0.85 to 1.16)
≥3	1.04 (0.89 to 1.21)	1.05 (0.90 to 1.23)
Comorbidity		
Cancer	1.15 (1.02 to 1.30)	0.85 (0.75 to 0.96)
Depression/anxiety	0.79 (0.60 to 1.05)	1.08 (0.82 to 1.41)
Pulmonary hypertension	0.88 (0.68 to 1.14)	1.10 (0.86 to 1.41)
GERD	1.15 (0.85 to 1.56)	0.85 (0.62 to 1.17)
N hospitalisations within 4 years before baseline	1.05 (1.02 to 1.07)	0.99 (0.97 to 1.01)
N hospitalised days within the 91 days before baseline	1.00 (1.00 to 1.01)	1.00 (1.00 to 1.01)

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DISCUSSION

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- Use of BDZ and opioids in fibrotic ILD was low (12% and 15% respectively)
- Depressed/anxious patients were much more likely to be prescribed BDZs and opioids
- Women were more likely to be prescribed opioids/BZDs
- no clear association between BDZ use and hospital admission BUT does suggest an association with mortality
- High dose BDZs associated with mortality may be due to higher use in those already dying

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LIMITATIONS

- Limited to Swedish database
- Only oxygen dependent ILD
- Convenience cohort- not powered for safety

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CONCLUSION

- No association between opioids and increased admissions or mortality
- High dose BUT not low dose BDZs associated with increased mortality
- Opioids and low dose BDZs should be used in symptomatic management of breathlessness for ILD patients BUT with caution
- A double blind RCT needed

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Thank you

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