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Phenobarbital compared to benzodiazepines in alcohol withdrawal treatment: A register-based cohort study of subsequent benzodiazepine use, alcohol recidivism and mortality

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ABSTRACT

Background: Long-acting benzodiazepines such as chlordiazepoxide are recommended as first-line treatment for alcohol withdrawal. These drugs are known for their abuse liability and might increase alcohol consumption among problem drinkers. Phenobarbital could be an alternative treatment option, possibly with the drawback of a more pronounced acute toxicity. We evaluated if phenobarbital compared to chlordiazepoxide decreased the risk of subsequent use of benzodiazepines, alcohol recidivism and mortality.
Methods: The study was a register-based cohort study of patients admitted for alcohol withdrawal 1998–2013 and treated with either phenobarbital or chlordiazepoxide. Patients were followed for one year. We calculated hazard ratios (HR) for benzodiazepine use, alcohol recidivism and mortality associated with alcohol withdrawal treatment, while adjusting for confounders.
Results: A total of 1063 patients treated with chlordiazepoxide and 1365 patients treated with phenobarbital were included. After one year, the outcome rates per 100 person-years in the phenobarbital versus the chlordiazepoxide cohort were 9.20 vs. 5.13 for use of benzodiazepine, 37.9 vs. 37.9 for alcohol recidivism and 29 vs. 59 for mortality. Comparing phenobarbital to chlordiazepoxide treated, the HR of subsequent use of benzodiazepines was 1.56 (95%CI 1.05–2.30). Similarly, the HR for alcohol recidivism was 0.99 (95%CI 0.84–1.16). Lastly, the HR for 30-days and 1 year mortality was 0.25 (95%CI 0.08–0.78) and 0.51 (95%CI 0.31–0.86).
Conclusion: There was no decreased risk of subsequent benzodiazepine use or alcohol recidivism in patients treated with phenobarbital compared to chlordiazepoxide. Phenobarbital treatment was associated with decreased mortality, which might be confounded by somatic comorbidity among patients receiving chlordiazepoxide.

1. Introduction

Alcohol dependence is associated with a significant burden of morbidity and mortality and is estimated to affect 3.4% of the European population (Rehm et al., 2015). The alcohol withdrawal syndrome occurs when alcohol consumption is suddenly reduced or stopped after a period of high and regular consumption. The condition is potentially life-threatening and characterized by agitation, tremor and tachycardia, and, in severe cases, by seizures and altered consciousness (Perry, 2014).

For some decades, long-acting benzodiazepines, agonists of the GABA system, have been recommended in international guidelines as the first-line treatment option for alcohol withdrawal (Mayo-Smith, 1997; Mayo-Smith et al., 2004; National Institute for Health and Care Excellence, 2010).

Benzodiazepines are known for their abuse and dependence liability, which is of particular concern in patients with alcohol problems (Lader, 2011; Nutt et al., 1989). Moreover, it has been suggested that use of benzodiazepines can increase the risk of alcohol

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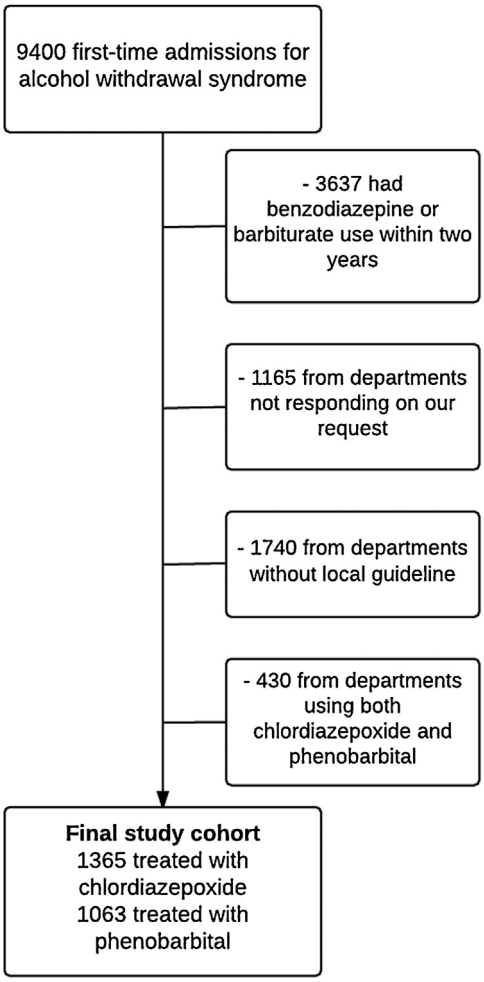

Fig. 1. Flowchart of included patients.

recidivism (Malcolm, 2003). As an example, preclinical studies have shown that modulation of the GABA(A)-benzodiazepine receptor complex plays a major role in the regulation of the brain reward system during alcohol abstinence (Malcolm, 2003). In rats, benzodiazepines have been suggested to facilitate alcohol consumption via an increase of alcohol's taste hedonic properties (Söderpalm and Hansen, 1998). In humans, studies in problem drinkers found that low-dose benzodiazepine use increased the motivation for alcohol consumption (Poulos and Zack, 2004; Zack et al., 2006).

Barbiturates might be an alternative treatment option. Like benzodiazepines, they act at the GABA(A)-receptor (Chiara et al., 2013; Perry, 2014). A few smaller studies have compared the efficacy and safety of these two treatments finding no significant difference (Borg et al., 1986; Hendey et al., 2011; Hjermø et al., 2010; Kaim, 1972; Kramp and Rafaelsen, 1978). To our knowledge, no evidence suggests that barbiturates, like benzodiazepines, should increase benzodiazepine use or facilitate alcohol consumption in problem drinkers (Lader, 2011). Nevertheless, the narrow therapeutic interval, the potentially strong respiratory suppressant effect and the lack of an antidote for barbiturates, together with solid evidence demonstrating benzodiazepines as superior to placebo in preventing seizures and being a safe treatment, have primed the status of benzodiazepines as the first-line treatment option (Amato et al., 2010; Mayo-Smith, 1997; Mayo-Smith et al., 2004).

For many years, chlordiazepoxide (a benzodiazepine) or phenobarbital (a barbiturate) have been used as standard inpatient treatment of alcohol withdrawal in Danish hospitals (Hjermø et al., 2010; Kramp and Rafaelsen, 1978), with somatic departments typically using chlordiazepoxide and psychiatric departments often using phenobarbital. Apart from the abuse concern with benzodiazepines if used in alcohol withdrawal treatment, Danish psychiatrists have argued a more efficient prevention and treatment of delirium tremens with phenobarbital (Hjermø et al., 2010; Kramp and Rafaelsen, 1978).

To further assess the safety of the two treatment options, we conducted a register-based cohort study among patients admitted for alcohol withdrawal for the first time in Danish hospitals 1998–2013, evaluating if phenobarbital compared to chlordiazepoxide treatment decreased the risk of subsequent use of benzodiazepines, alcohol recidivism and overall mortality during one year of follow-up.

2. Methods

In this register-based cohort study, we included patients admitted for the first time for the treatment of alcohol withdrawal during the years 1998–2013. Patients were followed for one year for use of benzodiazepines, readmission with heavy alcohol use (alcohol recidivism) and mortality. By comparing patients admitted to departments using phenobarbital in the treatment of alcohol withdrawal to patients admitted to departments using chlordiazepoxide, we estimated whether one or the other preference was associated with subsequent use of benzodiazepines, risk of readmission with heavy alcohol use (alcohol recidivism) and mortality.

2.1. Data sources

We obtained data from four nationwide registries: The Danish National Patient Register (Lynge et al., 2011), The Danish Psychiatric Central Research Register (Mors et al., 2011), The Danish National Prescription Registry (Kildemoes et al., 2011) and The Danish Civil Registration System (Pedersen, 2011). The registries are described in detail in Supplementary material A. Virtually all medical care in Denmark is furnished by the national health authorities, whereby these data resources allow true population-based studies covering all inhabitants of Denmark.

The data sources was linked by the personal identification number, a unique identifier assigned to all Danish residents since 1968 that encodes sex and date of birth (Sortso et al., 2011). All linkage was performed within Statens Serum Institute.

2.2. Setting

In Denmark, most departments undertaking alcohol withdrawal treatment have a local guideline dictating the observation regime and medical treatment of patients. According to local agreements, inpatient treatment of alcohol withdrawal is generally performed on either somatic or psychiatric departments. Exceptions apply to patients with severe somatic comorbidity such as unconsciousness, heart or respiratory failure in which case treatment will take place in somatic departments only. Apart from inpatient alcohol withdrawal treatment, all other treatment of alcohol use disorders is undertaken in specialized alcohol outpatient units, completely separated from Danish hospitals (Toftdahl et al., 2015).

We contacted all Danish internal medicine (non-specialized or gastroenterological) and non-specialized psychiatric departments offering acute care service and asked them whether they a) had provided inpatient alcohol withdrawal treatment during 1998–2013, b) had a local guideline on the treatment of alcohol withdrawal and c) if and when phenobarbital or chlordiazepoxide was used according to the guideline. The final list of hospital departments

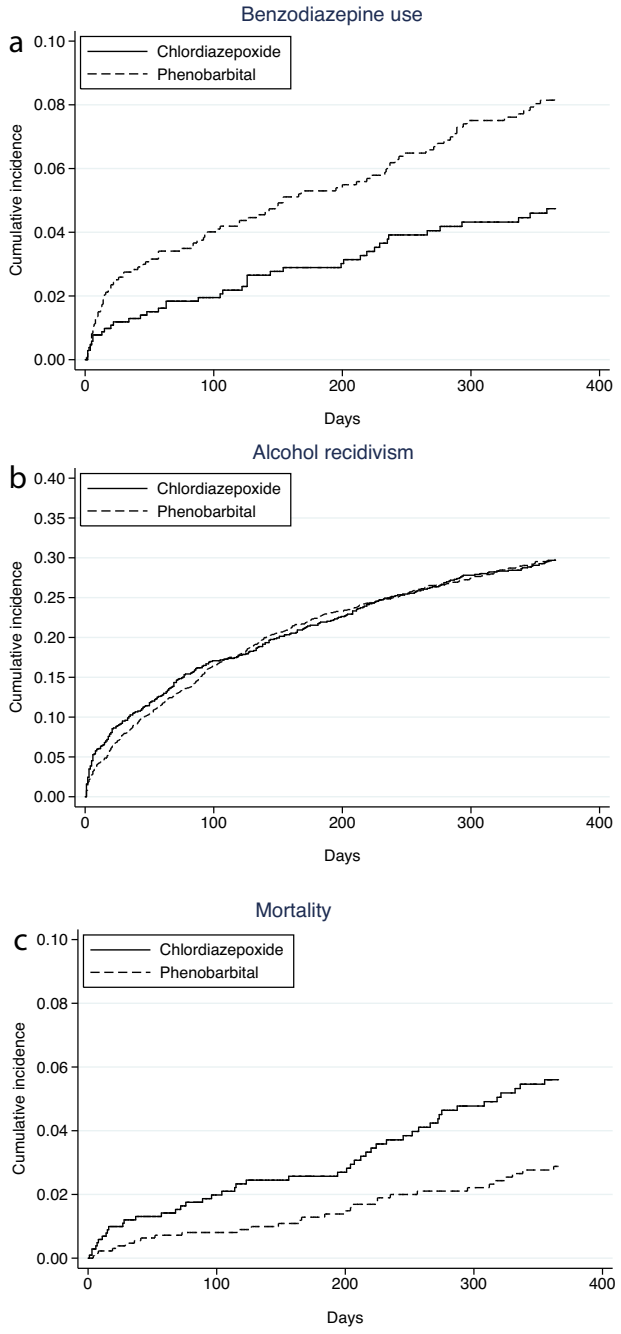

Fig. 2. Cumulative incidence of benzodiazepine use, alcohol recidivism and mortality according to alcohol withdrawal treatment. Kaplan–Meier estimate of benzodiazepine use (2a), alcohol recidivism (2b) and mortality (2c) according to alcohol withdrawal treatment.

and calendar-periods included in the analysis is found in Supplementary material B.

2.3. Cohorts

We included patients aged 18–60 with a first-time admission with alcohol withdrawal without delirium tremens (ICD-10: F103) in the period 1 January, 1998–31 December, 2013. Patients with delirium tremens were not included in the study since their condition might require transfer to an intensive care unit or change in medical treatment (Cavallazzi et al., 2012; Hill and Williams, 1993). Subjects entered the chlordiazepoxide cohort if they were admitted to a hospital using chlordiazepoxide on the admission date and similarly with phenobarbital.

We excluded individuals who had filled a prescription for any benzodiazepine (ATC, N05BA and N05CD) or barbiturate (ATC, N03AA) within two years prior to the alcohol withdrawal admission. Subjects were followed 12 months from the date of admission.

2.4. Validation

The assumption that patients admitted with alcohol withdrawal were treated according to a local clinical guideline is crucial to the analysis. To validate this assumption, we extracted a complete dataset of all first-time admissions with alcohol withdrawal in Denmark 1998–2013 and randomly selected 200 admissions. For these admissions, we contacted the respective department to retrieve information on the treatment provided for alcohol withdrawal.

2.5. Outcomes

Patients were followed for one year after their admission with regard to the following three outcomes:

1) Use of benzodiazepines, defined as filling a prescription of any benzodiazepine (ATC, N05BA and N05CD) apart from the long-acting benzodiazepines chlordiazepoxide and diazepam (ATC, N05BA02 and N05BA01), which might be prescribed for alcohol withdrawal by a general practitioner.
2) Alcohol recidivism, defined as any hospital contact with a diagnosis indicating heavy alcohol use (alcohol intoxication: F100, harmful use of alcohol: F101, active alcohol addiction: F1024, alcohol withdrawal: F103 and F104).
3) Mortality, both within 30 days (short-term) and one year (long-term).

2.6. Analysis

We compared treatment with phenobarbital to treatment with chlordiazepoxide in relation to subsequent benzodiazepine use, alcohol recidivism and all-cause mortality occurring up to one year after the admission for alcohol withdrawal using cox regression and adjusting for potential confounders. These confounders included the year of index admission, age, sex, and municipality of residence as a marker of socioeconomic classification (Cevea, 2015). Further, we adjusted for somatic comorbidity by means of the Charlson comorbidity index score and smoking-related diagnoses (ICD-8: 491, 492; ICD-10: J44 and F17; Thygesen et al., 2011b). To take severity of alcohol problems into account, we adjusted for the presence of alcohol diagnoses (ICD-8: 291 and 303; ICD-10: F100, F101, F1024) in relation to previous hospital contacts including inpatient, outpatient and emergency contacts, use of drugs for maintenance of abstinence in alcohol dependence (ATC: N07BB) and for diagnoses indicating polydrug abuse (ICD-8: 304, ICD-10: F11-19; Beresford et al., 2014). Finally, we adjusted for psychiatric comorbidity in terms of diagnoses and filled prescriptions: Schizophrenia and related disorders (ICD-8: 295, 298; ICD-10: F20-29), mood disorders (ICD-8: 296, 790; ICD-10: F30-39), anxiety and stress-related disorders (ICD-8: 300; ICD-10: F40-49), personality disorders (ICD-8: 301; ICD-10: F60-69), use of antidepressants (ATC: N06A), neuroleptics (ATC: N05A) and lithium (ATC: N05AN; Boschloo et al., 2012; Dawson et al., 2005; Hjorthøj et al., 2015; Lader, 2011). Comorbidity was assessed as lifetime comorbidity whereas drug use was assessed during the two years before the first admission with alcohol withdrawal.

Apart from the main analysis, we conducted analyses stratified by (i) age, (ii) sex, (iii) social class of residence and (iv) exclusion of patients with a previous alcohol diagnosis.

Lastly, as a sensitivity analysis, we redid all analyses using high dimensional propensity scores to adjust for confounding (Schneeweiss et al., 2011). In the propensity score model, we included age, sex, and year of inclusion alongside the 100 most prevalent diagnoses (e.g., E10, type 1 diabetes) as well as the 100 most prevalent drug classes (e.g., A02BC, proton pump inhibitors) and performed analyses both by adjusting for the resulting propensity score as a continuous variable and by stratification by propensity score deciles.

2.7. Other

All analyses were carried out in Stata, Release 14.0. All patient data were anonymized. Register-based studies do not require ethical approval in Denmark (Thygesen et al., 2011a). The Danish Data Protection Agency approved the study (reference no. 2008-58-0035). The National Board of Health gave permission to obtain medical charts on the random sample for the validation study (case number: 3-3013-498/1).

3. Results

3.1. Description of the cohort

A total of 9,400 patients experienced a first-time admission for alcohol withdrawal in Denmark 1998–2013 to the included departments. After exclusions, 1,063 patients treated with chlordiazepoxide and 1365 patients treated with phenobarbital were left for inclusion in the study (Fig. 1).

The majority of patients were men and the median age was 47 and 45 in the chlordiazepoxide and the phenobarbital cohort, respectively (Table 1). The alcohol withdrawal treatment was highly correlated with type of department, i.e., nearly all patients in the phenobarbital cohort were treated on psychiatric departments. As a result, the chlordiazepoxide cohort had a higher degree of somatic comorbidity than the phenobarbital cohort, whereas the phenobarbital cohort had more psychiatric comorbidity than the chlordiazepoxide cohort. The phenobarbital cohort had the longest duration of admission; 49% in the phenobarbital cohort were admitted at least three days compared to 38% in the chlordiazepoxide cohort.

Patient characteristics pointed to a slightly higher prevalence of alcoholism history in the phenobarbital cohort. The cohorts were similar regarding previous alcohol diagnoses (43% and 44%) and polydrug abuse (4.6% and 5.8%), while previous treatment with an alcohol abstinence drug was more prevalent in the phenobarbital cohort, 376 (28%), than in the chlordiazepoxide cohort, 183 (17%).

Table 1
Demographic and medical characteristics of patients admitted for alcohol withdrawal for the first time 1998–2013. Values are numbers (and percentages) unless otherwise indicate.

	Chlordiazepoxide	Phenobarbital
Number	1063	1365
Age, median (inter quartile range)	47 (40–53)	45 (39–51)
Male sex	849 (80)	1028 (75)
Social class		
High	202 (19)	401 (29)
Medium-low	820 (77)	928 (68)
Missing	41 (3.8)	36 (2.6)
Type of department		
Somatic	1037 (98)	129 (9.5)
Psychiatric	26 (2)	1236 (91)
Duration of admission, days		
median (inter quartile range)	2 (2–3)	2 (2–4)
1	167 (16)	109 (8.0)
2	488 (46)	592 (43)
3–9	339 (32)	544 (40)
≥10	69 (6.5)	120 (8.8)
Charlson comorbidity index, score		
0	730 (69)	1056 (78)
1	173 (16)	186 (14)
≥2	160 (15)	123 (9.0)
Smoking diagnoses	14 (1.3)	18 (1.3)
Previous alcohol diagnosis	457 (43)	594 (44)
Polydrug abuse	49 (4.6)	79 (5.8)
Schizophrenia and related disorders	41 (3.9)	103 (7.9)
Mood disorders	56 (5.3)	124 (9.1)
Anxiety and stress-related disorders	57 (5.4)	119 (8.7)
Personality disorders	23 (2.2)	63 (4.6)
Drug use		
Antidepressants	282 (27)	526 (39)
Neuroleptics	129 (12)	261 (19)
Alcohol abstinence drugs	183 (17)	376 (28)
Lithium	< 5 (< 0.5)	20 (1.5)

3.2. Validation of medical treatment according to information on local guideline

Of the 200 randomly selected admissions with alcohol withdrawal from the nationwide registry, we were able to access information from 157 medical charts (43 were either erased or had disappeared). Of those 157 patients, 147 (94%) received treatment according to the local guideline. The remaining 10 (6.4%) patients were either not treated for alcohol withdrawal or treated with a different drug.

3.3. Outcomes

The incidence rate of use of benzodiazepines after one year was 9.20 and 5.13 per 100 person-years in the phenobarbital and the chlordiazepoxide cohort (Table 2). Treatment with phenobarbital was, compared to chlordiazepoxide, associated with an increased risk of use of benzodiazepines; adjusted HR 1.56 (95%CI 1.05–2.30; Table 2 and Fig. 2a). In stratified analyses, this association was statistically significant in unadjusted analyses of men, patients ≥45 years, in medium-lower social class of residence and in patients without a previous alcohol diagnosis. Adjustment for confounders attenuated these associations. For example, in the stratified analysis of patients without a prior alcohol diagnosis were the unadjusted and adjusted HR 1.71 (1.03–2.85) and 1.45 (0.83–2.52).

The incidence rate of alcohol recidivism after one year was 37.9 per 100 person-years in both the phenobarbital and the chlordiazepoxide cohort (Table 3). Analyses indicated no association between phenobarbital treatment and risk of alcohol recidivism, with an overall adjusted HR of 0.99 (95%CI 0.84–1.16), see Table 3 and Fig. 2b.

When assessing short-term mortality (30 days), the incidence rate was 1.20 and 0.46 per 100 person-years in the phenobarbital and the chlordiazepoxide cohort (Table 4) whereas the incidence rate after one year was 29 and 59 per 100 person-years (Table 5). Phenobarbital use was associated with a decreased mortality risk compared to chlordiazepoxide treatment with an adjusted HR of mortality after 30 days and after one year of 0.25 (95%CI 0.08–0.78) and 0.51 (95%CI 0.31–0.86) respectively (Table 4 and 5 and Fig. 2c). This association was also statistically significant in patients more than 45 years and in those with high social class of residence in the stratified analyses.

Sensitivity analyses using high-dimension propensity scores with the 100 most prevalent co-morbid conditions and 100 most

Table 2
Risk of subsequent use of benzodiazepines according to alcohol withdrawal treatment. Hazard ratios (95% confidence intervals) for use of benzodiazepines defined as filling a prescription of a benzodiazepine within one year according to alcohol withdrawal treatment.

	Chlordiazepoxide		Phenobarbital			
	Person-years	Events	Person-years	Events	Crude HR[a]	Adjusted HR[a]
All	799	41	1022	94	1.78 (1.23–2.57)	1.56 (1.05–2.30)
Men	640	32	767	65	1.68 (1.10–2.57)	1.44 (0.91–2.27)
Women	160	9	255	29	2.00 (0.95–4.23)	1.93 (0.88–4.24)
Age <45 years	314	17	475	40	1.55 (0.88–2.73)	1.19 (0.65–2.18)
Age ≥45 years	485	24	547	54	1.99 (1.23–3.22)	1.88 (1.12–3.14)
Social class						
High	143	10	311	22	1.02 (0.48–2.15)	1.03 (0.46–2.33)
Medium-low	621	30	681	71	2.13 (1.39–3.26)	1.79 (1.13–2.82)
No previous alcohol diagnosis	384	22	456	45	1.71 (1.03–2.85)	1.45 (0.83–2.52)

[a] HR are estimated as phenobarbital treated compared to chlordiazepoxid treated.

Table 3
Risk of alcohol recidivism according to alcohol withdrawal treatment. Hazard ratios (95% confidence intervals) for alcohol recidivism within one year according to alcohol withdrawal treatment.

	Chlordiazepoxide		Phenobarbital			
	Person-years	Events	Person-years	Events	Crude HR[a]	Adjusted HR[a]
All	799	303	1022	387	0.99 (0.86–1.16)	0.99 (0.84–1.16)
Men	640	239	767	294	1.02 (0.86–1.21)	1.04 (0.86–1.25)
Women	160	64	255	93	0.90 (0.66–1.24)	0.86 (0.61–1.22)
Age <45 years	314	122	475	164	1.04 (0.83–1.30)	1.03 (0.80–1.32)
Age ≥45 years	485	181	547	193	0.95 (0.77–1.16)	0.96 (0.77–1.20)
Social class						
High	143	61	311	111	0.85 (0.62–1.16)	0.88 (0.63–1.25)
Medium-low	321	236	681	268	1.03 (0.86–1.22)	1.00 (0.82–1.21)
No previous alcohol diagnosis	384	104	456	121	0.98 (0.75–1.27)	1.05 (0.78–1.40)

[a] HR are estimated as phenobarbital treated compared to chlordiazepoxid treated.

Table 4
Risk of short-term mortality according to alcohol withdrawal treatment. Hazard ratios (95% confidence intervals) for mortality the first 30 days according to alcohol withdrawal treatment.

	Chlordiazepoxide		Phenobarbital			
	Person-years	Events	Person-years	Events	Crude HR[a]	Adjusted HR[a]
All	83	12	109	6	0.38 (0.14–1.02)	0.25 (0.08–0.78)
Men	67	9	82	5	0.45 (0.15–1.36)	0.35 (0.10–1.23)
Women	16	<5	27	<5	0.21 (0.02–1.99)	NA
Age <45 years	33	<5	51	<5	0.64 (0.09–4.54)	NA
Age ≥45 years	51	10	58	<5	0.35 (0.11–1.12)	0.22 (0.05–0.91)
Social class						
High	15	5	32	<5	0.10 (0.01–0.83)	0.09 (0.01–0.88)
Medium-low	65	7	73	5	0.63 (0.20–1.99)	0.39 (0.10–1.54)
No previous alcohol diagnosis	38	<5	46	<5	0.56 (0.09–3.32)	0.19 (0.01–2.41)

[a] HR are estimated as phenobarbital treated compared to chlordiazepoxid treated.

prescribed medications gave results similar to those of the main analyses (data not shown).

4. Discussion

In this observational cohort study among patients with a first-time admission with alcohol withdrawal treated with either chlordiazepoxide or phenobarbital, we found no decreased risk of subsequent benzodiazepine use or alcohol recidivism in patients treated with phenobarbital compared to chlordiazepoxide. We did find a decreased mortality risk with phenobarbital compared to chlordiazepoxide treatment, which is likely to be confounded by increased somatic comorbidity among the chlordiazepoxide compared to the phenobarbital treated.

The main strengths of our study are the use of nationwide data resources covering the entire Danish population, complete follow-up and high validity of information on outcomes (use of benzodiazepines, alcohol recidivism and mortality) and potential confounders including somatic and psychiatric comorbidity and drug use (Kildemoes et al., 2011; Lynge et al., 2011; Thygesen et al., 2011a,b). Furthermore, our validation showed high validity of the exposure classification obtained from local departments.

The main limitation was the strong correlation between the alcohol withdrawal treatment provided and the type of department (somatic or psychiatric), intertwining the influence of treatment

Table 5
Risk of long-term mortality according to alcohol withdrawal treatment. Hazard ratios (95% confidence intervals) for mortality within one year according to alcohol withdrawal treatment.

	Chlordiazepoxide		Phenobarbital			
	Person-years	Events	Person-years	Events	Crude HR[a]	Adjusted HR[a]
All	799	47	1022	30	0.50 (0.32–0.79)	0.51 (0.31–0.86)
Men	640	43	767	22	0.43 (0.25–0.71)	0.45 (0.25–0.79)
Women	160	<5	255	8	1.26 (0.38–4.19)	0.85 (0.20–3.55)
Age <45 years	314	7	475	10	0.94 (0.36–2.48)	0.86 (0.30–2.44)
Age ≥45 years	485	40	547	20	0.44 (0.26–0.76)	0.41 (0.22–0.76)
Social class						
High	143	14	311	8	0.27 (0.11–0.63)	0.15 (0.05–0.43)
Medium-low	621	33	681	22	0.61 (0.35–1.04)	0.66 (0.36–1.22)
No previous alcohol diagnosis	384	19	456	9	0.40 (0.18–0.88)	0.40 (0.16–1.02)

[a] HR are estimated as phenobarbital treated compared to chlordiazepoxid treated.

with chlordiazepoxide or phenobarbital and department type, which will be discussed in more detailed below. Another limitation is the lack of information on benzodiazepines provided on the black market. Lastly, the use of an alcohol-related hospital contact as the only marker for alcohol recidivism could have been improved had we had access to data on for example primary care contacts.

Contrary to the hypothesis that benzodiazepines used in inpatient alcohol withdrawal treatment increases the risk of subsequent benzodiazepine use, we found an increased risk associated with phenobarbital compared to chlordiazepoxide treatment (Lader, 2011; Nutt et al., 1989). This association might be explained by unmeasured confounding stemming from unmeasured psychiatric comorbidity among patients admitted to psychiatric departments (the phenobarbital treated). Benzodiazepines are used for alleviating anxiety in a range of psychiatric diseases such as anxiety disorders, depression and psychotic disorders (Lader, 2011). Although we did adjust for these diagnoses and associated use of medicine, psychiatric diagnoses are likely underreported in the registries. The attenuation of this association upon adjustment for confounders supports this explanation. Also, we could not find evidence in the literature suggesting that phenobarbital treatment in particular lead to benzodiazepine use (Lader, 2011). It is important to note that our study included inpatient treatment only and thus does not address whether benzodiazepines used in outpatient alcohol withdrawal treatment increase the risk of benzodiazepine use compared to other drugs.

To our knowledge, no previous studies have compared the risk of alcohol recidivism after alcohol withdrawal treatment between benzodiazepines or barbiturates (Borg et al., 1986; Hendey et al., 2011; Hjermø et al., 2010; Kaim, 1972; Kramp and Rafaelsen, 1978). We found a high cumulative incidence of alcohol recidivism (about 30% after one year, see Fig. 2b) with no apparent association to the alcohol withdrawal treatment provided. Whether barbiturates, as benzodiazepines, increase the motivation for alcohol intake is unknown (Poulos and Zack, 2004; Söderpalm and Hansen, 1998). However, there is also no evidence of barbiturates having alcohol abstinence supporting properties (National Institute for Health and Clinical Excellence, 2011). Therefore, future studies examining the impact of drugs with alcohol abstinence supporting properties e.g., gabapentin and baclofen and their effect on the rate of alcohol recidivism after alcohol withdrawal are warranted (Addolorato et al., 2006; Myrick et al., 2010; National Institute for Health and Clinical Excellence, 2011).

Regarding mortality, we found a decreased risk of death within 30 days and after one year associated with phenobarbital compared to chlordiazepoxide treatment. Unmeasured somatic comorbidity is likely to be associated with admission on a somatic department compared to a psychiatric department, thus leading to a false association between chlordiazepoxide treatment and increased mortality. Undiagnosed disease is especially prevalent in patients with alcohol problems (Allhoff et al., 2001; Søgaard Nielsen et al., 1999). Previous studies, although small, observed no difference in mortality between barbiturate and benzodiazepine treatment and a Cochrane review of benzodiazepines in alcohol withdrawal treatment found no increased mortality risk associated with benzodiazepine treatment compared to placebo (Amato et al., 2010; Borg et al., 1986; Hendey et al., 2011; Hjermø et al., 2010; Kaim, 1972; Kramp and Rafaelsen, 1978). We, therefore, interpret the association of chlordiazepoxide with increased mortality compared to phenobarbital treatment as confounded by unmeasured somatic comorbidity.

In conclusion, this observational study of patients admitted for alcohol withdrawal for the first time suggests no decreased risk of subsequent benzodiazepine use or alcohol recidivism associated with phenobarbital compared to chlordiazepoxide treatment. Phenobarbital treatment was associated with decreased risk of mortality, which is likely to be explained by residual confounding by somatic comorbidity.

Role of funding

Nothing declared.

Conflict of interest

The authors declare that there are no conflicts of interest.

Contributors

Conception and design: all authors, collection of data: GA and KGM, data analysis: AP and JH, writing the manuscript: GA and AP, critically revising the manuscript: all authors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2016.02.016.

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