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ORIGINAL COMMUNICATION

Associations between co-medications and survival in ALS—a cohort study from Austria

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Abstract The aim of this study was to evaluate associations between co-medications and survival of patients with amyotrophic lateral sclerosis (ALS). Prescription databases of the Austrian sickness funds covering more than 5 million people formed the basis of this study. ALS cases were deduced from riluzole prescriptions during the study period from January 1, 2008, to June 30, 2012. After adjusting for potential confounding factors associations between co-medications and ALS survival were analyzed. A total of 522 ALS patients could be identified during the study period. Sixteen of the most frequently used drug classes were considered for the survival analyses of which two were nominally associated with ALS survival. Proton pump inhibitors (PPI) were negatively correlated with survival (HR 1.34, 95 % CI 1.04–1.73) and centrally acting muscle relaxants (CAMR) showed a positive association (HR 0.56, 95 % CI 0.39–0.81). After correcting for multiple testing, the association between CAMR and ALS survival remained significant ($p = 0.03$). In conclusion, this is the first study systematically evaluating potential associations between commonly used drugs and ALS disease course. We report a positive association between CAMR use and survival, which may have derived from an indication bias representing the better prognosis of the upper motor neuron predominant disease variant. However, this is still interesting since it demonstrates the sensitivity of our study design to pick up survival effects. The use of large prescription registries could thus provide a valuable basis to find clues to underlying pathophysiological mechanisms in ALS.

Keywords Amyotrophic lateral sclerosis · Cohort study · Co-medication · Muscle relaxants, central · Proton pump inhibitors

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Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by a predominant loss of motor neurons. Growing evidence suggests that the disease is, in fact, a multisystem disorder affecting many functional systems. Clinical features and disease progression are highly heterogeneous among patients and an increasing number of disease-modifying factors have been reported in the literature [1].

There is an intensive search for novel therapies in ALS. Clinical trials based on animal models have failed to show efficacy in human beings. Thus, more accurate models or innovative search strategies for novel therapies are needed [2]. One conceivable way to identify molecular targets amenable for therapeutic intervention in ALS might be to investigate the potential impact of existing, licensed drugs on survival in affected patients [3]. An obvious first step in such an analysis could be to retrospectively screen

available repositories on the impact of drugs used by ALS patients on their survival.

In the current cohort study, we pursued this idea and evaluated possible associations between co-medications and mortality in patients with ALS. For this purpose, we took advantage of a large national Austrian prescription database, which allowed us to ascertain ALS patients by their prescription of riluzole.

Methods

Data source

The data of this retrospective cohort study are based on patient registries of the nine regional sickness funds (Gebietskrankenkassen, GKK) covering all nine provinces of Austria. Together the registries capture 76 % of the total Austrian population and can be taken as representative for the whole country [4]. They comprise each insurant's prescription data, hospital discharge diagnoses and demographic details but contain no clinical information. They are primarily maintained for administrative purposes and the reimbursement of pharmacy claims. In Austria, prescribed drugs are exclusively dispensed by pharmacies and the pharmacy dispensing records are submitted electronically to the Austrian sickness funds. The completeness of the submitted data is a prerequisite for the reimbursement, which guarantees their accuracy. These data include personal details of the insurants (name, sex, date of birth, residence and the social security number) and of the prescribed drugs (including the Anatomical Therapeutic Chemical code and a nation-wide identifying number for the pharmaceutical products).

To identify patients with ALS, we searched the registries for all adult patients ($\geq$20 years of age) who were prescribed riluzole during the study period from January 1, 2008, to June 30, 2012. Since ALS is the only diagnosis for which riluzole is approved for and for which the costs are remunerated by the sickness funds, the diagnosis of ALS could be reliably deduced from riluzole prescriptions. About 60 % of ALS patients use riluzole in Austria [5]. Thus, our methodology enabled us to capture a great part of the total ALS population in Austria.

After identifying ALS patients, the following demographic parameters were extracted from the GKK database: gender, date of birth, time of death, packages of all prescriptions with the dates of the first and last dispensing for each drug class and the total duration of all inpatient stays with the dates of the first and last hospitalization. The time point of ALS diagnosis was assumed to be either (1) the day of the first riluzole prescription, or (2) the day of the first hospital discharge during the study period (provided the main discharge diagnosis was ICD-10 G12.2 for ALS), whichever was earlier. After data extraction, individual patients were pseudonymized with a thirty-two digit number before being analyzed further.

Exposure to co-medications

All dispensed drugs other than riluzole ("co-medications") were categorized by the Anatomical Therapeutic Chemical (ATC) codes, a system developed by the World Health Organization classifying all available medicines into groups according to the organ or system on which they act (http://www.whocc.no/atc/structure_and_principles/). The system is based on five different levels of classification defining the therapeutic, pharmacological and chemical properties of the drugs. In our study, we classified drugs up to the fourth level, which allowed the differentiation between drug classes but not between drugs of the same class. Drug exposure was defined by the prescription of at least two packages of a drug class with the start of therapy before ALS diagnosis or in the first 90 days after diagnosis. This classified patients into a categorical variable with drug users and drug-naive patients. Patients starting their therapy after the first 90 days were excluded from this analysis. The purpose of this time limit was to reduce the selection bias towards a longer survival introduced by patients starting their co-medication long after diagnosis (i.e., the immortal time bias) [6, 7]. To achieve statistically meaningful results, we restricted our analysis to drug classes used by at least ten percent of the total ALS cohort. Prescriptions during the study period but prior to the diagnosis were included since the mechanisms underlying the pathophysiology of ALS are supposed to begin long before diagnosis [8]. Any drug use before ALS diagnosis could thus have influenced ALS survival if any disease modifying effect was present.

Comorbidities of ALS patients

Three scores of comorbidity, as validated predictors of mortality, were considered as potential confounding factors [9, 10]. The original and the revised Chronic Disease Scores (CDS-1 and CDS-2, respectively), were calculated as previously described [11, 12]. The number of distinct drug classes prescribed to an individual person was calculated as another validated comorbidity measure predicting mortality [9]. ATC coded co-medications at the time of diagnosis were used to calculate the scores. Drugs that became available after the development of the CDS were attributed to the most appropriate category.

Statistical analysis

All demographic variables were analyzed using descriptive statistics including median, interquartile range (IQR) and 95 % confidence intervals (CI). Comparisons between medians were made with the Mann–Whitney *U* test.

The Cox proportional hazard regression analysis was used to evaluate the association between drug classes and ALS survival. Drug exposure was defined as a categorical variable (0 = "no drug", 1 = "drug user"). A time-dependent covariate for the drug exposure was used to avoid misclassification of drug users' survival time before the first prescription as the exposed follow-up time [6]. Kaplan–Meier analyses were additionally performed to calculate survival times.

For all Cox proportional hazard regression analyses age at diagnosis, the different comorbidity scores, the total duration of hospitalizations and the duration of riluzole use expressed by the therapy ratio [5] were considered as potential confounding factors. Gender was used as a stratification variable to accommodate the models for different baseline hazards. We applied the Bonferroni correction to account for multiple testing. Data processing was performed using the statistical package SPSS v20 (IBM Corp. Released 2011).

Results

Out of 5,194,837 individuals recorded in the national insurance database, a total of 522 individual patients with ALS were identified by their prescription of riluzole during the study period of four and a half years. Two hundred and seventy-nine (53.4 %) of those were men and 243 (46.6 %) women with a median age at diagnosis of 65.6 years (IQR 56.8–72.3). Two hundred and eighty-four patients (54.4 %) died during the observation period resulting in a median survival time of 676 days (95 % CI 589–763) (Table 1). These epidemiological figures match the parameters of other clinically well-characterized ALS cohorts [13, 14].

The majority of the ALS cohort (97.5 %) was prescribed other drugs than riluzole at some time during the observation period. On average, each patient received medications falling into nine different drug classes according to the fourth level of the ATC codes (median, IQR 5–13). Sixteen drug classes were used by at least ten percent of the total ALS cohort (Table 2). We evaluated whether exposure to any of these sixteen drug classes altered the patients' chances of survival. Age at diagnosis, the total duration of hospitalizations during the study period and the therapy ratio for riluzole were independently associated with survival and thus have been considered as co-factors, whereas gender was used as a stratification variable (Table 3). The comorbidity scores lacked an independent association with survival and thus were not included in the final calculations. Two of these sixteen drug classes were associated with survival before correction for multiple testing. Proton pump inhibitors (PPI) were negatively correlated with survival (HR 1.34, 95 % CI 1.04–1.73) whereas centrally acting muscle relaxants (CAMR) were associated with a higher chance of survival (HR 0.56, 95 % CI 0.39–0.81) (Table 2). The corresponding median survival times were 534 days in patients using PPI and 1002 days in patients using CAMR (Fig. 1). However, after Bonferroni correction just the association between CAMR and ALS survival remained significant ($p = 0.03$), while there was no association with the use of PPI anymore.

Discussion

This is the first large study using an administrative database to systematically investigate associations between commonly used drugs and survival in ALS. The diagnosis of ALS in 522 individuals was based on their recorded prescription of riluzole though for the time point of diagnosis, a prior hospital discharge diagnosis of ALS was considered. Although the patients' diagnoses could not be individually confirmed by reviewing medical charts, there can be little doubt on the accuracy of the diagnosis on the whole because ALS is the only indication for which riluzole is approved and remunerated for by the Austrian sickness funds. Moreover, all key demographic parameters such as age at diagnosis, gender distribution and survival times correspond well to typical ALS cohorts as reported in other studies [13, 14].

A big advantage of the employed automated database with regards to the current question was that the capture of co-medications was not influenced by a recall bias and can thus be regarded as comprehensive. The database approach also allowed us to reliably identify a number of confounding variables. We corrected for gender, age at diagnosis, duration of hospitalizations during the study period, various measures of comorbidity and the duration of riluzole use as expressed by the therapy ratio [5]. Finally, the inclusion of the sixteen different ATC drug classes was only determined by their frequency of usage and not by any prior candidate status of these medicines. Our inclusion of drugs can, therefore, be considered as unbiased by selection as it should be demanded in a hypothesis generating study.

We describe a positive correlation between the use of centrally acting muscle relaxants and ALS survival with a 44 % reduction of mortality risk in drug-using patients. This finding might well have been the result of an

Table 1 Demographic characteristics of the total ALS cohort and of users of CAMR and PPI

Basic demographic details	Overall ALS cohort	CAMR user	PPI user
Number (%)	522 (100)	112 (21.5)	284 (54.4)
Men (%)	279 (53.4)	46 (41.1)	138 (48.6)
Women (%)	243 (46.6)	66 (58.9)	146 (51.4)
Median age at diagnosis, years, (IQR)	65.6 (56.8–72.3)	63.9 (53.0–70.6)	67.0 (59.5–73.1)
Median duration of riluzole use, days, (IQR)	308 (140–588)	448 (224–721)	308 (168–532)
Median days hospitalized, (IQR)	10 (0–25)	10 (0–24)	12 (0–31)
Deceased patients (%)	284 (54.4)	50 (44.6)	170 (59.9)
Median survival time, days, (95 % CI)	676 (589–763)	870 (598–1142)	582 (506–658)
Comorbidity scores			
Median number of drugs, (IQR)	4 (2–6)	4 (2–8)	5 (3–8)
Median CDS-1, (IQR)	1 (0–4)	1 (0–4)	3 (1–6)
Median CDS-2, (IQR)	3308 (1733–5383)	3161 (1629–5564)	4609 (2761–6808)
Details of co-medications			
Number of patients starting therapy before or with ALS diagnosis (%)	–	68 (60.7)	201 (70.8)
Median time of therapy start in relation to ALS diagnosis, days, (IQR)	–	0 (−344 to 80)	−204 (−797 to 0)
Median duration of therapy, days, (IQR)	–	493 (222–1029)	607 (261–1159)

CDS-1 Original Chronic Disease Score, *CDS-2* Revised Chronic Disease Score, *IQR* Interquartile range

ALS patients were considered users of the respective drugs if they were prescribed at least two packages of the medication. Patients starting their therapy later than 90 days after diagnosis were excluded. Days hospitalized refer to days spent in hospitals as in-patients during the study period

indication bias, since CAMR are mainly prescribed to ALS patients with spasticity due to upper motor neuron lesion. The observed beneficial effect, therefore, most likely represents the better prognosis of the upper motor neuron predominant disease variant [15, 16]. This is nevertheless interesting since it confirms the sensitivity of our methodology using automated prescription databases to detect survival effects in ALS patients.

There is a lack of studies assessing the effect of centrally acting muscle relaxants on ALS survival [17]. Just a single double-blind, placebo-controlled trial, limited by the low number of enrolled patients and the short follow-up time, assessed the effect of baclofen on spasticity and ALS disease course and could not find an effect [18].

The second noteworthy result was the nominal negative association of PPI with survival. There are a number of reports in the literature linking PPI use with a detrimental effect on neurodegenerative diseases [19, 20], which share pathomechanisms with motor neuron disease. An effect of PPI on the disease course in ALS has not been examined yet. The observed nominal association with ALS in our study failed to survive correction for multiple testing and therefore remains speculative.

Another interesting observation was the absent association of selective serotonin reuptake inhibitors (N06AB according to the ATC code) or of HMG CoA reductase inhibitors (C10AA, commonly known as statins) with survival in ALS. This is relevant as both drugs have been discussed to have an impact on the disease progression in ALS [21, 22]. For both comparisons, our patient numbers were large enough to detect relevant effects; hence, our data argue against a major adverse influence of these drugs on ALS.

Finally, we could find no significant association between the use of angiotensin-converting enzyme inhibitors (ACEI) (C09AA according to the ATC code) and ALS survival in our study (though a trend towards a beneficial effect denoted a higher chance of survival in patients using ACEI). This is in contrast to a recent study which has reported a beneficial association between the use of ACEI and the chance of developing ALS with a 57 % risk reduction [23]. One reason for this discrepancy could be the relatively low number of patients on ACEI included in our study, which might have been insufficient to detect a minor drug effect.

There are some general limitations to be addressed when using automated prescription data [24, 25]. The accuracy and completeness of the data are one major concern in database studies though pharmacy dispensing records represent the gold standard of information on drug exposure in pharmacoepidemiology [24].

The prescription data of the Austrian sickness funds used in our study are derived exclusively from pharmacies, which are the only institutions allowed to dispense drugs in

Table 2 Cox proportional hazard regression analysis in users of selected drug classes (according to the ATC codes)

ATC Code	Drug class	*n* Drug using patients (%)	*n* Drug using patients, drug started ≤90 days after diagnosis (%)	Adjusted HR (95 % CI)	*p* value
A02BC	Proton pump inhibitors	284 (54.4)	241 (46.2)	1.34 (1.04–1.73)	0.022*
N06AB	Selective serotonin reuptake inhibitors	219 (42.0)	165 (31.6)	1.21 (0.92–1.58)	0.18
N06AX	Other antidepressants	156 (29.9)	117 (22.4)	1.14 (0.87–1.51)	0.35
M01AB	Acetic acid derivatives and related substances	134 (25.7)	111 (21.3)	1.24 (0.93–1.66)	0.15
C10AA	HMG CoA reductase inhibitors	132 (25.3)	117 (22.4)	1.01 (0.76–1.34)	0.94
A06AD	Osmotically acting laxatives	122 (23.4)	62 (11.9)	1.20 (0.85–1.69)	0.30
M03BX	Centrally acting muscle relaxants	112 (21.5)	84 (16.1)	0.56 (0.39–0.81)	0.002*
C09AA	ACE inhibitors, plain	98 (18.8)	83 (15.9)	0.75 (0.53–1.05)	0.10
C07AB	Beta blocking agents, selective	97 (18.6)	87 (16.7)	1.27 (0.93–1.73)	0.13
A11DB	Vitamin B1 in combination with vitamin B6 and/or vitamin B12	91 (17.4)	76 (14.6)	1.17 (0.86–1.61)	0.32
B01AB	Heparin group	85 (16.3)	62 (11.9)	1.15 (0.79–1.66)	0.47
C09BA	ACE inhibitors and diuretics	77 (14.8)	69 (13.4)	0.95 (0.66–1.35)	0.77
C08CA	Dihydropyridine derivatives	72 (13.8)	63 (12.1)	0.76 (0.52–1.10)	0.14
N06DX	Other anti-dementia drugs	65 (12.5)	54 (10.3)	1.24 (0.86–1.78)	0.25
H03AA	Thyroid hormones	64 (12.3)	58 (11.1)	1.21 (0.83–1.76)	0.32
A12AX	Calcium, combinations with vitamin D and/or other drugs	58 (11.1)	53 (10.2)	0.91 (0.60–1.39)	0.67

The listed sixteen 4th level ATC drug classes were selected as they were used by at least 10 % of the ALS cohort. Cox proportional hazard regression analysis was performed. HR expresses the hazard ratio of mortality in comparison to non-users of the drug class. Age at diagnosis, the total duration of hospitalizations during the study period and the therapy ratio for riluzole were adjusted for. Gender was used as a stratification variable. To exclude the "immortal time" bias only patients who started the co-medication before or within 90 days of diagnosis were considered. In addition, a time-dependent covariate was used to exclude the survival time after diagnosis but before the start of the co-medication from the exposed follow-up time

* Significant results

Table 3 Influence of potentially confounding variables on Cox proportional hazard ratios for mortality in ALS patients

Variables investigated	Centrally acting muscle relaxants			Proton pump inhibitors		
	Unadjusted HR (95 % CI)	Adjusted HR (95 % CI)	*p* value	Unadjusted HR (95 % CI)	Adjusted HR (95 % CI)	*p* value
Drug class	0.61 (0.42–0.87)	0.56 (0.39–0.81)	0.002*	1.56 (1.22–2.01)	1.34 (1.04–1.73)	0.022*
Age at diagnosis		1.03 (1.01–1.04)	<0.0001*		1.03 (1.02–1.04)	<0.0001*
Duration of hospitalization		1.005 (1.001–1.009)	0.008*		1.004 (1.001–1.008)	0.017*
Riluzole therapy ratio		4.17 (2.71–6.41)	<0.0001*		3.61 (2.35–5.54)	<0.0001*
CDS-1		1.00 (0.96–1.05)	0.83		0.98 (0.94–1.03)	0.44
CDS-2		1.00 (1.00–1.00)	0.80		1.00 (1.00–1.00)	0.24
Number of different drug classes used		1.01 (0.98–1.04)	0.61		0.98 (0.94–1.01)	0.22

The table lists different variables that were considered in the Cox proportional regression analyses. For all models gender was considered as a stratification variable, to accommodate the model for different baseline hazards for both genders. The comorbidity scores were not considered in the final calculations because they were not significantly associated with survival. Only patients who started the medication before or within 90 days after ALS diagnosis were included

* Significant results

Austria. They submit the dispensing records of prescribed drugs electronically to the insurers for reimbursement. Data quality assurance is maintained by specific computer applications of the Austrian sickness funds. A manual review of discordance regarding the insurants' personal details and the prescribed drugs further improves the

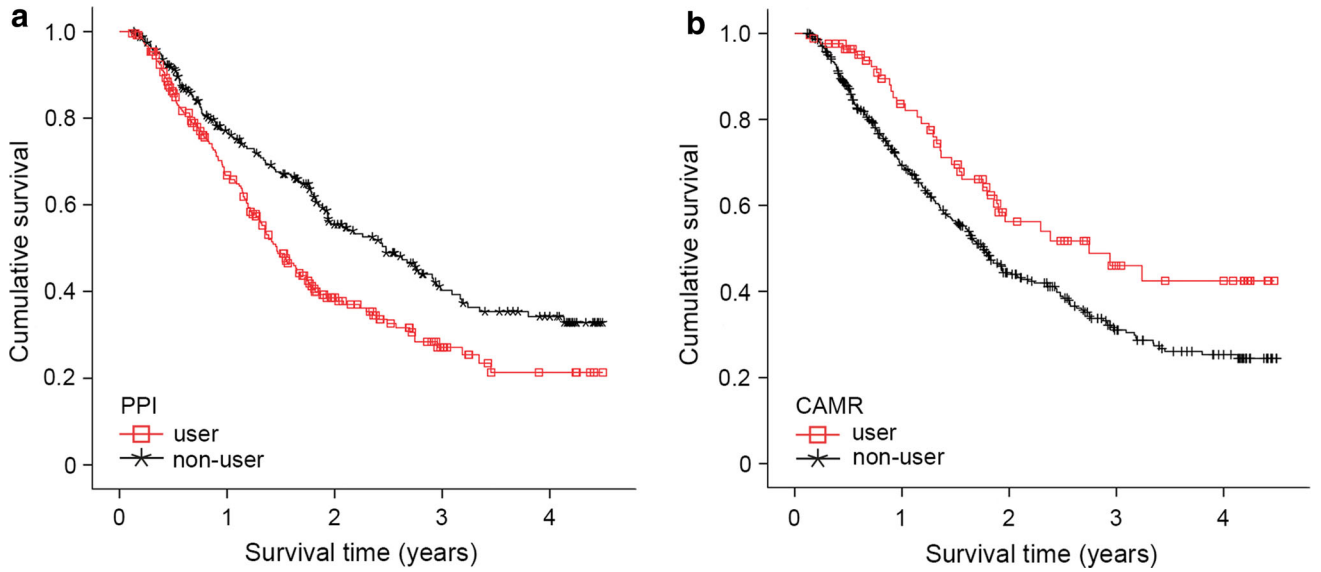

Fig. 1 Survival curves of ALS patients according to their use of centrally acting muscle relaxants (CAMR) or proton pump inhibitors (PPI). Kaplan–Meier (KM) survival curves of patients with ALS after excluding individuals starting their therapy with CAMR or PPI after the first 90 days of diagnosis. **a** Patients using PPI ($n = 241$) lived 370 days shorter compared to patients not using PPI [median survival of 534 days (95 % CI 460–608) and 904 days (95 % CI 700–1108), respectively; $p < 0.001$]. **b** Patients using CAMR ($n = 84$) lived 357 days longer compared to patients not using CAMR [median survival of 1002 days (95 % CI 546–1458) and 645 days (95 % CI 574–716), respectively; $p = 0.007$]

accuracy of the data, which can, therefore, be considered as sufficiently complete and accurate.

Another general limitation of insurance-based prescription data is the lack of information on over-the-counter (OTC) drugs. Thus, a significant use of OTC drugs could have affected our results. However, most of the drugs analyzed in our study are among the prescription drugs in Austria (including centrally acting muscle relaxants), which precludes their OTC dispensation by law. The ALS cohort in our study also consisted entirely of members of the regional health insurances who receive drugs for a very low prescription charge, which abolishes any financial incentives to buy OTC medicines. Based on these factors, we do not consider the use of OTC drugs as a major confounding problem in our study. Moreover, previous studies have established prescription claims as a valid data source for association studies, despite the fact that some of the drugs are available OTC [26, 27].

Another potential bias in pharmacoepidemiological studies might result from a misclassification of drug user's survival time before the first prescription as an exposed follow-up time (i.e., the immortal time bias) [6]. Not accounting for this factor would have introduced a survival benefit in patients receiving their medication late in the disease course. We corrected for immortal time by limiting the allowed therapy start to a maximum of 90 days after the diagnosis and applied a time-varying covariate for the drug exposure [6, 7].

The patient registries of the Austrian sickness funds were primarily maintained for administrative and financial purposes and lacked clinical details. Not adjusting for comorbidities could bear the risk of a potential bias due to clinical confounders [9]. In our study, we corrected all survival analyses for three different validated scores of comorbidity but could not find a significant association with ALS survival. An explanation could be that our ALS cohort already had a very reduced life expectancy and that most patients did not live long enough so that potential comorbidities had no significant impact on their survival. Since comorbidity is a function of individually used drug classes in our study, our observation could also be due to underprescription in more severely affected ALS patients. Underprescription has been described before and is generally applicable to older people and people with a reduced life expectancy [28, 29]. The total duration of hospitalizations during the study period was another factor we adjusted for to correct for differences in disease severity. Its significant correlation with ALS survival might indicate that severely affected patients were more likely to be hospitalized. This is supported by studies showing that complications including dehydration and malnutrition, pneumonia and respiratory failure were among the most common causes for the hospitalization of ALS patients [30, 31].

Because of the lack of clinical details, we did not have information on the disease onset nor on the time of

diagnosis. Instead, we identified ALS patients by their riluzole medication, which is a reliable method as ALS is the only indication for which this drug is approved and remunerated for by the sickness funds. The key demographic parameters of our ALS cohort correspond well to typical cohorts reported in other studies [13, 14]. This corroborates that patients were identified on average soon after diagnosis. It was previously estimated that about 60 % of all ALS patients in Austria uses riluzole [5], which is comparable to other European countries [32, 33]. Thus, we are confident to have captured a great part of the total ALS population in Austria. Nevertheless, the omission of 40 % of the total ALS population could have introduced a selection bias as patients without riluzole might not have got the drug because of milder symptoms or a more advanced disease stage. Another potential confounding element could derive from the fact that all included patients had been using riluzole insofar as the detected association between co-medication and ALS survival could have been due to a direct interaction of the respective drugs with riluzole.

In conclusion, by using a large prescription registry, we investigated the effect of commonly used drugs on survival in ALS in an unbiased manner. Since ALS is a complex disease with multiple exogenous and genetic factors contributing to its pathogenesis, it is conceivable that some of the concomitantly used drug classes with their diverse modes of action might have an impact on the survival in this disease. In line with other studies using medical reports [34, 35] or automated databases [23, 35], the use of large prescription registries could represent an alternative valuable tool for the identification of pathophysiological mechanisms and potential drug targets in ALS.

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Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards The study was approved by the ethical committees of Burgenland and of the Medical University of Vienna. The manuscript does not contain clinical studies or clinical patient data.

References

1. Turner MR, Swash M (2015) The expanding syndrome of amyotrophic lateral sclerosis: a clinical and molecular odyssey. J Neurol Neurosurg Psychiatry. doi:10.1136/jnnp-2014-308946
2. Turner MR, Hardiman O, Benatar M, Brooks BR, Chio A, de Carvalho M, Ince PG, Lin C, Miller RG, Mitsumoto H, Nicholson G, Ravits J, Shaw PJ, Swash M, Talbot K, Traynor BJ, Van den Berg LH, Veldink JH, Vucic S, Kiernan MC (2013) Controversies and priorities in amyotrophic lateral sclerosis. Lancet Neurol 12(3):310–322. doi:10.1016/S1474-4422(13)70036-X
3. Bedlack RS (2010) Amyotrophic lateral sclerosis: current practice and future treatments. Curr Opin Neurol 23(5):524–529. doi:10.1097/WCO.0b013e32833c7ac2
4. Hofmarcher MM, Quentin W (2013) Austria: health system review. Health Syst Transit 15(7):1–291
5. Cetin H, Rath J, Fuzi J, Reichardt B, Fulop G, Koppi S, Erdler M, Ransmayr G, Weber J, Neumann K, Hagmann M, Loscher WN, Auff E, Zimprich F (2015) Epidemiology of amyotrophic lateral sclerosis and effect of riluzole on disease course. Neuroepidemiology 44(1):6–15. doi:10.1159/000369813
6. Suissa S (2008) Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 167(4):492–499. doi:10.1093/aje/kwm324
7. Zhou Z, Rahme E, Abrahamowicz M, Pilote L (2005) Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. Am J Epidemiol 162(10):1016–1023. doi:10.1093/aje/kwi307
8. Eisen A, Kiernan M, Mitsumoto H, Swash M (2014) Amyotrophic lateral sclerosis: a long preclinical period? J Neurol Neurosurg Psychiatry. doi:10.1136/jnnp-2013-307135
9. Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ (2001) Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol 154(9):854–864
10. Quail JM, Lix LM, Osman BA, Teare GF (2011) Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts. BMC Health Serv Res 11:146. doi:10.1186/1472-6963-11-146
11. Von Korff M, Wagner EH, Saunders K (1992) A chronic disease score from automated pharmacy data. J Clin Epidemiol 45(2):197–203 **0895-4356(92)90016-G [pii]**
12. Clark DO, Von Korff M, Saunders K, Baluch WM, Simon GE (1995) A chronic disease score with empirically derived weights. Med Care 33(8):783–795
13. Murphy M, Quinn S, Young J, Parkin P, Taylor B (2008) Increasing incidence of ALS in Canterbury, New Zealand: a 22-year study. Neurology 71(23):1889–1895. doi:10.1212/01.wnl.0000336653.65605.ac
14. Huisman MH, de Jong SW, van Doormaal PT, Weinreich SS, Schelhaas HJ, van der Kooi AJ, de Visser M, Veldink JH, van den Berg LH (2011) Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. J Neurol Neurosurg Psychiatry 82(10):1165–1170. doi:10.1136/jnnp.2011.244939
15. Gordon PH, Cheng B, Katz IB, Pinto M, Hays AP, Mitsumoto H, Rowland LP (2006) The natural history of primary lateral sclerosis. Neurology 66(5):647–653. doi:10.1212/01.wnl.0000200962.94777.71
16. Turner MR, Parton MJ, Shaw CE, Leigh PN, Al-Chalabi A (2003) Prolonged survival in motor neuron disease: a descriptive study of the King's database 1990-2002. J Neurol Neurosurg Psychiatry 74(7):995–997
17. Diana ASV, Bongioanni P, Miller RG, Moore DH (2006) Gamma aminobutyric acid (GABA) modulators for amyotrophic lateral sclerosis/motor neuron disease (Protocol). Cochrane Database Syst Rev. doi:10.1002/14651858.CD006049
18. Norris FH Jr, KS U, Sachais B, Carey M (1979) Trial of baclofen in amyotrophic lateral sclerosis. Arch Neurol 36(11):715–716
19. Nielsen HH, Qiu J, Friis S, Wermuth L, Ritz B (2012) Treatment for Helicobacter pylori infection and risk of Parkinson's disease in Denmark. Eur J Neurol 19(6):864–869. doi:10.1111/j.1468-1331.2011.03643.x
20. Fallahzadeh MK, Borhani Haghighi A, Namazi MR (2010) Proton pump inhibitors: predisposers to Alzheimer disease? J Clin Pharm Ther 35(2):125–126. doi:10.1111/j.1365-2710.2009.01100.x

21. Koschnitzky JE, Quinlan KA, Lukas TJ, Kajtaz E, Kocevar EJ, Mayers WF, Siddique T, Heckman CJ (2014) Effect of fluoxetine on disease progression in a mouse model of ALS. J Neurophysiol 111(11):2164–2176. doi:10.1152/jn.00425.2013
22. Dupuis L, Corcia P, Fergani A, Gonzalez De Aguilar JL, Bonnefont-Rousselot D, Bittar R, Seilhean D, Hauw JJ, Lacomblez L, Loeffler JP, Meininger V (2008) Dyslipidemia is a protective factor in amyotrophic lateral sclerosis. Neurology 70(13):1004–1009. doi:10.1212/01.wnl.0000285080.70324.27
23. Lin FC, Tsai CP, Kuang-Wu Lee J, Wu MT, Tzu-Chi Lee C (2014) Angiotensin-converting enzyme inhibitors and amyotrophic lateral sclerosis risk: a total population-based case–control study. JAMA neurology. doi:10.1001/jamaneurol.2014.3367
24. Schneeweiss S, Avorn J (2005) A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 58(4):323–337. doi:10.1016/j.jclinepi.2004.10.012
25. Ray WA (2011) Improving automated database studies. Epidemiology 22(3):302–304. doi:10.1097/EDE.0b013e31820f31e1
26. Yood MU, Campbell UB, Rothman KJ, Jick SS, Lang J, Wells KE, Jick H, Johnson CC (2007) Using prescription claims data for drugs available over-the-counter (OTC). Pharmacoepidemiol Drug Saf 16(9):961–968. doi:10.1002/pds.1454
27. Lam JR, Schneider JL, Zhao W, Corley DA (2013) Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA 310(22):2435–2442. doi:10.1001/jama.2013.280490
28. Holmes HM (2009) Rational prescribing for patients with a reduced life expectancy. Clin Pharmacol Ther 85(1):103–107. doi:10.1038/clpt.2008.211
29. Cherubini A, Corsonello A, Lattanzio F (2012) Underprescription of beneficial medicines in older people: causes, consequences and prevention. Drugs Aging 29(6):463–475. doi:10.2165/11631750-000000000-00000
30. Lechtzin N, Wiener CM, Clawson L, Chaudhry V, Diette GB (2001) Hospitalization in amyotrophic lateral sclerosis: causes, costs, and outcomes. Neurology 56(6):753–757
31. Dubinsky R, Chen J, Lai SM (2006) Trends in hospital utilization and outcome for patients with ALS: analysis of a large US cohort. Neurology 67(5):777–780. doi:10.1212/01.wnl.0000233849.47744.60
32. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O (2003) An outcome study of riluzole in amyotrophic lateral sclerosis—a population-based study in Ireland, 1996–2000. J Neurol 250(4):473–479. doi:10.1007/s00415-003-1026-z
33. Chio A, Mora G, Leone M, Mazzini L, Cocito D, Giordana MT, Bottacchi E, Mutani R (2002) Early symptom progression rate is related to ALS outcome: a prospective population-based study. Neurology 59(1):99–103
34. Seelen M, van Doormaal PT, Visser AE, Huisman MH, Roozekrans MH, de Jong SW, van der Kooi AJ, de Visser M, Voermans NC, Veldink JH, van den Berg LH (2014) Prior medical conditions and the risk of amyotrophic lateral sclerosis. J Neurol 261(10):1949–1956. doi:10.1007/s00415-014-7445-1
35. Ji J, Sundquist J, Sundquist K (2015) Association of alcohol use disorders with amyotrophic lateral sclerosis: a Swedish national cohort study. Eur J Neurol. doi:10.1111/ene.12667