

Drug Use in Older Adults with Amyotrophic Lateral Sclerosis Near the End of Life

Giulia Grande^{1,2}  · Lucas Morin¹ · Davide Liborio Vetrano^{1,3} · Johan Fastbom¹ · Kristina Johnell¹

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Abstract

Background Amyotrophic lateral sclerosis (ALS), with its certain prognosis and swift progression, raises concerns regarding the adequacy of pharmacological treatment, including the risk–benefit profiles of prescribed drugs.

Objective Our objective was to evaluate the use of prescription drugs over the course of the last year of life in older adults with ALS.

Methods We conducted a nationwide retrospective cohort study of older adults who died with ALS in Sweden between 2007 and 2013. The primary outcome was the number of prescription drugs to which individuals were exposed during the last 12 months before death.

Results The overall proportion of individuals receiving ten or more different prescription drugs increased from 19% at 12 months before death to 37% during the last month of life. Institutionalization was independently associated with polypharmacy near the end of life (odds ratio 1.84; 95% confidence interval 1.42–2.39).

Conclusion Future research is needed to assess the time to benefit of treatments and to develop guidelines for medication discontinuation in advanced ALS.

Key Points

Amyotrophic lateral sclerosis (ALS) represents the paradigm of a disease with a definite final trajectory for which end-of-life decisions are required and risk–benefit profiles of drugs should be properly evaluated.

We found that older people with ALS receive significantly more prescription drugs over the last year of life, with 37% of such patients being treated with ten or more drugs during the last month.

Future research is needed to assess the time to benefit of treatments in this condition, and guidelines should be developed for medication discontinuation in advanced ALS.

Giulia Grande and Lucas Morin contributed equally to the manuscript

✉ Giulia Grande
giulia.grande@ki.se

¹ Aging Research Center, Department of Neurobiology, Care Sciences, and Society (NVS), Karolinska Institutet and Stockholm University, Gävlegatan 16, 11330 Stockholm, Sweden

² Center for Research and Treatment on Cognitive Dysfunctions, Biomedical and Clinical Sciences Department, “Luigi Sacco” Hospital, University of Milan, Milan, Italy

³ Department of Geriatrics, Catholic University of Rome, Rome, Italy

1 Introduction

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease characterized by degeneration of the upper and lower motor pathways, leading to a progressive muscle weakness compromising vital functions such as swallowing and breathing [1]. Its prevalence is 5.4/100,000, with the highest incidence in people aged 54–67 years (incidence rate 2.1/100,000 per year) [2]. The average time from diagnosis to death is 30 months, with only 10% of

individuals living more than 10 years [1]. Infections and respiratory failure dominate the clinical picture, leading to frequent hospital admissions, institutionalization, and death.

Recent improvements in the care of patients with ALS, namely non-invasive ventilation techniques [3] and percutaneous gastrostomy [4], have increased overall survival. Individuals with ALS are therefore more likely than previously to reach an advanced age and thus to experience an accumulation of multiple chronic comorbidities. The necessity of treating these comorbid conditions in addition to the main disease increases the number of prescribed drugs and the risk of iatrogenic events [5].

Clinical complications associated with life-limiting illnesses, together with the age-related accumulation of other chronic diseases, increase the demand for healthcare near the end of life [5]. As the disease progresses, hospitalizations and specialist consultations become frequent events that increase the burden of polypharmacy [6]. However, no study has previously addressed this issue in subjects with ALS.

We evaluated the use of prescription drugs over the course of the last year of life in older adults with ALS.

2 Methods

We conducted a nationwide retrospective cohort study of older adults who died with ALS in Sweden between 1 January 2007 and 31 December 2013. Individuals were included in the study cohort if they were aged >65 years at the time of death and if a diagnosis of ALS (International Classification of Diseases, 10th edition code G12.2) was reported on the death certificate as underlying or contributing to the cause of death [7]. Death certificate data were then linked at the individual level with the Swedish Prescribed Drug Register, the National Patient Register, and the Social Services Register.

The primary outcome was the number of prescription drugs to which individuals were exposed during each of the last 12 months before death. Data were extracted from the Swedish Prescribed Drug Register, using the date of death as the index date to retrieve the history of drug dispensing during the final year of life. Drugs were classified according to the Anatomical Therapeutic Chemical classification code [8]. Drug exposure was estimated for each drug using the dispensing date, the total amount dispensed to the individual, and the daily dose indicated on the prescription [9, 10]. We also examined changes in the use of the most commonly prescribed drugs during the last year of life.

Based on the methodology proposed by Calderón-Laraña et al. [11], we identified chronic comorbidities using death certificate data (including all contributing causes of

death), data from the National Patient Register (including all inpatient and specialized outpatient diagnoses reported during the last 24 months before death), and data from the Swedish Prescribed Drug Register (detecting the use of medications that unequivocally indicate a specific condition). Living arrangement was categorized as “community-dwelling” or “institutionalized” using data from the Social Services Register. Level of education was derived from the national Education Register and operationalized as “primary,” “secondary,” and “tertiary” education according to the International Standard Classification of Education.

Trends in the number of prescription drugs over the course of the last year of life were described as mean differences between the 12th and the final month before death. The prevalence of polypharmacy (defined as the monthly use of ten or more different prescription drugs) was computed for each month separately and presented as a percentage of the total cohort. A logistic regression model adjusted for age, sex, and number of comorbidities was fitted to investigate the association between institutionalization and likelihood of being exposed to polypharmacy during the last month of life. Finally, we analyzed the prevalence of the 20 most common drug classes during the 12th, 6th, and final month before death.

3 Results

A total of 1603 older adults died with ALS between 2007 and 2013 in Sweden. Mean age at time of death was $76.5 \pm$ standard deviation (SD) 6.9 years, with 14% of decedents aged ≥ 85 years. No comorbidity was reported for 5.1% of these individuals. One-fifth of individuals were institutionalized, and about one-half died in hospitals (Table 1). The mean number of concomitant prescription drugs increased over the course of the final year of life, from 5.7 to 8.3 drugs among community-dwelling individuals (mean difference 2.6, 95% confidence interval [CI] 2.4–2.8) and from 7.5 to 9.7 among institutionalized individuals (mean difference 2.2, 95% CI 1.7–2.6). Overall, the proportion of individuals with ALS exposed to ten or more prescription drugs increased throughout the last year of life, from 19% during the 12th month before death to 37% during the last month (Fig. 1). During the last month before death, institutionalized individuals were found to be more likely to receive ten or more prescription drugs than those living in the community (adjusted odds ratio [OR] 1.84, 95% CI 1.42–2.39).

Psycholeptics, analgesics, laxatives, psychoanaleptics, and other drugs affecting the nervous system (i.e., riluzole) were the five most commonly used drug classes during the final months before death (Table 2). There was an increase in the use of symptom-oriented medications: anxiolytics,

Table 1 Characteristics of the study population at death ($n = 1603$)

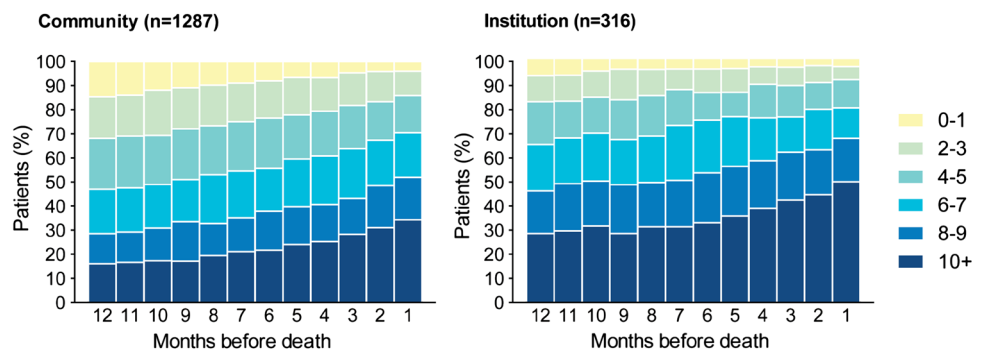
Characteristics	N (%) ^a
Sex	
Men	820 (51.2)
Women	783 (48.8)
Age at time of death, years	
Mean \pm standard deviation	76.5 \pm 6.9
66–74	684 (42.7)
75–84	691 (43.1)
85–94	218 (13.6)
≥ 95	10 (0.6)
Number of chronic comorbidities	
0	82 (5.1)
1	230 (14.3)
2	306 (19.1)
3	287 (17.9)
≥ 4	698 (43.5)
Living arrangement	
Community	1287 (80.3)
Institutionalized	316 (19.7)
Level of education ^b	
Primary education	616 (39.0)
Secondary education	708 (44.8)
Tertiary education	257 (16.3)
Place of death	
Usual place of living	848 (53.0)
Hospital	751 (47.0)

^a Unless otherwise indicated

^b Missing values: 22

sedatives, analgesics (including strong opioids), antidepressants, gastroprotective agents, and anti-emetics. Use of lipid-lowering drugs decreased steadily over the course of the last year of life, from 18% during the 12th month to 11% during the final month. The proportion of individuals exposed to antithrombotics, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, mineral supplements, and anti-dementia drugs remained stable.

Fig. 1 Change in the number of prescription drugs during the last 12 months of life in patients with amyotrophic lateral sclerosis (Sweden, 2007–2013)



4 Discussion

Our results show that polypharmacy is highly prevalent in the last year of life of older people with ALS, particularly among institutionalized individuals. In addition, we found that the total number of drugs significantly increased as death approached, and long-term chronic medications were often continued.

Previous studies have investigated polypharmacy in the general adult population with life-limiting conditions [6, 12] and have emphasized the need to reconsider the appropriateness of drugs near the end of life [13]. This article addresses the specific situation of older adults dying with ALS, an incurable and relentlessly neurodegenerative disease with a dreadful prognosis. ALS embodies the paradigm of diseases for which end-of-life decisions are required [14] and where the risk–benefit of drugs must be properly evaluated.

The concept of time to benefit, i.e., the time after which the benefit of a drug becomes clinically relevant [13], raises clinical and ethical issues in individuals dying with ALS. Given their limited life expectancy, the continuation of medications for which benefits are expected to be achieved in a timeframe that exceeds survival should be questioned. Prescriptions should also be weighed against the goals of care. As the disease progresses, the therapeutic strategy should become increasingly palliative, with the primary goal of relieving burdensome symptoms and providing comfort care. In this context, analgesics, antiemetics, anxiolytics, and emollients may have a positive effect on quality of life.

We describe an increasing prescription of symptomatic drugs over the last 12 months of life, in line with the well-known worsening of the clinical picture and flare-up of comorbidities in subjects with ALS who approach death [15]. At the same time, several drug classes were often de-prescribed, e.g., drugs acting on the renin-angiotensin system, calcium channel blockers, and lipid-modifying agents. Hemodynamic changes and perceived poor benefit during late disease stages might explain this de-prescription process. However, during the last month of life, 10%

Table 2 Change in the most commonly used prescription drugs in the last year before death (*N* = 1603)

	Percentage of patients receiving drug		
	12th month	6th month	Final month
Psycholeptics	32.8	39.2	57.4
Antipsychotics	2.7	3.4	4.9
Anxiolytics	15.7	20.7	38.2
Hypnotics and sedatives	23.8	27.9	39.2
Analgesics	26.0	32.9	47.2
Opioids	11.6	15.9	31.1
Other analgesics and antipyretics	21.0	25.9	33.9
Drugs for constipation	21.3	32.3	46.5
Other nervous system drugs	26.9	38.3	45.2
Riluzole	26.7	37.9	45.0
Psychoanaleptics	28.4	37.0	44.1
Antidepressants	26.4	34.3	42.4
Anti-dementia drugs	3.2	3.9	3.4
Antithrombotic agents	37.1	38.2	36.9
Vitamin K antagonists	4.9	5.0	4.6
Heparin group	1.2	1.2	2.9
Aspirin	30.6	31.0	29.4
Cough and cold preparations	17.3	24.3	31.9
Beta-blocking agents	26.5	27.3	27.3
Diuretics	24.0	24.7	25.2
High-ceiling diuretics	13.1	15.0	17.8
Drugs for acid-related disorders	16.8	18.6	24.5
Agents acting on the renin-angiotensin system	25.2	23.8	22.1
Antianemic preparations	17.5	19.3	20.0
Emollients and protectives	12.7	15.1	17.7
Ophthalmologicals	12.6	13.8	15.6
Drugs for obstructive airway diseases	10.7	12.1	15.3
Drugs for functional gastrointestinal disorders	4.4	6.7	14.9
Antibacterials for systemic use	9.5	9.5	14.2
Calcium channel blockers	16.1	14.6	12.7
Mineral supplements	11.7	12.1	11.3
Calcium	9.1	9.1	7.5
Potassium	2.9	3.3	3.8
Antiemetics and anti-nauseants	3.5	5.7	10.9
Lipid-modifying agents (including statins)	18.2	15.1	10.8

of subjects were still receiving statins. Interestingly, we found a significant increase in the prescription of riluzole during the last year of life. This could be explained by the expectation of a slightly longer survival and of a delayed use of mechanical ventilation associated with riluzole, as suggested in recent studies [16]. Prescription of antibacterials and medications for obstructive airway diseases also increased during the last year of life, which might be driven by recurrent episodes of lower respiratory tract infections occurring in advanced stages of disease.

In older adults with complex health problems, polypharmacy is often the result of a prescribing cascade

[17]. For instance, the use of aspirin as an anti-thrombotic agent can trigger the use of proton pump inhibitors, leading in turn to the prescription of other drugs to counteract their adverse effects. The extent to which this type of prescribing cascade affects ALS subjects warrants further research.

As in other life-limiting conditions, drug de-prescription [18] should be contemplated in an appropriate and timely manner as a valid option in individuals with ALS. De-prescribing may in fact improve quality of life and reduce potential harms deriving from complex drug regimens [19].

We found that institutionalized older people with ALS were more likely to be exposed to polypharmacy. This

represents a missed opportunity, since institutionalization is an occasion for optimizing the pharmacological treatment of frail patients with life-limiting conditions.

Both strengths and limitations should be considered when interpreting these findings. Our study is based on a large cohort of people with ALS, covering the entire country of Sweden and including all older individuals who died with ALS as cause of death over a period of 7 years. However, the lack of clinical data regarding ALS severity, functional status, and prognosis prevents us from speculating about the appropriateness of drugs prescribed during the last months of life. Finally, the Swedish Prescribed Drug Register does not contain information regarding in-hospital drug dispensing or over-the-counter drugs.

5 Conclusion

Older adults with ALS near the end of life are often prescribed multiple medications, including long-term preventive drug treatments. To help clinicians balance the benefits and the harms of complex drug regimens in the context of limited life expectancy, future research needs to assess the time to benefit of treatments. There is also a need for guidelines for medication discontinuation in advanced stages of ALS to be developed.

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Author contributions GG, LM, and DLV contributed to the conception and design of the study. KJ, JF, and LM contributed to the acquisition of the data. LM conducted the statistical analyses. All authors contributed to interpretation of the results. GG, LM, and DLV drafted the manuscript. KJ and JF critically revised the manuscript for important intellectual content. All authors made a significant contribution to the research and the development of the manuscript and approved the final version for publication.

Compliance with Ethical Standards

The Regional Ethical Review Board in Stockholm, Sweden, approved the Study (Nos. 2013/1941-31/3 and 2015/1319-32).

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Conflict of interest Giulia Grande, Lucas Morin, Davide Liborio Vetrano, Johan Fastbom, and Kristina Johnell have no conflicts of interest relevant to the content of this study.

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