LETTER

Symptomatic pharmacotherapy in ALS: data analysis from a platform-based medication management programme

INTRODUCTION

Although symptomatic medicines constitute an important intervention in amyotrophic lateral sclerosis (ALS), few systematic investigations into drug management have been reported so far.[1] Furthermore, symptomatic pharmacotherapy is constantly evolving with an increasing number of drugs being used. Therefore, more detailed information on drug prescription must be obtained to monitor the current standards of care, identify potential shortcomings in drug management and elucidate progress in symptomatic pharmacotherapy. Thus, the aims of the present study were to (i) identify the spectrum of symptomatic drugs; (ii) rank symptomatic drugs according to their frequency of use; (iii) assign symptomatic drugs to pharmacological domains and (iv) determine the number of symptomatic drugs per patient. We hypothesised that the pharmacological spectrum and frequency of use range widely. Furthermore, we supposed that symptomatic drug treatment may vary substantially among patients with ALS and may be highly personalised.

METHODS

A prospective, multicentre, cross-sectional observational study was conducted. The participants met the following criteria: (1) diagnosis of ALS[2]; (2) one or more ALS-related drug prescriptions; (3) participation in a case management programme for ALS medication; (4) consent to data capture using a digital research platform.[3] The cohort encompassed patients who had received treatment at nine specialised ALS centres in Germany between July 2013 and December 2019. Participant's demographic and clinical data are summarised in figure 1A. Detailed methods and the setting of the study are listed in the online supplementary file 1.

RESULTS

A cohort of 2392 patients with ALS including 7562 prescriptions of ALS-related medicines was captured. A total of 1157 patients (48.4%) had died during the observation. Riluzole was the drug most commonly used (93% of patients; n=2219). Symptomatic drugs were assorted to pharmacological domains and to the attainment of treatment goals (figure 1B). An overview and ranking of symptomatic drugs are summarised in the online supplementary file 2. Based on the number of patients who received the drug, the following top 10 symptomatic medicines were identified (in decreasing order): mirtazapine, ipratropium bromide, pirenzepine, citalopram, lorazepam, baclofen, metamizole, quinine, fentanyl and tetrahydrocannabinol:cannabidiol. Patients with ALS were provided with a mean number of 3.2 symptomatic drugs. However, the number of drugs per patient varied substantially (figure 1D). Furthermore, we identified an increasing number of prescribed drugs per patient in correlation to advanced stages of King's clinical stages of ALS (figure 1C).[4]

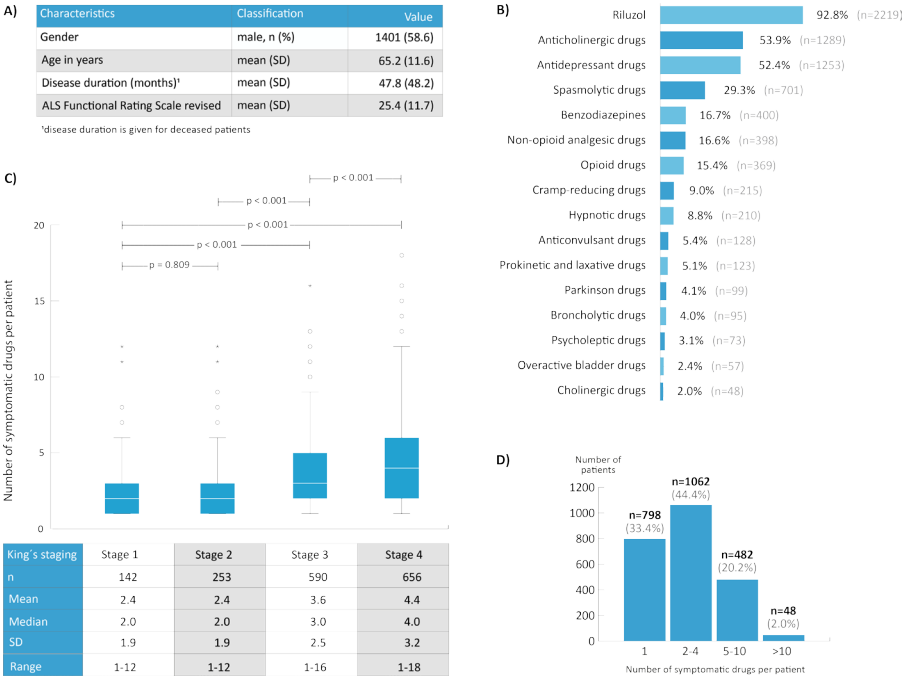
DISCUSSION

The symptomatic medication was analysed at specialised ALS centres in Germany collaborating on multidisciplinary managed care. Data assessment was facilitated by the common use of

A)

Characteristics	Classification	Value
Gender	male, n (%)	1401 (58.6)
Age in years	mean (SD)	65.2 (11.6)
Disease duration (months)[1]	mean (SD)	47.8 (48.2)
ALS Functional Rating Scale revised	mean (SD)	25.4 (11.7)

[1]disease duration is given for deceased patients



King´s staging	Stage 1	Stage 2	Stage 3	Stage 4
n	142	253	590	656
Mean	2.4	2.4	3.6	4.4
Median	2.0	2.0	3.0	4.0
SD	1.9	1.9	2.5	3.2
Range	1-12	1-12	1-16	1-18

Figure 1 (A) Characteristics of the study participants. (B) Assignment of symptomatic drugs to pharmacologic domains and ranking according to the frequency of use. The number and percentage of patients is shown who received the drug during the course of ALS treatment. Symptomatic drugs were assorted the leading domains of symptomatic drugs: (1) anticholinergic drugs: pirenzepine, ipratropium bromide, amitriptyline, atropine, scopolamine, bornaprine, (2) antidepressant drugs: mirtazapine, citalopram, amitriptyline, escitalopram, opipramol, dextromethorphan/quinidine, agomelatine, venlafaxine, sertraline, trimipramine, duloxetine, paroxetine; (3) antispasmodic drugs: baclofen, tetrahydrocannabinol:cannabidiol, tizanidine, 4-aminopyridine, botulinum toxin, tolperisone; (4) benzodiazepines: lorazepam, diazepam; (5) non-opioid analgesic drugs: metamizole, ibuprofen, diclofenac, etoricoxib; (6) opioid drugs: fentanyl, oxycodone, tilidine, tramadol, morphine sulfate, tapentadol, tramadol, codeine; (7) cramp-reducing drugs: quinine; (8) hypnotic drugs: zopiclone, zolpidem, melatonin; (9) anticonvulsant drugs: pregabalin, gabapentin, carbamazepine; (10) prokinetic and laxative drugs: polyethylene glycol, domeridone, metoclopramide; (11) Parkinson drugs: levodopa, rotigotine, pramipexol, ropinirole; (12) broncholytic drugs: acetylcysteine, tyloxapol, carbomer, salbutamol, ambroxol; (13) psycholeptic drugs: olanzapine, quetiapine, melperone; (14) overactive bladder drugs: oxybutynin, trospium, butylscopolamine; (15) cholinergic drugs: pyridostigmine. (C) Number of symptomatic drugs per patient in relation to the King's clinical stage of ALS; stage 1=involvement of one clinical region; stage 2=involvement of second clinical region; stage 3=involvement of third clinical region; stage 4=nutritional or respiratory failure. (D) Number of symptomatic drugs per patient. The number of drugs per patient referred to all drugs of any given patient that were applied during the course of disease. Detailed methods are listed in the online supplementary file 1. n, number of patients; SD, standard deviation.

a digital management platform that allowed for an assessment of ALS pharmacotherapy in the largest cohort so far. Moreover, this study included patients at all stages of the disease. In contrast, symptomatic drugs were previously collected in the context of clinical trials or in late-stage ALS.[5 6] In this study, we identified about 100 different drugs administered for symptomatic treatment in ALS. This impressive number may give rise to the conclusion that symptomatic pharmacotherapy is highly diverse and variable, supposedly an underestimated fact. The ranking of drugs revealed striking differences in the frequency of use ranging from frequently used to rarely applied agents. The highest-ranking drugs encompassed agents for the treatment of excessive salivation, depression and/or emotional lability, spasticity, anxiety, moderate pain and severe pain or dyspnoea, and fasciculations (online supplementary file 2). By allocating symptomatic drugs to pharmacological domains, it becomes even clearer how these drugs rank (figure 1B).

The data on symptomatic drugs as prescribed by ALS specialists are intended to provide a broad benchmark of ALS drug management. It may offer support to neurologists and other physicians who seek guidance in symptomatic treatment, which is very much an individual issue and moreover, an evolving subject as new medications come to market. This goal of our work corresponds to the objective of other studies that described how experienced clinicians manage a patient with treatment-resistant symptoms.[1 7] The comparison with previous studies demonstrates that different approaches (in terms of selection or ranking of drugs) are used to treat dominating symptoms such as sialorrhoea.[7]

Despite the methodological advantages of our study, the generalisability was limited by the diverging extent to which platform-based medication management was utilised. Furthermore, all participating study sites were specialised ALS centres with limited coverage of 15% to 20% of all patients with ALS in Germany. Thus, it is conceivable that the more complex symptomatic drug provision and the use of riluzole may be over-represented. Also, patients in the advanced stages of the disease may be under-represented as only a few palliative care teams have actually used the platform. Furthermore, this study was limited to patients with ALS in Germany. Comparative investigations in other countries would be worthwhile, given the national variability in legal and social frameworks of drug treatment.

The high number of medicines per patient (mean 3.2 drugs) underlines the relevance of symptomatic pharmacotherapy. One fifth of patients requested more than four symptomatic drugs. The actual frequency of prescriptions may even higher as some symptomatic drugs are likely to have been prescribed outside the platform. Strikingly, the number of drugs requested per patient ranged widely (range 1 drug to 18 medicines). Such variability may be due to the different stages of ALS covered with this cohort. In fact, the finding of an increasing number of drugs per patient in advanced stages of King's clinical stages of ALS is contributing to this notion (figure 1C, online supplementary file 3). Further investigations are of interest to correlate classes of symptomatic medicines (and distinct drugs) to stages of disease (or to specific symptoms).

In conclusion, symptomatic drug treatment was a frequent and ongoing healthcare intervention in the cohort studied. Pharmacotherapy in ALS was complex, individualised and included multiple drugs. Despite its pivotal importance to ALS care, for most of the many symptomatic drugs, the level of evidence was rather low and mostly confined to individual cohort studies or case series. Additional studies are needed to further specify the indication criteria, optimal timing and dosing for symptomatic drugs and to incorporate them in national and European ALS treatment guidelines.

Thomas Meyer ,[1,2] **Dagmar Kettemann**,[1] **André Maier** ,[1] **Torsten Grehl**,[3] **Ute Weyen**,[4] **Julian Grosskreutz** ,[5] **Robert Steinbach**,[5] **Jenny Norden**,[1] **Annette George**,[1] **Andreas Hermann** ,[6,7] **René Guenther**,[8,9] **Susanne Petri**,[10] **Olivia Schreiber-Katz**,[10] **Johannes Dorst**,[11] **Albert C Ludolph** ,[11] **Bertram Walter**,[1] **Christoph Münch**,[1,2] **Susanne Spittel** [1,2]

[1]Department of Neurology, Center for ALS and other Motor Neuron Disorders, Charité - Universitätsmedizin Berlin, Berlin, Germany
[2]Ambulanzpartner Soziotechnologie APST GmbH, Berlin, Germany
[3]Department of Neurology, Center for ALS and other Motor Neuron Disorders, Alfried Krupp Krankenhaus, Essen, Germany
[4]Department of Neurology, Center for ALS and other Motor Neuron Disorders, Berufsgenossenschaftliches Universitatsklinikum Bergmannsheil, Bochum, Germany
[5]Hans Berger Department of Neurology, Jena University Hospital, Jena, Germany
[6]Department of Neurology, Translational Neurodegeneration Section Albrecht Kossel, Universitätsmedizin Rostock, Rostock, Germany
[7]Research Site Rostock/Greifswald, DZNE, German Center for Neurodegenerative Diseases, Rostock, Germany
[8]Department of Neurology, Technische Universität Dresden, Dresden, Germany
[9]Research Site Dresden, DZNE, German Center for Neurodegenerative Diseases, Dresden, Germany
[10]Department of Neurology, Hannover Medical School, Hannover, Germany
[11]Department of Neurology, University of Ulm, Ulm, Germany

Correspondence to Professor Thomas Meyer, Department of Neurology, Center for ALS and other Motor Neuron Disorders, Charité - Universitätsmedizin Berlin, 10117 Berlin, Germany; thomas.meyer@charite.de

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Competing interests TM and CM are founders of the digital management platform 'APST' and hold shares in Ambulanzpartner Soziotechnologie APST GmbH.

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ORCID iDs
Thomas Meyer http://orcid.org/0000-0002-2736-7350
André Maier http://orcid.org/0000-0003-2473-4116
Julian Grosskreutz http://orcid.org/0000-0001-9525-1424
Andreas Hermann http://orcid.org/0000-0002-7364-7791
Albert C Ludolph http://orcid.org/0000-0002-5401-0904
Susanne Spittel http://orcid.org/0000-0001-9471-7798

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