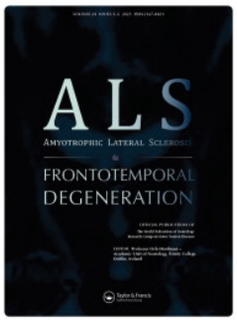

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

Crushing riluzole tablets: evaluation of loss of powder and active principle in a home-simulation experiment

Antonella Casiraghi, Andrea Gentile, Ivan Marjanovic & Adriano Chiò

To cite this article: Antonella Casiraghi, Andrea Gentile, Ivan Marjanovic & Adriano Chiò (2023): Crushing riluzole tablets: evaluation of loss of powder and active principle in a home-simulation experiment, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2023.2245860

To link to this article: https://doi.org/10.1080/21678421.2023.2245860

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2023; 0: 1–7

RESEARCH ARTICLE

Crushing riluzole tablets: evaluation of loss of powder and active principle in a home-simulation experiment

ANTONELLA CASIRAGHI[1], ANDREA GENTILE[1], IVAN MARJANOVIC[2] & ADRIANO CHIÒ[3,4]

[1]*Department of Pharmaceutical Sciences, University of Milan, Milan, Italy,* [2]*Zambon Biotech SA, Cadempino, Switzerland,* [3]*'Rita Levi Montalcini' Department of Neuroscience, University of Turin, Turin, Italy, and* [4]*Neurology 1, AOU Città della Salute e della Scienza Hospital of Turin, Turin, Italy*

Abstract

Objective: Swallowing difficulties cause patients with amyotrophic lateral sclerosis (ALS) to crush oral medications, falling outside the labeling instructions and entailing some risks. To date, there is no evidence about consequences of crushing riluzole tablets in a home setting. This simulation experiment evaluated the loss of powder and active principle ingredient (API) mimicking the home setting with two alternative crushing methods (A and B). *Methods:* The tests were carried out by 15 volunteers without experience in the preparation of medication. Each volunteer manually crushed 5 tablets with a meat tenderizer (method A) or two spoons pressed against each other (method B). Riluzole was weighed before (W1) and after crushing (W2). Then, a subsample of crushed tablets was analyzed by HPLC to measure API content. The loss of powder was calculated as a percentage of the intact tablet weight, and the loss of API as a percentage of the labeled API content. *Results:* The quantitative analysis showed a mean percentage loss of 6.27% corresponding to a mean (SD) loss of powder of 13(±13) mg. The API loss was directly related to the powder loss: overall the mean percentage of API loss was 8.53% (corresponding to a mean API loss of 4.27 ± 4.50 mg). The difference in powder and API loss was highly statistically significant. *Conclusion:* Crushing riluzole tablets in a simulated home setting determined a significant loss of powder and API. These results support neurologists to evaluate formulations that minimize the need to alter the product and can improve ALS patient journey.

Keywords: *ALS, API loss, crushing tablets, powder loss, Riluzole*

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, ultimately fatal neurodegenerative disease marked by the gradual degeneration of motor neurons in the central nervous system that controls voluntary muscle movement (1). Difficulty in swallowing, defined as dysphagia, is a frequent symptom that can be seriously exacerbated by the progression of ALS, and causes difficulties in oral consumption of food, liquids and, hence, also the drugs to treat the disease (1,2).

Riluzole is indicated for ALS treatment and is the active principle ingredient (API) in Rilutek. Riluzole is a glutamate antagonist that reduces the release of glutamate; it is a disease-specific therapy that has been shown to slow disease progression in patients with probable and definitive ALS with symptom onset <5 years and proved to be effective also prolonging the late stages of the disease (1,3). It is available as either film-coated 50 mg tablets administered twice a day to reach the effective daily dose of 100 mg or as oral suspension formulation in a 300-mL multiple-dose amber bottle. Riluzole treatment showed a positive and dose-dependent effect on tracheostomy-free survival, with an optimal efficacy-safety-balance at a 100 mg daily dose. Therefore, it is important to adhere to the daily administration dose, according to the approved indication, to guarantee the ideal biopharmaceutical profile (4). Recent publications using a large database spanning five to ten years suggested that riluzole is associated with a

Correspondence: Antonella Casiraghi, Department of Pharmaceutical Sciences, University of Milan, Milan, Italy. E-mail: antonella.casiraghi@unimi.it

Supplemental data for this article can be accessed online at https://doi.org/10.1080/21678421.2023.2245860.

(Received 31 May 2023; revised 2 August 2023; accepted 3 August 2023)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2023.2245860

median survival prolongation of up to 21 months, and supported early initiation and long-term persistence in treatment (5,6). Therefore, the latest EFNS guidelines emphasize the need to start riluzole at the correct dose as soon as possible after diagnosis and do everything possible to preserve patient's autonomy for longer (7). Moreover, the "Five Rights of Medication Administration" states it is important not to alter a solid-dose oral formulation, in order to help reduce the risk of medication errors and recommends that "the right medicine is given to the right person, at the right time, using the right dose, in the right form" (8).

Unfortunately, the onset and severity of swallowing difficulty can compromise treatment management. Difficulty in swallowing solid oral dosage forms occurs even in the general adult population without dysphagia, and the consequent splitting or crushing of the tablets is used to improve treatment management (9). Swallowing difficulty is very frequent in ALS patients: although dysphagia may be the presenting symptom in some 30% of patients, it occurs in approximately 80% of patients during the advanced phases of the disease (10). Crushing the tablet, using liquids or food to facilitate ingestion, or switching to the oral suspension formulation are strategies used in real life by 44% of ALS patients in order to manage their riluzole therapy (10).

Crushing tablets, in particular, can lead to several issues: (1) a potential loss of API; (2) modification of the formulation can alter the drug pharmacokinetics, because absorption speed and rate can be impacted; (3) on the contrary, a risk of under-dosing because gastric juices or interaction with liquid/food can degrade the API; (4) secondary effects caused by interactions with buccal membranes, i.e., mouth numbness, or a change in smell or taste; (5) higher risk of respiratory infections due to microaspiration of particles when a crushed tablet is given with food; (6) a health and safety hazard for the caregiver that crushes the tablet without personal protective equipment and could inhale or accidentally ingest the powder (8,11–14). The crushed tablets also carry the risk of occlusion of the Percutaneous Endoscopic Gastrostomy (PEG) tube: this event occurred in up to 35% of patients, with the crushed tablets being a common cause, making both medication administration and food intake impossible until the tube was unblocked or replaced (15,16). Mixing the medication with a patient's food raises further concerns: (1) the patient may not receive the correct dosage of medication since there might be residuals in the plate or in the glass and (2) the food could affect the blood concentration of API after administration (17).

ALS poses many challenges for clinicians, who have to determine the best route of administration in relation to the patient's condition and sensitize patients and caregivers to the potential risk of altering riluzole formulation. Many studies have investigated crushing tablets in general hospitals and specialized geriatric units and evaluated their consequences (11–13,16,18). Despite all the mentioned negative effects, there is tangible evidence that some patients take unauthorized, and often unreported decisions regarding their therapy administration because of their swallowing problems, with a possible consequence in treatment adherence (2). This study aims to evaluate the impact of crushing riluzole tablets on powder and API loss in a home-simulation experiment.

2. Materials and methods

2.1. Volunteers

Crushing was carried out by 15 different subjects. The operators were healthy and had no experience in the preparation of medication in a clinical setting. In order to represent real-life conditions, each volunteer was free to choose (1) the force applied, (2) the endpoint of the crushing, i.e., the particle size of the powder (3) how to collect the powder after crushing (e.g. with the help of a hand, a knife or paper). The volunteers used two different methods with common tools available in a household, a meat tenderizer or two stacked spoons. Grinders, mortar, pestle, or other instruments frequently used in a hospital setting were unavailable.

This study was performed according to the Declaration of Helsinki. The authorization for the processing of personal data carried out for scientific research purposes was provided by all participants.

2.2. Crushing methods

The crushing test was carried out on 150 coated tablets obtained from three different packs of Rilutek (50mg riluzole, Sanofi, Batch 0MU5E, expiration date 06/2023). Each volunteer was asked to manually crush 10 tablets, 5 tablets with each method:

- The meat tenderizer method (method A) - the tablet was crushed under the force exerted by the volunteer with a meat tenderizer. The volunteer was free to choose the surface on which to complete the test (i.e. directly on the table or on paper). The powder was collected through paper or by sliding a knife across the table, placed into a weighing boat, and then transferred to a volumetric flask.
- The spoon method with two stacked spoons (method B) - the tablet was crushed using a spoon pressed against another spoon (one on top of the other). With this method, the volunteers collected the powder in the lower spoon,

placed it into a weighing boat, and transferred it to a volumetric flask.

2.3. Powder loss

The weight of the intact tablets (W1) and the powder obtained after the crushing (W2) was determined with a laboratory balance, analytical scale, Gibertini E50S/2 (Italy), readability 0.01 mg. Both weights were determined using the same weighing boat, exactly at the moment before and after the crushing. The difference between the weights was due to powder remaining in the device and dust lost in the environment.

2.4. Content of API in the recovered powder

From the entire set of crushed tablets, we selected the two samples with the highest powder loss in order to evaluate the "worst-case scenario of API recovery". Test sample preparation was adapted from the protocol "Uniformity of Dosage Unit Samples (200 µg/mL Riluzole)" used by the pharmaceutical company Zambon, Italy. Each individually crushed tablet was transferred into a separate 100.0 mL volumetric flask. Approximately 50 mL of diluent (0.1 N HCl in ACN, *v/v* 20/80) was added. Samples were sonicated for 5 min, allowed to cool down to room temperature and mechanically shaken for 15 min to dissolve the drug. Then, the volume was filled up to 100.0 mL. The solution was mixed and filtered through a 0.45 µm PVDF membrane filter (VWR International, Italy) and an aliquot of 4.0 mL was taken and further diluted in a 10.0 mL volumetric flask. HPLC analysis was performed using an Agilent 1100 series HPLC system in a total run time of 10 min. Chromatographic conditions were according to the validated protocol "Riluzole identifications, assay, uniformity of dosage units and related substances (HPLC-UV)" by Zambon: column, Luna C18(2), 3 µm, 4,6 × 150 mm (Phenomenex, Italy); mobile phase, 50:50 acetonitrile (ACN): ammonium acetate buffer (5 mM, pH 6.5); flow rate, 1.0 mL/min; column temperature, 30 °C; sample storage, room temperature; injection volume, 5 µl. The UV wavelength was 220 nm. The recovery of the riluzole active ingredient was calculated with respect to the labeled content of 50mg.

2.5. Statistical analysis

The loss was calculated as the weight of the individual tablet (W1) minus the weight of the crushed tablet recovered (W2). The residue (loss) was calculated as a percentage out of the intact tablet weight. Mean and Standard deviation (SD) were calculated overall (all crushing tablets regardless of the methods used) and for each method.

Tests for significant differences between means were performed by Student's *t*-test and the linear regression was calculated with JMP, Pro Version 16 (SAS Institute Inc., Cary, NC, 1989–2023). Differences were considered significant at the $p < 0.05$ level.

3. Results

3.1. Study population

This study enrolled 15 Italian volunteers (6 male, 9 female) with a mean age (±SD) of 46 ± 7 years (men 51 ± 6 years, women 43 ± 7 years). Demographics and further details on support for crushing they used are summarized in Supplementary Table 1.

3.2. Powder loss after crushing tablets

The mean weight of residual powder collected after crushing (W2) was significantly reduced versus the mean weight of the intact tablet (W1) (191 ± 13 mg versus 204 ± 2 mg, $p < 0.001$). The mean (SD; min-max) loss of powder was 13 (±13; 0.005–84.6) mg, corresponding to a mean percentage loss of 6.27%, with values ranging from 0.02% to 41%. (Table 1). The mean percentage of powder loss was higher with method A (8.17%) and consistent with powder loss for method B (Table 1).

According to the FDA recommendation (19), the loss of mass after manipulation should not be above 3% of the total drug mass to prevent impairments on effective dosage: 99 out of 150 values (66%) were out of this range; 37.5% ($n = 56$) of the sample showed more than 6% of powder loss and 7.4% ($n = 11$) more than 15% loss (Figure 1). The crushing surfaces (paper towel or just table surface) chosen by volunteers with method A did not show any significant difference (Supplementary Table 2).

3.3. API evaluation in the residual powder

The API remaining in the residual powder was in agreement with the results of the powder loss: assuming the labeled amount of 50 mg as the arbitrary overall amount of API in the intact tablet, the mean percentage of API loss overall was 8.54% (corresponding to mean API loss of 4.27 ± 4.50 mg), with values ranging from 0% to 41%.

As previously noted in the loss of powder quantification, the mean API loss in the samples of method A was higher (11.17%) than in method B (5.90%) (Table 2). The graphical relation between the API contents and the recovered powder in the two methods showed a linear relation: the higher the powder loss through crushing and collecting, the higher the API loss (R^2 [method A]: 0.98; R^2 [method B]: 0.86) (Figure 2).

Table 1. Analysis of powder loss, overall and per two crushing methods.

	Mean W1 (mg ± SD)	Mean W2 (mg ± SD)	Powder loss (W1-W2 mg mean ± SD; min-max)	Percentage of powder loss (mean; min-max)	*p*-value (W1 vs W2)	*p*-value (Method A vs method B)
Overall	204 ± 2	191 ± 13	13 ± 13;	6.27%;	< 0.0001	–
N = 150			0.005-84.6	0.02-41%		
Method A	204 ± 2	187 ± 14	17 ± 15;	8.17%;	< 0.0001	0.0004
N = 75			0.005-84.6	0.02-41%		
Method B	204 ± 2	195 ± 11	9 ± 11;	4.37%;	< 0.0001	
N = 75			0.011-60	0.05-29.6%		

W1: weight before crushing; W2: weight after crushing; Method A: meat tenderizer; Method B: double spoon; SD: standard deviation.

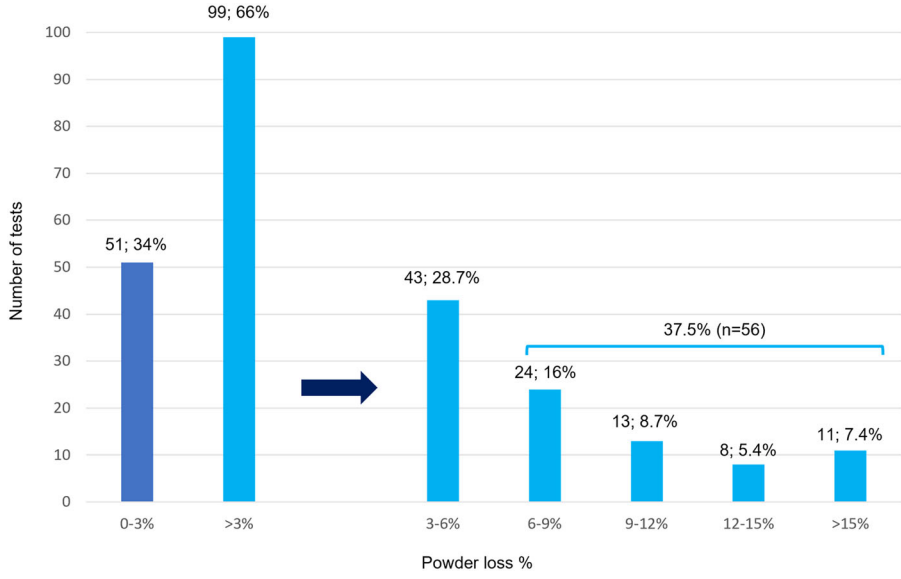

Figure 1. Tests classification by number of tests and percentage of powder loss. The graph on the right side details the distribution of the tests with >3% powder loss.

Table 2. Analysis of API measured in residual powder, overall and in the two crushing methods.

	Mean API recovered (mg ± SD)	API loss* (mg mean ± SD; min-max)	Percentage of powder loss (mean; min-max)	*p*-value (method A vs method B)
Overall	45.73 ± 4.50	4.27 ± 4.50;	8.53%;	–
N = 60		0-20.5	075	
			41%	
Method A	44.41 ± 4.85	5.59 ± 4.85;	11.17%;	0.022
N = 30		0.3-20.5	0.6-41%	
Method B	47.05 ± 3.77	2.95 ± 3.77;	5.90%;	
N = 30		0-16.2	0-32.5%	

Method A: meat tenderizer; method B: double spoon; SD: standard deviation; API: active principle ingredient. *The reference value was 50 mg as per riluzole labeled dosage.

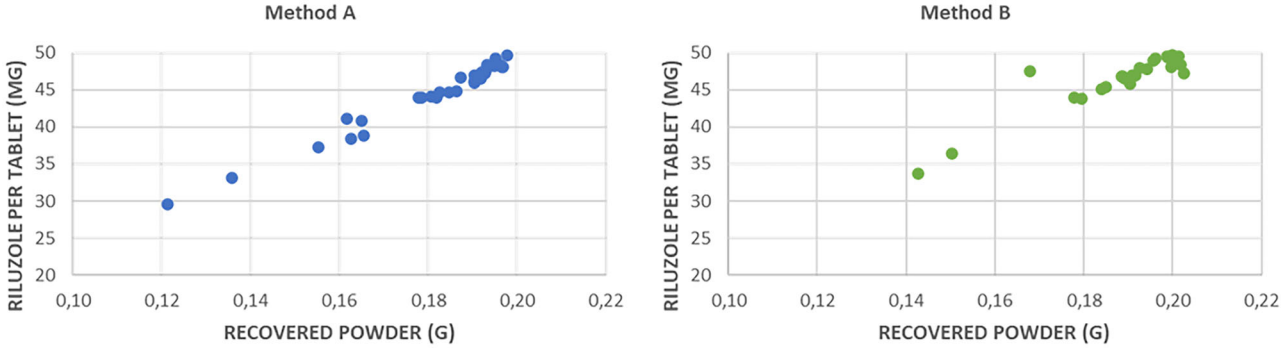

Figure 2. Relation between recovered powder and API after crushing and collecting with both method A and method B.

4. Discussion

This research demonstrated that crushing riluzole tablets led to a mean overall powder loss of 6.27% (with values ranging from 0% to 41%); the difference in weight before and after crushing was high and statistically significant. The mean percentage of powder lost was even higher with method A (8.17%) while method B showed a consistent 4% powder loss. The surface used for crushing the tablets (paper towel or table) with method A did not impact on powder collected.

The study also showed a related mean loss of API of 8.53%: the highest API loss (11.7%) was observed when crushing a riluzole tablet with a meat tenderizer (method A). As expected, there was a linear relationship between the loss of powder and the loss of API for both methods (R^2:0.98 for method A and R^2: 0.86 for method B). The relation between the loss of powder and the risk of underdosing is already proved also in the case of splitted tablets: in this case, the splitting may impact the uniformity and residual effective dosage of the manipulated samples (20,21). When evaluating the distribution of the powder loss according to FDA recommendation, 66% of the samples lost more than 3% of powder, with a potential decrease of the effective dosage (14,19).

This was the first study to evaluate the consequences of crushing riluzole tablets in a simulated home setting. The results showed that crushing the tablets led to a significant loss of powder and API and they probably even underestimated the loss of powder in real-life, because of the experiment setting, the mean age of the volunteers, and the health status of the participants. Although we mimicked the household setting with common tools, this research was, nonetheless, conducted in a controlled laboratory setting, i.e., without any other possible confounders. In addition, the mean age of our volunteers was lower than the mean age of ALS caregivers (46 ± 7 years vs 55.7 ± 12.8 years) (22). Assuming that the higher age of ALS patients and caregivers goes along with less awareness of the related risks, lower strength, and possibly lower accuracy in these preparation tasks, this experimental condition might have positively influenced the efficiency of crushing the tablets and the powder collection. Finally, the research was carried out by healthy volunteers who did not have a motor disability and, reasonably, might have performed better than ALS patients would do.

Our results were aligned with another experimental research performed on a different drug (23): crushing tablets with different professional tools significantly impacted the loss of powder and API. Interestingly, two other publications also showed that the loss of API could significantly be influenced by the formulation of the drug, and they determined that a significant part of the loss of API was linked to the alteration of the film-coating (24,25). Riluzole tablets are film-coated and the impact of crushing might therefore be more significant than for other tablets.

Although EFNS guidelines recommend the need to start riluzole treatment early and ensure that the patient's dosage and autonomy are preserved at different stages of the disease, crushing tablets is a very common practice in managing drug treatments in ALS patients, to overcome swallowing problems with oral medications, due to the early occurrence of dysphagia and reduction of fine motor skills (1,2,7,10). Nevertheless, there is evidence that crushing tablets is a practice that entails many other risks (8,11–14,17). Besides powder and API loss, risks can include additional administration or absorption issues, risk of underdosing and adverse events or secondary effects, with possible impact on patient adherence and persistence. Although only a small side arm ($n = 6$) of the main study and the different routes of administration, a recent publication showed that sublingual administration of a crushed riluzole tablet for a period of two minutes decreased the area under the curve (AUC_0) and the concentration (C_{max}) of riluzole by 94% and 90%, respectively, compared to swallowing the whole tablet (26).

About the adverse events, it is important to underline that riluzole has anesthetic effects, due to its partial blockage of sodium channels (10). The practice of crushing riluzole tablets alters the film-coating and as a consequence could impair the ability to swallow the powder, increasing the risk of aspiration (10). In addition, tablet manipulation could also entail a risk of possible contamination of the powder (14). Although the crushing is performed precisely for improving the patient's comfort, such downsides may contribute to exactly the opposite effect and may promote premature discontinuation of the treatment: if the treatment is prematurely discontinued, this may lead to lower survival of ALS patients (27).

Besides the administration and absorption risks of crushed tablets, it is well documented that patients often mix crushed powder with food or thickened fluids to facilitate drug intake (27). This practice entails important consequences and, in particular, the risk of leaving residuals in the plates or glass, which will additionally impact the correct medication dosage, as well as the risk of promoting different alterations in the pharmacokinetics of the drug (17,27). In particular, the riluzole Summary of Product Characteristics stated that this drug should not be administered with high-fat food: the rate and extent of absorption were reduced when riluzole was administered with fat meals (decrease in Cmax of 44%, decrease in AUC of 17%) (28).

In patients with PEG, crushing tablets carries the risk of tube occlusion, which may cause

dehydration, malnutrition, and the need for additional surgery – these consequences are an additional inconvenience for the patient and increase costs. Consequently, in these patients, a liquid formulation of riluzole or other preventive measures should be used to avoid clogging of the tube (15,29,30). Unfortunately, the riluzole oral suspension also brings other potential problems: some patients found the oral liquids "for children", the glass bottle of their medication difficult to handle, and about 54% of patients found the oral suspension very unpleasant (1,31)

Overall, we can consider crushing riluzole tablets and consequent API loss, the first of subsequent manipulations that can lead to a further reduction of API, potentially resulting in inadequate dosage and treatment inefficacy or an undesired reduced adherence to the therapy. Therefore, unauthorized practices such as crushing tablets remain a crucial challenge in real-life clinical practice.

Our study did not evaluate possibly altered pharmacokinetics, effectiveness and safety risks, or side effects during administration. Moreover, whereas the selection of lay people already differed from trained medical staff, they were still not completely representative of ALS patients and their caregivers.

Despite the extensive literature on the effects of crushed tablets on the pharmacokinetics and bioavailability of other active ingredients, it is crucial to know what happens after crushing riluzole tablets and to investigate the impact of other manipulations of the powder (i.e., mixing it with food or liquids). Further studies comparing the current formulations with new, different oral formulations in terms of pharmacokinetics and bioavailability and in the view of long-term adherence and effectiveness are also highly needed.

5. Conclusions

This was the first study that investigated the impact of crushing riluzole tablets with common household tools and with healthy volunteers without any formal scientific background, with the aim of simulating the manipulation of riluzole tablets in a real-life setting. We documented a significant loss of powder and API after the crushing which may impact the effectiveness of the treatment, expose patients to potential risks, and finally influence adherence in the long term, globally reducing the survival benefit of riluzole treatment. This evidence may be even underestimated due to the simulation setting, used in the research scope, and reinforces the need for further studies to verify how crushing tablets could impact pharmacokinetics and long-term effectiveness and to evaluate the differences with other new oral formulations. These results can support neurologists to evaluate available formulations, that minimize the need for the patient to alter the product and can be more suitable for ALS patients.

Acknowledgments

The authors thank all participating volunteers for their support. The authors also thank Daniela Longo, PhD, of PopMed company, for medical writing and editorial support.

Authors' contributions

ACa and AG contributed to the realization of the research and critical revision of the results;

ACh and IM contributed to the critical revision of the results.

All authors revised the manuscript for important intellectual concepts, read and approved the final version of the manuscript.

Declaration of interest

Data collection and analysis were carried out by Antonella Casiraghi and Andrea Gentile. Article processing charges were funded by Zambon Biotech S.A. PopMed was contracted by Zambon Biotech S.A. for medical writing and editorial support.

Adriano Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Biogen, Roche, Denali Pharma, VectorX, Cytokinetics, Lilly, Zambon Biotech S.A., and Amylyx Pharmaceuticals. He has received a research grant from Biogen. He serves as a member of the independent DSMB for ABScience, AL-S Pharma AG, and Orion.

Ivan Marjanovic is a medical consultant for Zambon S.p.A and Zambon Biotech S.A.

Funding

This study was funded by Zambon Biotech S.A. Antonella Casiraghi and received a research grant from Zambon Biotech S.A. Dr. Gentile has no conflict of interest with this work.

ORCID

Antonella Casiraghi http://orcid.org/0000-0003-3683-8510
Andrea Gentile http://orcid.org/0009-0007-2312-2376
Adriano Chiò http://orcid.org/0000-0001-9579-5341

Data availability statement

The data that support the findings of this study are available from Dr. Antonella Casiraghi from the University of Milan, Milan, Italy; restrictions apply to

the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request by e-mail to antonella.casiraghi@unimi.it and with permission of the Department of Pharmaceutical Sciences, University of Milan, Via G. Colombo 71, 20133 Milan, Italy.

References

1. Dyer AM, Smith A. Riluzole 5 mg/mL oral suspension: for optimized drug delivery in amyotrophic lateral sclerosis. Dddt. 2017;11:59–64.
2. Stegemann S, Gosch M, Breitkreutz J. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. Int J Pharm. 2012;430:197–206.
3. Fang T, Al Khleifat AA, Meurgey JH, Jones A, Leigh PN, Bensimon G, Al-Chalabi A. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. Lancet Neurol. 2018; 17:416–22.
4. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Lancet 1996;347:1425–31.
5. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2012;2012:CD001447.
6. Andrews JA, Jackson CE, Heiman-Patterson TD, Bettica P, Rix Brooks B, Pioro EP. Real-world evidence of riluzole effectiveness in treating amyotrophic lateral sclerosis. Amyotroph Lateral Scler Front Degener. 2020; 0:1–10.
7. Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme F, et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force. European J Neurol.2012; 19:360–75.
8. Povedano Panades M, Couratier P, Sidle K, Sorarù G, Tsivgoulis G, Ludolph AC. Administration of riluzole oral suspension during the different stages of amyotrophic lateral sclerosis. Front Neurol. 2021; 12:633854.
9. Radhakrishnan C, Forough AS, Cichero JAY, Smyth HE, Raidhan A, Nissen LA, et al. A difficult pill to swallow: an investigation of the factors associated with medication swallowing difficulties. Ppa. 2021; 15:29–40.
10. Onesti E, Schettino I, Gori MC, Frasca V, Ceccanti M, Cambieri C, et al. Dysphagia in amyotrophic lateral sclerosis: impact on patient behavior, diet adaptation, and riluzole management. Front Neurol. 2017;8:94.
11. Fodil M, Nghiem D, Colas M, Bourry S, Poisson-Salomon AS, Rezigue H, et al. Assessment of clinical practices for crushing medication in geriatric units. J Nutr Health Aging. 2017;21:904–8.
12. Mercovich N, Kyle GJ, Naunton M. Safe to crush? A pilot study into solid dosage form modification in aged care. Australas J Ageing.2014; 33:180–4.
13. Paradiso LM, Roughead EE, Gilbert AL, Cosh D, Nation RL, Barnes L, et al. Crushing or altering medications: what's happening in residential aged-care facilities? Australas J Ageing.2002; 21: 123–7.
14. Stubbs J, Haw C, Dickens G. Dose form modification: a common but potentially hazardous practice. A literature review and study of medication administration to older psychiatric inpatients. Int Psychogeriatr 2008; 20:616–27.
15. Brooks BR, Bettica P, Cazzaniga S. Riluzole oral suspension: bioavailability following percutaneous gastrostomy tube-modeled administration versus direct oral administration. Clin Ther. 2019;41:2490–9.
16. Kelly J, Wright D, Wood J. Medicine administration errors in patients with dysphagia in secondary care: a multi-centre observational study. J Adv Nurs. 2011; 67:2615–27.
17. Gill D, Spain M, Edlund BJ. Crushing or splitting medications unrecognized hazards. J Gerontol Nurs. 2012;38:8–12.
18. Palese A, Bello A, Magee J. Triturating drugs for administration in patients with difficulties in swallowing: evaluation of the drug lost. J Clin Nurs. 2011;20:587–90.
19. FDA Guidance for Industry - Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation 2013_Available from: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
20. Jacques ER, Alexandridis P. Tablet scoring: current practice, fundamentals, and knowledge gaps. Appl Sci. 2019; 9:3066.
21. Casiraghi A, Musazzi UM, Franceschini I, Berti IO, Paragò V, Cardosi L, et al. Is propranolol compounding from tablet safe for pediatric use? Results from an experimental tests. Minerva Pediatr 2014; 66:355–62.
22. Thong MY, Manrique YJ, Steadman KJ. Drug loss while crushing tablets: Comparison of 24 tablet crushing devices. PLoS One. 2018; 13:e0193683.
23. Woerdenbag HJ, Visser JC, Leferink op Reinink MPAM, van Orsoy RR, Eissen AC, Hagerdoorn P, et al. Performance of tablet splitters, crushers, and grinders in relation to personalized medication with tablets. Pharmaceutics 2022; 14:320.
24. Papiez A, Odehnalova K, Sramek V, Suk P. Comparison of active substance losses and total weight losses of tablets administered via feeding tube. Pharmacology 2019;103: 246–9.
25. Mandrioli J, Malerba SA, Beghi E, Fini N, Fasano A, Zucchi E, et al. Riluzole and other prognostic factors in ALS: a population-based registry study in Italy. J Neurol. 2018;265:817–27.
26. Qureshi I, Lovegren M, Wirtz V, Larouche R, Tanguay M, Anderson MS, et al. A pharmacokinetic bioequivalence study comparing sublingual riluzole (BHV-0223) and oral tablet formulation of riluzole in healthy volunteers. Clin Pharmacol Drug Dev. 2020; 9:476–85.
27. Manrique-Torres YJ, Lee DJ, Islam F, Nissen LM, Cichero JAY, Stokes JR, et al. Crushed tablets: does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release? J Pharm Pharm Sci. 2014; 17:207–19.
28. Emilyf (R) Summary of Product Characteristics_Revised on October 2022.
29. Rahnemai-Azar AA, Rahnemaiazar AA, Naghshizadian R, Kurtz A, Farkas DT. Percutaneous endoscopic gastrostomy: indications, technique, complications and management. Wjg. 2014; 20:7739–51.
30. Malhi H, Thompson R. PEG tubes: dealing with complications. Nursing Times 2014; 110:18–21.
31. Introna A, D'Errico E, Modugno B, Scarafino A, Fraddosio A, Distaso E, et al. Adherence to riluzole in patients with amyotrophic lateral sclerosis: an observational study. Ndt. 2018; 14:193–203.