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# 10 years of riluzole use in a tertiary ALS clinic

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**Abstract**

*Objectives:* Riluzole is a glutamate inhibitor approved for the treatment of amyotrophic lateral sclerosis (ALS). There are scant data regarding factors associated with riluzole initiation and adherence. The goal of this study was to describe the use of riluzole at the Penn State Hershey Medical Center (PSHMC) ALS clinic.

*Methods:* A retrospective medical record review of ALS patients seen at PSHMC from January 2007 to December 2016. A timeline of riluzole use was established for each patient. Factors contributing to dose changes or discontinuations were recorded. Riluzole adherence was assessed using the proportion of days covered (PDC) calculated by the patient-reported length of riluzole use divided by total time from prescription to death/censor. Multivariable analysis was performed to evaluate the association of demography and clinical course with adherence.

*Results:* 723 records were screened, with 508 (307 men, 201 women) meeting criteria for inclusion. The median length of riluzole use was 435 days (range 0-3773). The median PDC for the group was 64%. Those with higher initial overall function and slower rate of decline were more likely to have a larger PDC. No trends in patient demographics, riluzole use, and tracheostomy-free survival were found over time.

*Discussion:* A high rate of riluzole initiation and adherence was found in this sample. The most common reasons for dose modification were related to adverse effects, though social, economic, and patient related factors were also common. The characteristics of riluzole prescription and use have remained relatively unchanged in a single tertiary ALS center over the last ten years.

**Keywords:** riluzole, adherence, amyotrophic lateral sclerosis, management, outcome measure

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## Introduction

Symptomatic treatment of amyotrophic lateral sclerosis (ALS) by a multidisciplinary approach optimizes survival and quality of life (1-6). There are currently only two FDA-approved medications that have been shown to modify the course of ALS (7,8). Riluzole, thought to function as a glutamate signalling inhibitor, has been in use for more than two decades (7,9,10), having been demonstrated to prolong survival in ALS by 2-3 months compared to placebo in two pivotal randomized controlled trials (RCTs) (7,11). Retrospective analysis of a large number of studies of riluzole in clinical practice found prolongation of median survival to be 6-19 months (12). While adherence is generally high in RCTs, it is not known how riluzole adherence in the treatment setting differs from that in the trial setting and, consequently, how this may affect riluzole effectiveness in clinical practice.

To maximize therapeutic benefits, medications should be taken as prescribed. Most relevantly, the portion of disease duration for which riluzole is used appears to impact survival (13). The extent to which a patient takes a medication as prescribed, and the length of the period for which the patient conforms to prescribed therapy are referred to as adherence and persistence respectively (14-16). Factors influencing adherence are broad and include socioeconomic status as well as therapy-related, patient-related, and condition-related factors (17). While these have been extensively studied in other conditions such as hypertension, diabetes, and HIV infection, there are only two studies reporting adherence patterns of riluzole in ALS (18,19). Introna et al. (18) reported widely varying adherence to riluzole based on the 8-question Morisky adherence scale in a study of 45 ALS patients. Notably, gastrointestinal symptoms including nausea, abdominal pain, and dysgeusia were the most common reasons for discontinuation while formulation and comorbidities had no effect on adherence. Parola et al. (19) reported adherence patterns in a group of 77 ALS patients over a 10-year

period. They found that 67% had adherence rates of more than 80% based on drug dispensing and that 16% discontinued therapy. The most common reason for discontinuation of therapy in the latter study was lack of belief in the efficacy of riluzole, possibly for those with advanced ALS, and only one patient discontinued due to gastrointestional intolerance. While these offer valuable insight into riluzole-use patterns, there remains a need for a descriptive account of riluzole use patterns in a large population over a prolonged period of time in a multidisciplinary ALS clinic, in order to better contextualize the clinical survival advantage noted in retrospective studies from clinical practice.

The goal of this retrospective study is to describe the pattern of riluzole adherence over a ten-year period in a large multidisciplinary ALS clinic and to identify changes in adherence over time due to patient demographics and disease characteristics.

## Methods

### *Medical Record Review and Data Collection*

This was a retrospective study, approved by the Penn State Health Institutional Review Board Protocol #00011293. The requirement for informed consent was waived for this study. The initial identification of patients was obtained by review of a database that has been maintained for more than 15 years of patients followed at Penn State Health M.S. Hershey Medical Center (PSHMC) and registered with The ALS Association Greater Philadelphia Chapter. Information on these patients from the 10-year period from January 2007 to December 2016 was extracted from the database and from their medical records at PSHMC. Inclusion criteria were: 1) age 18 years or older; 2) diagnosis of possible, probable laboratory-supported, probable, or definite ALS according to revised El Escorial criteria (20); 3) prescribed riluzole while receiving care

at PSHMC; and 4) followed until death, tracheostomy, or for at least six months after initial riluzole prescription. For those who died or underwent tracheostomy, follow-up required the patient to be seen in ALS clinic in the 90-days prior to that event.

For patients meeting inclusion criteria, further demographic data (age, gender) and clinical history were extracted from their medical records. The date of onset was defined as the time that the patient initially noted weakness, determined from the patient narrative in the initial outpatient clinic evaluation, estimated to the nearest month. The date of diagnosis was determined by the date of the clinic note establishing ALS as the primary diagnosis with other potential diagnoses ruled out. Percutaneous endoscopic gastrostomy (PEG) tube placement and tracheostomy dates were retrieved from the medical record. The dates of the first and final outpatient clinic visits were collected. From the clinical documentation associated with these visits, the King's College stage was determined by a study team member (RA) following a standard operating procedure (21). The summary score of the ALS Functional Rating Scale-Revised (ALSFRS-R) (22) from those visits was also collected from the medical record, if available, and a rate of ALSFRS-R decline calculated from the scores assessed at the first and last clinic visits. Date of death was recorded, if available. Those with no record of death were censored at their last ALS clinic visit at PSHMC.

Riluzole usage was assessed based on self-report as documented in the electronic medical record. At each outpatient clinic visit, patients are asked by the nurse or the physician or both to review all medications they are taking, and to confirm the dose of each. The date of prescription was recorded as the date at which riluzole was prescribed at PSHMC, whether it was a new riluzole prescription or continuation of an existing prescription. For those prescribed riluzole, the date of starting riluzole, if

available, was defined as the time of the first clinical follow-up at which the patient confirmed riluzole use.

The dose and frequency of administration of riluzole were also recorded. For purposes of this study, 50 mg daily and 25 mg twice daily were both considered 50 mg daily. Dosing information was captured at initial prescription and following any dose modifications, including dose changes, discontinuations, or restarts. A dose change refers to change of dose with no associated discontinuation. A discontinuation refers to stopping riluzole therapy completely for any reported period of time. A restart event was classified as re-initiation of riluzole following a discontinuation event. Dates for dose changes, discontinuations, and restarts were gathered from notes in the electronic medical record. Reasons for changes to riluzole use were documented when possible by using a predefined bank of reasons, for which a single dose change could warrant one or more selections: 1) laboratory-identified neutropenia; a complete blood count with differential is checked prior to riluzole initiation, then monthly for the first 3 months following riluzole initiation, then once every 3 months if normal, but monthly or more frequently if abnormal, 2) abnormal liver function test (AST or ALT); these are checked prior to riluzole initiation, then monthly for the first 3 months following riluzole initiation, then once every 3 months if normal, but monthly or more frequently if abnormal; creatine kinase levels are checked at the time of diagnosis, and if they are elevated and the AST and ALT are also mildly elevated (presumably from muscle, not liver), then the latter are considered to be of concern only if subsequent values are above this baseline, 3) gastrointestinal symptoms, 4) PEG placement, 5) increase in weakness or fatigue, 6) cost, 7) patient preference, 8) other, or 9) unknown determination. Reasons for drug discontinuations were also captured, using the same item bank with the addition of ‘advanced disease’ as an option.

Length of riluzole use was defined as the cumulative time on drug between the date of first use and the last reported use or tracheostomy/death. Riluzole adherence was defined using the proportion of days covered (PDC), calculated as the length of riluzole use divided by total time eligible for drug (from prescription to death/censor). Individuals who, as a result of dosage adjustment, were taking riluzole at a dose lower than 50 mg twice daily were still considered to be adherent.

### *Analysis*

The study cohort was described in terms of demographic and clinical variables. Descriptive statistics are given for rate of riluzole prescription, initiation, dosing changes, discontinuations, and restarts. Documented reasons for dose modifications are presented in aggregate.

Multivariable quantile regression was performed to evaluate the association of demography, clinical variables, and medication delays with riluzole adherence (see Table 1 for listing of variables). Quantile regression was utilized due to the non-normality of the dependent variables, and was implemented using the *quantreg* package in R. Two versions of this analysis were performed, using either PDC or the total length of riluzole use as the adherence outcome. The analysis included subjects with a complete set of outcome and predictor data who started riluzole (Length of Riluzole Use and PDC greater than zero). The variance inflation factor was used to describe multi-collinearity between predictors. Testing for longitudinal trends occurring in these clinical, demographic, and adherence metrics over the 10-year period was performed using regression with the date of prescription as the independent variable.

## Results

***Demographics***

The flowchart in Figure 1 describes the proportion of patients included in the study, starting riluzole, and experiencing dose modifications. A total of 723 records were screened, with 508 meeting criteria for inclusion in the analysis. The median age at disease onset was 62.4 years (range 26-89); 307 men (60.4%) and 201 women (39.6%) were included in the analysis. The median ALSFRS-R at first evaluation was 39 (range 13-48), which decreased to 19 (range 0-44) at the final evaluation. At initial evaluation, the numbers of patients in King's Stage 1, 2, 3, 4a, and 4b were 18, 244, 194, 11, and 41, respectively. At final evaluation, this distribution had shifted to 0, 35, 42, 44, and 376, with stage unknown for 11 participants. Twenty-nine patients received tracheostomy and 251 underwent PEG placement. A total of 463 patients were followed until record of death for a median of 580 (3-3839) days. The remaining 45 individuals were censored at their last recorded clinic date, and followed for a median of 1448 (188-3859) days. The median tracheostomy-free survival after the date of disease onset was 978 days (range 124-5689).

***Riluzole use***

The median time from disease onset to prescription of riluzole (at the first visit to our clinic at which at the diagnosis was confirmed) was 360 (32-4165) days. Of all patients included in the study, 460 (91%) started riluzole. The median time from prescription to report of starting riluzole was 59 (0-1101) days. Overall, the median length of riluzole use was 378 days (0-3773), although this was significantly shorter in those patients with an outcome of death (350 days) than in those whose data was censored (1078 days) ($p<0.001$). Of the 232 patients who started riluzole and received a PEG, 193 (83%) remained on riluzole after PEG placement. When necessary, tablets

were crushed and administered via the PEG. Of the 28 who started riluzole and went on to receive a tracheostomy, 13 (46%) remained on riluzole after the start of mechanical ventilation.

***Dose adjustments***

Of those starting riluzole, 319 (69%) continued on their initial dose throughout treatment, whereas others changed dose, stopped, or restarted the drug, sometimes more than once (Figure 1). A detailed depiction of riluzole dosing is given in Figure 2. Nearly all patients who started riluzole (448/460, or 97%) initially received a prescription for 50 mg bid. Forty-one patients (9%) changed dose at least once, for a total of 68 dose changes. When a dose change occurred, the first adjustment was most often to lower the dose to 50 mg daily (28/41, or 68% of first dose changes). The second dose change was most often to increase to 50 mg bid from a lower dose. There were 121 patients who stopped taking riluzole at least once, resulting in a total of 134 discontinuations. Most initial dose discontinuations occurred in patients prescribed 50 mg bid. When riluzole was initially restarted, 50 mg bid was the most common dose, but more than one-third were restarted at a reduced dose of 50 mg daily. Overall, 380 patients who started riluzole (83%) continued to use it in some form until at least 30 days before their final clinical encounter. More than 90% (356) of these patients were taking 50 mg bid at this time, 15 were on 50 mg daily, and the remaining 9 were on other doses or an unknown dose.

There were 75 reasons documented for 68 dose changes (Figure 3), the most common of which was an abnormal liver function test (21%), followed by gastrointestinal symptoms (9%). The majority of 'other' reasons (15/25) were related to dose increases at subsequent dose changes (improved tolerance, liver panel

normalization). There were 161 reasons documented for 134 dose discontinuations (Figure 3). Like dose changes, these were often a result of LFT elevation (10%) or gastrointestinal complications (12%), though cost of the medication (11%), patient preference (11%), and advanced disease (8%) were also common reasons for discontinuation. "Other" reasons occurred 38 times: unlisted side effects (32), transition to hospice (3), medication unavailability (no further details provided, 2), and hospitalization (1).

Data for the time to first dose reduction for elevated liver function tests was available for 11 of 12 patients. The mean was 280 days (median 163, range 61-1175, IQR 107-404) after prescribing riluzole. Excluding one outlier of 1175 days, the longest time was 439 days. Seven of the 11 initial dose reductions occurred within 6 months. Data for the time to first dose discontinuation for elevated liver function tests was available for 14 of 14 patients. The mean was 276 days (median 290, range 48-693, IQR 85-420) after prescribing riluzole. Six of the 14 initial dose discontinuations occurred within 6 months. Neutropenia occurred in 1 patient, resulting in 3 dose changes. The first dose change occurred 119 days after riluzole was prescribed.

***Adherence***

The median PDC for the group was 0.64 (range 0 -1) (Figure 4a). Adherence peaked 122 days after prescription with 74.5% of patients on drug by that point (Figure 4b). This coincides with the approximate time between subsequent clinic visits. When excluding patients who died between the prescribing and first follow-up clinic visit, the maximal drug adherence of patients shifted to 84.9% and occurred at 223 days. By normalizing each patients' duration of disease to a standard scale from prescription to death/censor, we observe that eligible days spent not on drug mostly occurred just after

prescription and at the end stage of disease, with the latter contributing more to reduced adherence (Figure 4c).

Multiple quantile regression was performed separately with the length of riluzole use and the PDC as outcomes (Table 1). High initial ALSFRS-R and slower rate of decline in this score from initial to final clinic visit was associated with higher PDC and greater length of overall riluzole use. Those older at prescription were at greater risk of a shorter course of riluzole, but age was not a significant moderator of PDC. Delay between prescription and reported use of riluzole was also identified as a significant hazard for reduced PDC. Finally, subjects receiving PEG-supplemented nutrition demonstrated increased adherence measured by length of riluzole use and PDC. The variance inflation factors for all the predictor variables included in the analysis were all less than 1.5, indicating low multi-collinearity among model factors. No trends in patient demographics, riluzole use, or tracheostomy-free survival were found as a function of time (Supplementary Figure 1). Also not observed was a change over time in the interval from disease onset to prescription of riluzole or the proportion of people starting riluzole. There was a weak but statistically significant correlation between PDC and survival (Spearman's $\rho = 0.32$, $p < 0.0001$)

**Discussion**

Our study shows that the majority of patients in our multidisciplinary clinic are prescribed and initiate riluzole. Although riluzole is offered to all patients without medical contra-indications at diagnosis (meaning virtually all newly-diagnosed ALS patients), some decline the prescription, or later choose not to start it. While a considerable portion either changed the dose or discontinued the drug at least once, many of those who initially decreased the riluzole dose later increased it, and many who

discontinued it restarted riluzole when the reason for discontinuation was resolved. These data suggest that there was an ongoing effort to have patients on the maximally tolerated dose of riluzole and that simply tracking riluzole use to the point of non-adherence to the initially-prescribed dose (decreased dose or discontinuation) would have only captured a portion of the total riluzole use pattern.

Common reasons for disruptions in riluzole adherence in our series included adverse effects, particularly elevated liver enzymes and gastrointestinal effects, similar to what has been previously reported (17,18). Elevation of liver enzymes has been noted in more than half of patients on riluzole, according to Lexicomp (23). Our findings of high initial adherence are consistent with those of Parola et al. (19). That series found discontinuation for gastrointestinal symptoms rare, but the small size, different definition of adherence, and short period of follow-up preclude direct comparison with our series. Although reasons for dose changes in our study were predominately associated with adverse effects, discontinuations also resulted from condition-related (disease progression) and socioeconomic reasons (cost).

Initial dose reductions or discontinuations resulting from elevated liver enzymes occurred over a very broad time frame, and so did not provide clinically useful information regarding the frequency of monitoring this measure. Because neutropenia resulted in an initial dose reduction in only one patient, and because we did not record the extent of neutropenia, we also cannot provide recommendations for frequency of such monitoring.

Adherence patterns have been more extensively studied for other medication classes. We compared our findings in riluzole to those of statins because the latter are a single class of medications that provide survival benefits without symptomatic improvement. Non-adherence to statins appears to begin soon after prescription

initiation and to progressively increase over time (24-28). One factor that complicates the comparison of riluzole and statin adherence is the dosing frequency, as statins are dosed once daily, a frequency that is associated with higher adherence than the twice a day dosing used with riluzole (29,30). Adherence to statins was worse in individuals for whom these were prescribed for coronary artery disease or primary prevention than for those in whom they were prescribed for acute coronary syndrome. This suggests that sicker patients are more adherent to statins (28).

In contrast, ALS patients with better functional status at the time of prescription and slower progression had higher rates of riluzole adherence. The reasons for this are uncertain, but could be related to patients' perceptions of the drug's greater potential for slowing disease progression earlier in the course or perceptions of its effectiveness over time (slower decline in function being equated with greater drug efficacy and self-justification for adherence). It may also reflect the burden ALS imposes on patients and caregivers (31-33). If function is poor and progression rapid, the patient and caregiver often are consumed by day-to-day management of disease. The majority of patients receiving PEG continued on the drug, and those undergoing this procedure demonstrated relatively greater overall adherence than those without PEG-supplemented feeding.

***Limitations***

This study was limited to the data available in the electronic medical record. Medication use was recorded from patient self-reports and thus may be subject to overestimation of adherence. Adherence can also be measured through records of prescription refills, but that could have its own limitations. Pharmacy records for this cohort of patients have broad distribution by geography and health care system.

Furthermore, patients may refill prescriptions but not take medications as prescribed. Likewise, clinical data were recorded when available, which may have led to some ambiguity regarding follow-up of patients who transferred to/from PSHMC during their period of ALS care. For this reason, we adopted rules for inclusion in the study that retained those who received the majority of their ALS care at PSHMC. There were also uncertainties in some records about care at end-of life, related to the date of last medication dosing. We adopted a consistent method for censoring patients who had incomplete records.

Riluzole dosage adjustments and discontinuations were based on clinical judgement and not on a pre-defined protocol. In general, AST and ALT values 2-3 times the upper limit of normal resulted in a dose reduction, and AST or ALT values more than 3 times the upper limit of normal resulted in drug discontinuation. Monthly monitoring of AST and ALT then occurred, with re-initiation of riluzole or increase in dose based on these guidelines. The results of this study represent the population of a single ALS center in the United States, which may not be representative of prescribing practices elsewhere. Furthermore, insurance coverage in the US varies widely, and discontinuation of riluzole for reasons of cost by our patient population may not reflect practices elsewhere in the US, or in the rest of the world.

**Conclusions**

Our study shows that while the vast majority of patients in a multidisciplinary ALS clinic who were prescribed riluzole started taking the medication, about a thirdexperienced disruptions in therapy at some point during their treatment course. Reasons for these disruptions were varied. A considerable portion of these patients eventually restarted riluzole or had their dosage increased back to the initial dose,

suggesting the importance of regular follow-up visits for dose monitoring and adjustment. Our data also demonstrate that riluzole persistence decreases over time, suggesting that physicians should be mindful to continually encourage riluzole use in their longer-term patients. Because our data suggest that those with more advanced disease and with faster progression had lower adherence to riluzole, it is reasonable to state to patients that riluzole has been demonstrated to prolong survival on average, even in those with advanced ALS (34).

**Abbreviations**:

ALS – amyotrophic lateral sclerosis

ALSFRS-R – ALS Functional Rating Scale - Revised

ALT – alanine aminotransferase

AST – aspartate aminotransferase

BID – twice per day

FDA – Food and Drug Administration

HIV – human immunodeficiency virus

IQR – inter-quartile range

LFT – liver function test

PDC – proportion of days covered

PEG - percutaneous endoscopic gastrostomy

PSHMC – Penn State Hershey Medical Center

RCT – randomized controlled trial

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**Table 1**. Multiple quantile regression for two outcome variables. Results shown for subset of patients who started riluzole and had complete data (n = 358).

| | PDC | | Length Of Riluzole Use | |
|---|---|---|---|---|
| | Coefficient | p-value | Coefficient | p-value |
| Gender | 0.029 | 0.259 | 68.867 | 0.054 |
| Age | -0.001 | 0.291 | **-7.376** | **<0.001** |
| Initial Kings | -0.011 | 0.530 | -23.883 | 0.276 |
| Initial ALSFRS-R | **0.007** | **0.005** | **15.397** | **<0.001** |
| ALSFRS-R Slope | **1.778** | **<0.001** | **3014.405** | **<0.001** |
| Prescription Delay | 0.000 | 0.405 | 0.108 | 0.112 |
| Start Delay | **-0.001** | **0.005** | 0.465 | 0.285 |
| PEG | **0.090** | **0.002** | **81.291** | **0.014** |
| Tracheostomy | **-0.162** | **0.002** | 276.851 | 0.117 |

PDC: Proportion of days covered

**Figure 1**. Inclusion/exclusion criteria, riluzole status, dose modifications, and outcomes for the patients evaluated in the study.

**Figure 2**. Riluzole dosing. A) Riluzole doses at initial prescription. B) New dose at first, second, and third dose changes, if they occurred. C) Dose that was discontinued at the first and second discontinuation, if they occurred. D) New dose at the first and second restarts, if they occurred.

**Figure 3**. Reasons for dose modification. The upper row shows the distribution of reasons for the first, second, and third dose changes, if they occurred. The lower row shows the distribution of reasons for the first and second dose discontinuations, if they occurred.

**Figure 4**. Riluzole coverage in the study cohort. A) Histogram of PDC (proportion of days covered) values for 415 individuals. 45 of these individuals had PDC = 0. B) The number of subjects on drug relative to the date of prescription. C) The number of subjects on drug with the time from prescription to death normalized for each subject.

**Figure 1**

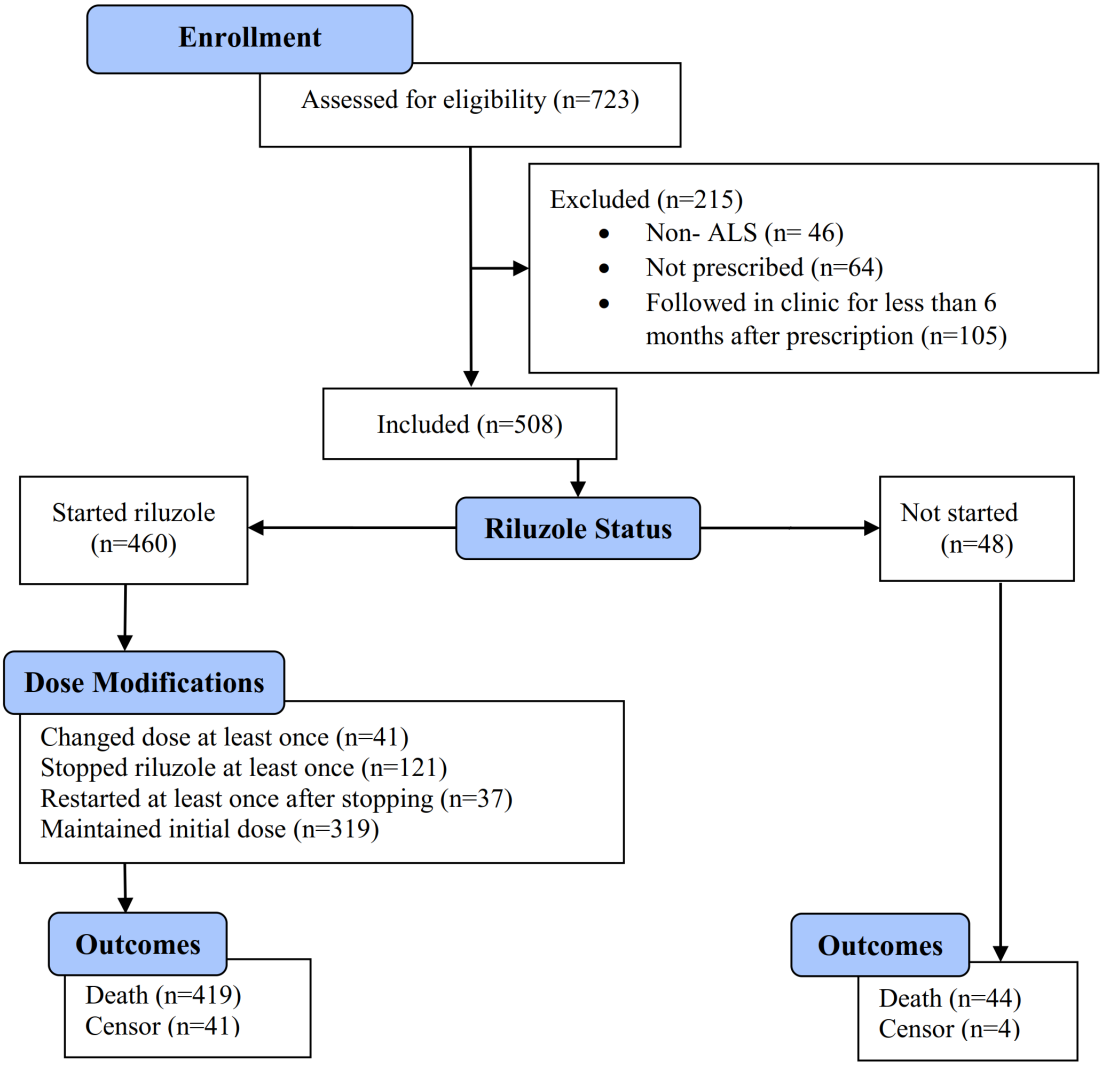


**Figure 2**

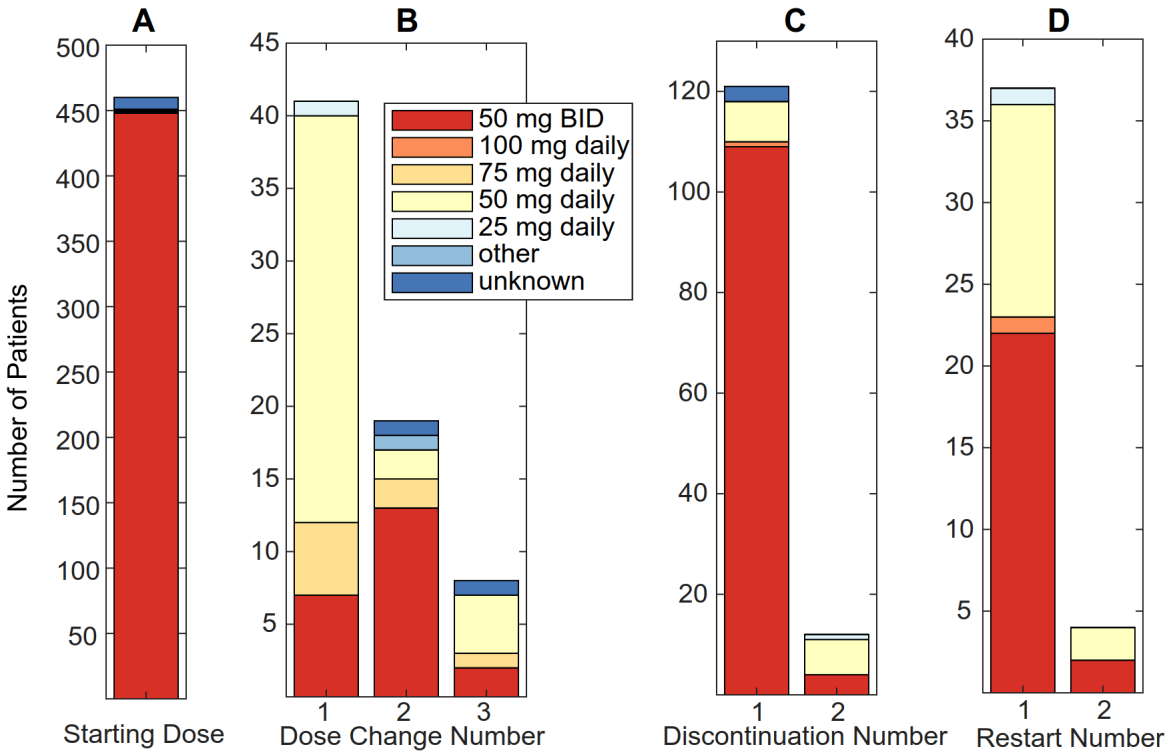


**Figure 3**

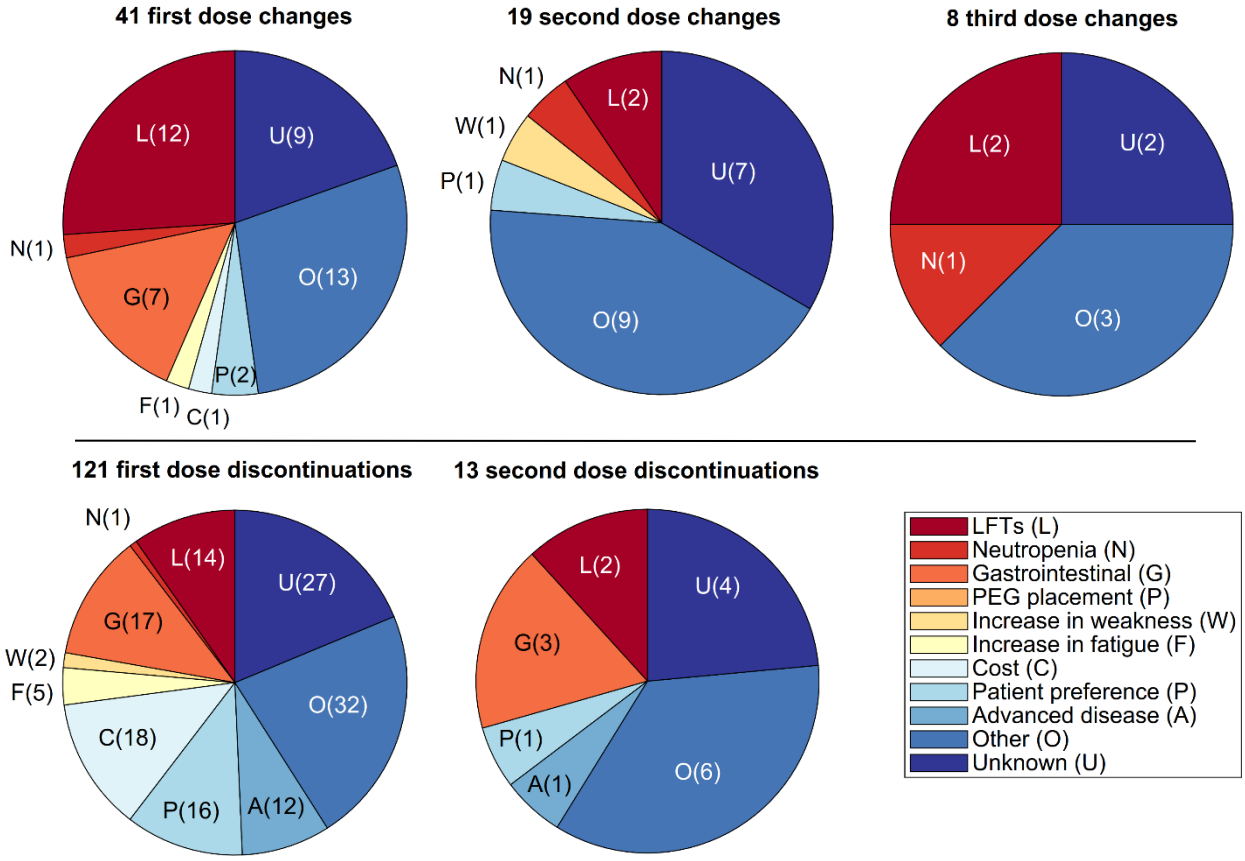


**Figure 4**

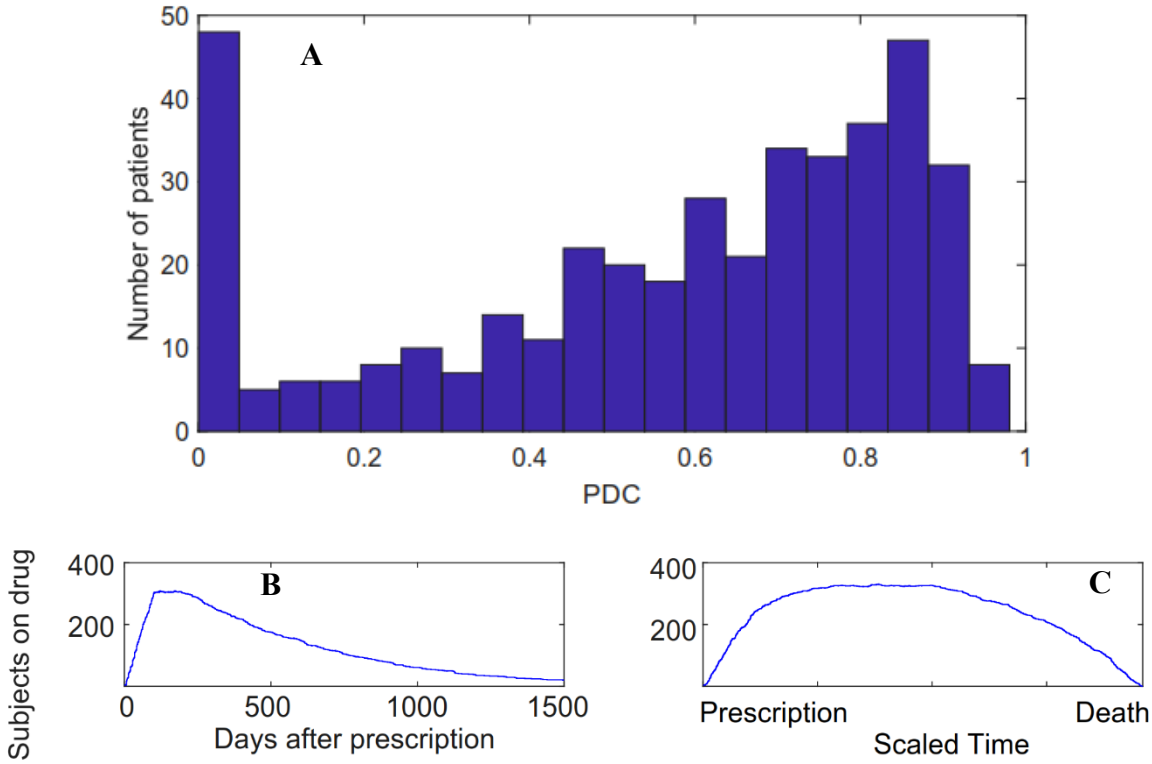
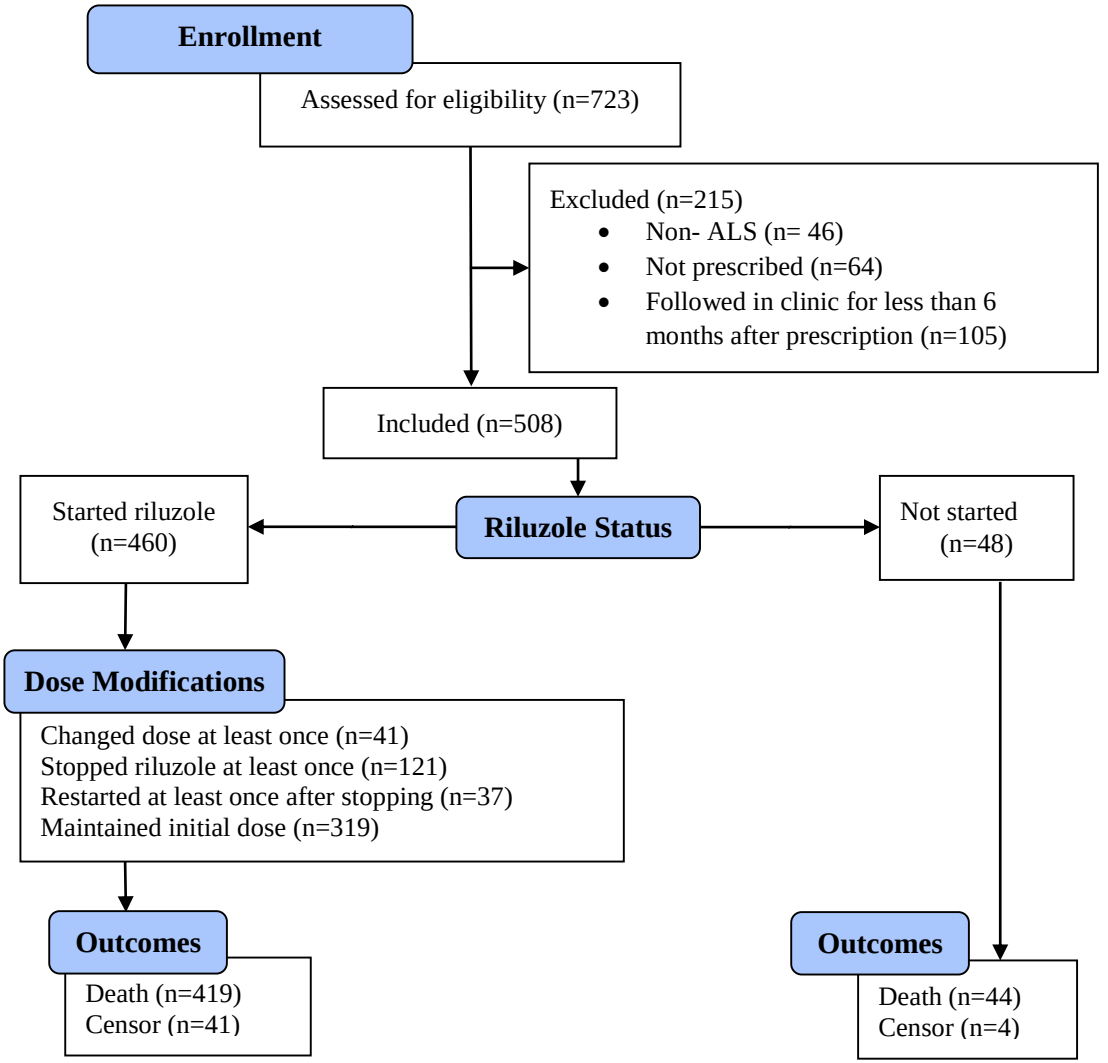
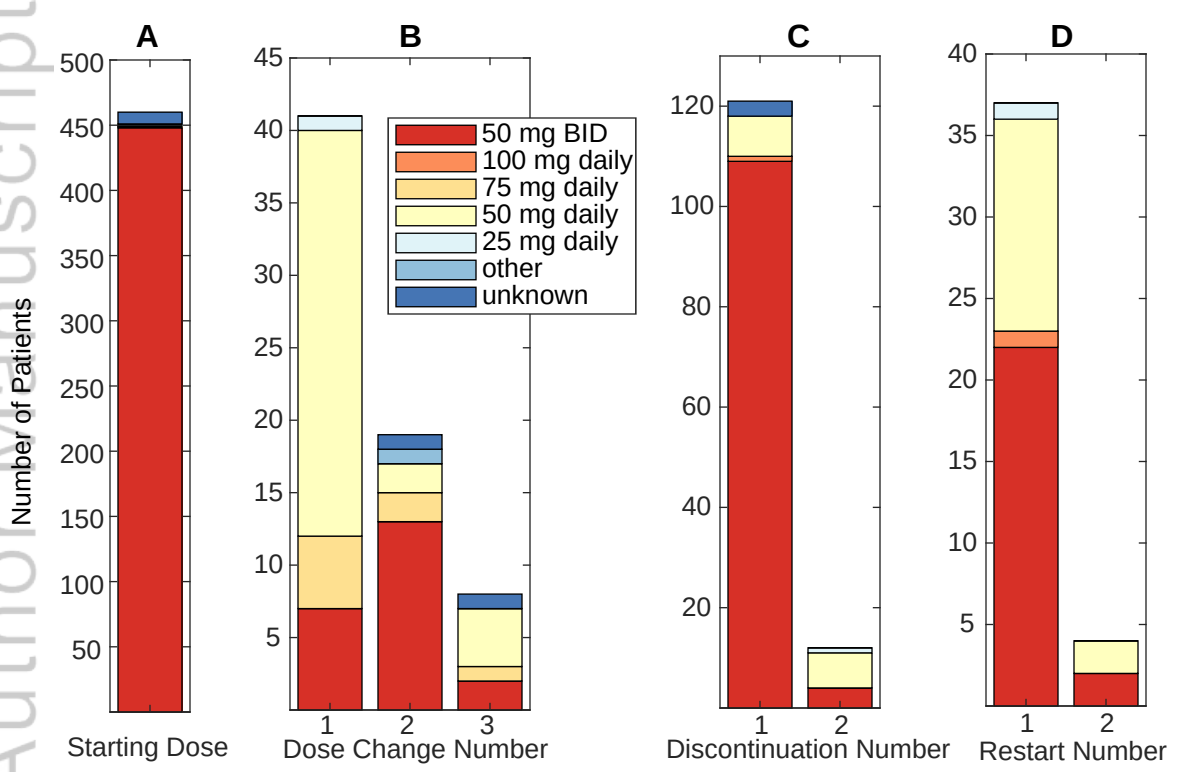
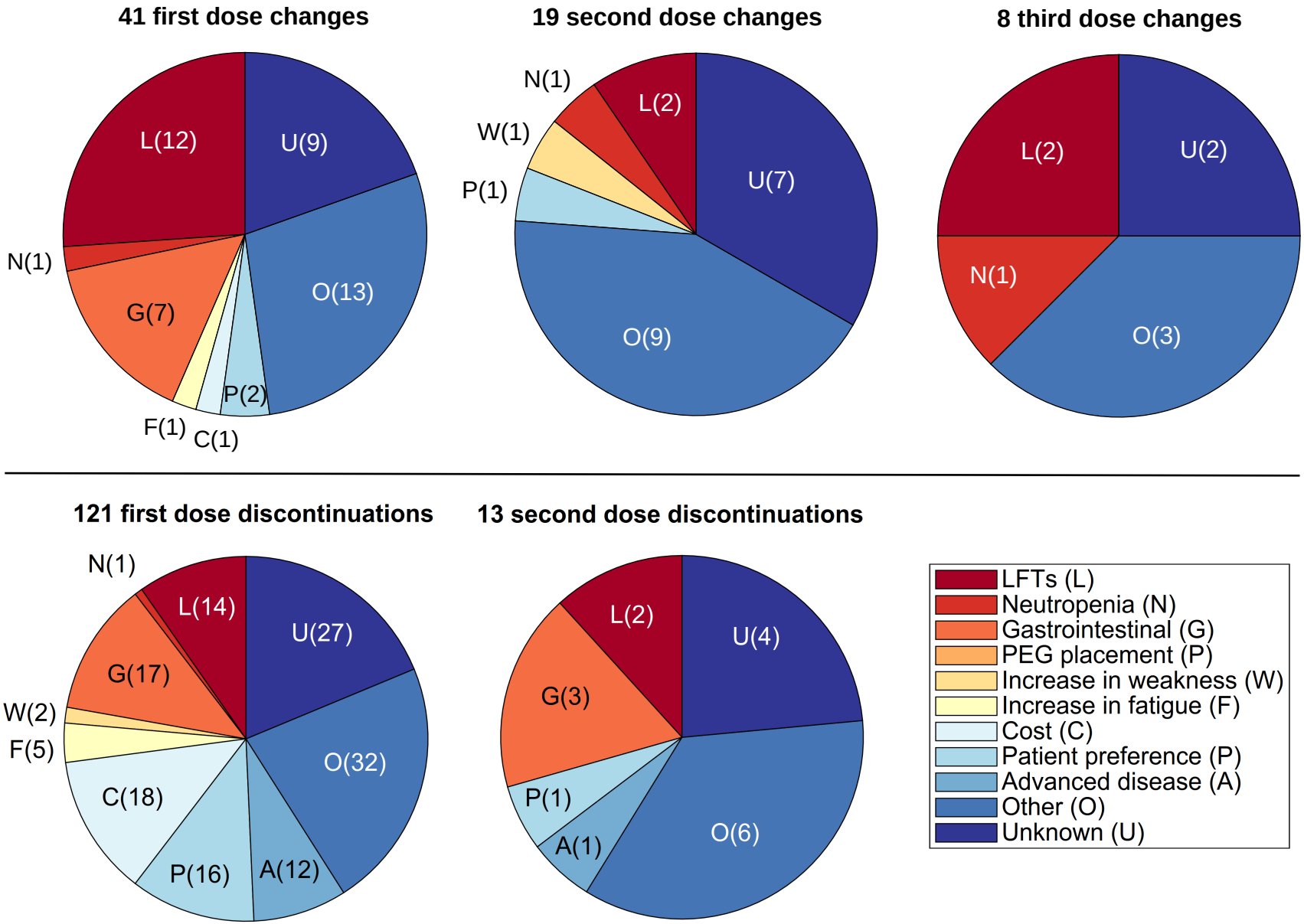
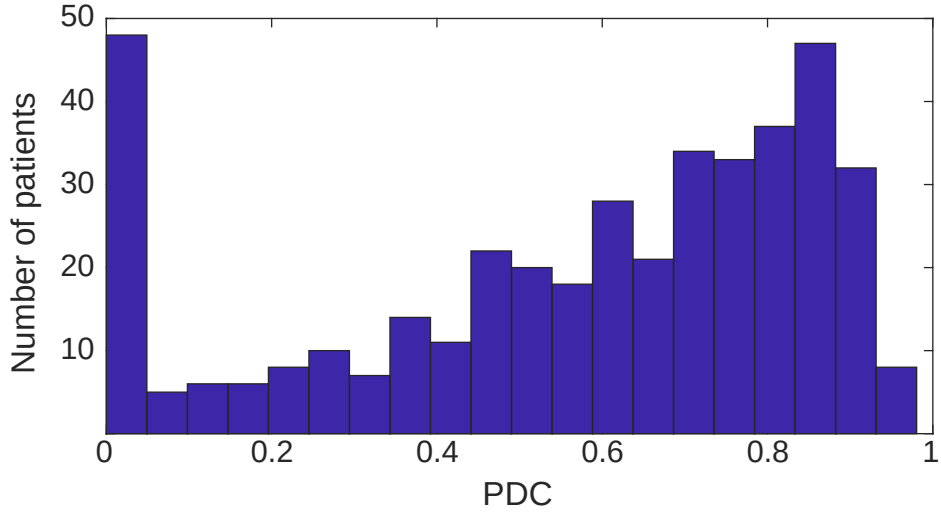


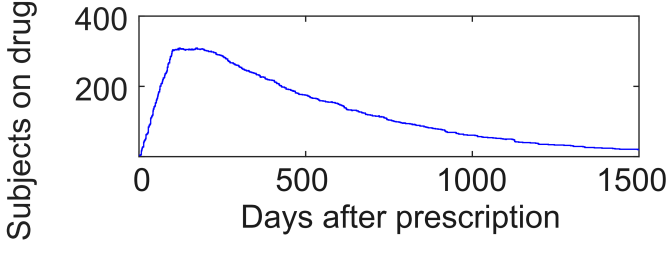
**Figure 1**

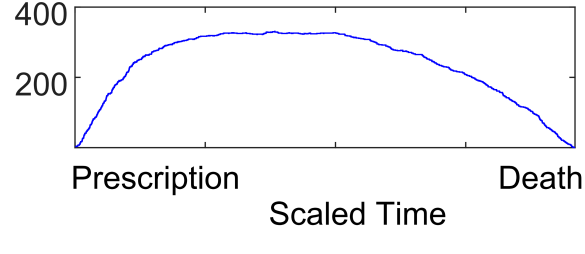

Enrollment
Assessed for eligibility (n=723)
Excluded (n=215)
Non- ALS (n= 46)
Not prescribed (n=64)
Followed in clinic for less than 6 months after prescription (n=105)
Included (n=508)
Started riluzole (n=460)
Riluzole Status
Not started (n=48)
Dose Modifications
Changed dose at least once (n=41)
Stopped riluzole at least once (n=121)
Restarted at least once after stopping (n=37)
Maintained initial dose (n=319)
Outcomes
Death (n=419)
Censor (n=41)
Outcomes
Death (n=44)
Censor (n=4)


A
B
C
D
Number of Patients
500
450
400
350
300
250
200
150
100
50
45
40
35
30
25
20
15
10
5
120
100
80
60
40
20
1
2
3
50 mg BID
100 mg daily
75 mg daily
50 mg daily
25 mg daily
other
unknown
Starting Dose
Dose Change Number
Discontinuation Number
Restart Number


41 first dose changes
L(12)
U(9)
N(1)
G(7)
O(13)
P(2)
F(1)
C(1)
19 second dose changes
N(1)
L(2)
W(1)
U(7)
P(1)
O(9)
8 third dose changes
L(2)
U(2)
N(1)
O(3)
121 first dose discontinuations
N(1)
L(14)
U(27)
G(17)
W(2)
F(5)
O(32)
C(18)
P(16)
A(12)
13 second dose discontinuations
L(2)
U(4)
G(3)
P(1)
A(1)
O(6)
LFTs (L)
Neutropenia (N)
Gastrointestinal (G)
PEG placement (P)
Increase in weakness (W)
Increase in fatigue (F)
Cost (C)
Patient preference (P)
Advanced disease (A)
Other (O)
Unknown (U)


Number of patients
50
40
30
20
10
0
0.2
0.4
0.6
0.8
1
PDC


Subjects on drug
400
200
0
500
1000
1500
Days after prescription


400
200
Prescription
Death
Scaled Time