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Mubeen Janmohamed

Nicholas Lawn

Katrina Spilsbury

Josephine Chan

John Dunne

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TITLE PAGE

Starting a new anti-seizure medication in drug resistant epilepsy: add-on or substitute?

Mubeen Janmohamed [1,4,] Nicholas Lawn [1], Katrina Spilsbury [3], Josephine Chan [1], John Dunne [1,2].

[1] WA Adult Epilepsy Service, Perth, Australia
[2] School of Medicine, Royal Perth Hospital Unit, University of Western Australia, Australia
[3] Institute for Health Research, The University of Notre Dame Australia, Fremantle, Australia
[4] Central Clinical School, Monash University, Australia

Contact information of Corresponding Author:

Mubeen Janmohamed
M.Janmohamed@alfred.org.au
The Alfred Centre, Central Clinical School, Level 6, 99 Commercial Rd, Melbourne VIC 3004

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Summary and Keywords

Objectives Randomized studies in drug resistant epilepsy (DRE) typically involve addition of a new anti-seizure medication (ASM). However, in clinical practice, if the patient is already on multiple ASMs then substitution of one of the current ASMs commonly occurs, despite little evidence supporting this approach.

Methods Longitudinal prospective study of seizure outcome after commencing a previously untried ASM in DRE patients. Multivariable time-to-event and logistic regression models were used to evaluate outcomes by whether the new ASM was introduced by addition or substitution.

Results 816 ASM changes in 436 adult DRE patients between 2010 and 2018 were analyzed. The new ASM was added on 407 (50.1%) occasions and substituted on 409 (49.9%). Mean patient follow-up was 3.2 years. Substitution was more likely if the new ASM was enzyme-inducing or in patients with a greater number of concurrent ASMs. ASM add-on was more likely if a GABA-agonist was introduced or if the patient had previously trialed a higher number of ASMs. The rate of discontinuation due to lack of tolerability was similar between the add-on and substitution groups. No difference between the add-on and substitution ASM introduction strategies was observed for the primary outcome of $\geq$50% seizure reduction at 12 months.

Significance: Adding or substituting a new ASM in DRE has the same influence on seizure outcomes. The findings confirm that ASM alterations in drug resistant epilepsy can be individualized according to concurrent ASM therapy and patient characteristics.

Key words: Epilepsy, drug-resistant, substitution, anti-seizure medications, outcomes.

Key Findings

- *Number of current anti-seizure medications (ASMs) and clinician preference were the most important factors in choosing new ASM substitution over addition.*
- *ASM introduction by add-on or substitution did not influence seizure outcomes.*
- *ASM discontinuation due to side effects was no different between the two groups.*

Introduction

The cornerstone of the medical management of drug resistant epilepsy (DRE) is sequential alteration of anti-seizure medication (ASM), aiming for seizure freedom and improved quality of life. Although the availability of multiple new ASMs has not resulted in a significant improvement in overall prognosis[1], a small but important minority of DRE patients eventually become seizure free after continued changes to ASM treatment[2-4]. Commencing a previously unused ASM is a routine part of management of DRE, but there is relatively little data on how this should be approached and the "art" of rational polytherapy continues to be based on clinician preference and past successes[5-7].

Although multiple factors influence the choice of the ASM including seizure type, epilepsy syndrome, patient-based factors and concurrent ASMs/other medications, an important decision is whether to add the new ASM to the existing ASM combination or to substitute it for one of the ASMs currently being taken. Efficacy data for new ASMs in DRE are based on add-on randomised controlled trials,[8] but in clinical practice the addition of a new ASM may not be possible because of the side effects of the combined drug load, adverse pharmacokinetics or other issues, and substitution is recommended. This decision involves balancing the risk of a significant exacerbation of seizures after discontinuing a potentially useful ASM or ASM combination, perhaps only becoming apparent with ASM withdrawal, versus the risk of side effects and premature cessation of the newly-introduced and potentially helpful ASM because of poor tolerability due to the accumulated drug load.

The aims of this study were to a) identify patient and clinical factors associated with the decision to introduce ASM by addition or substitution, b) to assess the retention of the introduced ASM and how this varied by method of introduction and c) to assess whether

method of ASM introduction influenced seizure response, tolerability and mortality outcomes.

Methods

1. Study design

This was a longitudinal prospective study of patients attending a single epilepsy service between 2010 and 2018. To be eligible, patients needed to have epilepsy of at least two years duration, to have failed two or more ASMs, and with disabling and countable seizures occurring at least once a month. Detailed socio-demographic and clinical information was systematically recorded at the time of enrolment. Electroclinical syndrome was categorised as focal epilepsy, genetic (idiopathic) generalized epilepsy, and developmental and epileptic encephalopathy (symptomatic generalized epilepsy). Drop attacks were defined as tonic or atonic seizures or unspecified seizures other than tonic-clonic seizures associated with a fall or loss of postural tone. Epileptogenic lesions were classified as mesial temporal sclerosis (MTS), malformations of cortical development (MCD) or other. Prior surgery included lesionectomy, anterior temporal lobectomy (ATL), other focal cortical resections, corpus callosotomy and vagal nerve stimulation (VNS).

Patients were followed up at regular clinic visits following all new ASM introductions. Side effects, ASM cessations and seizure outcomes were recorded at each visit until 30th September 2018, date of death or date of last clinic visit if lost to follow up. The study was approved by the Royal Perth Hospital Human Research Ethics Committee (EC 2012/025).

2. Exposure measures

The exposure of interest was whether the new ASM was introduced by addition to the existing ASM combination or whether it was substituted by withdrawing an existing ASM.

All new ASM introductions that occurred before 30th September 2018 and with >90 days follow-up were identified and assessed. Patients' seizure control was assessed at each visit and if suboptimal and dose changes of the current ASMs were constrained, then a new ASM was offered. Substitution was defined as introduction of a new ASM with a clear and specific plan to wean and stop a concurrent ASM. Typically, this involved titration of the new ASM to an initial target dose without any change to the concurrent ASMs and then gradual discontinuation of one of the concurrent ASMs. Add-on categorization required that no specific plan to alter the concurrent ASMs was in place at the time of the introduction of a new ASM.

The choice of drug was based on seizure type, epilepsy syndrome, clinical context, treating doctor preferences and patient wishes. At the time of starting the new ASM, the concurrent ASMs and doses of these documented with the baseline ASM "load" calculated as the sum of prescribed daily dose (PDD) divided by the defined daily dose (DDD) for each co-prescribed ASM[9, 10]. Patients were followed up at regular intervals, typically 1 to 3 months after each ASM change and then further assessed every 3 to 6 months after dose optimization of the ASM, depending on seizure outcome and tolerability. If the new ASM was effective it was continued, and if not the new ASM was either withdrawn, substituted with another ASM or left in place and a new ASM commenced. All patients enrolled had one or multiple separate new ASMs introduced over the course of their follow up.

ASMs were categorised according to primary mode of action as follows: Sodium Channel Blocker (SCB), Gamma-AminoButyric Acid (GABA) analogue, Synaptic Vesicle Protein 2A Binding (SV2A) and Other. Introduced and concomitant ASMs were also categorised as 'older agents' (phenytoin, carbamazepine, benzodiazepines, valproate, phenobarbitone, primidone, ethosuximide) and 'newer agents' (all others). Lastly ASMs were also classified as hepatic enzyme inducing or non-inducing (see supporting information, table S1).

2. Outcome measures

Tolerability and efficacy outcomes were analyzed following each ASM introduction. Retention was assessed by the rate of ASM discontinuations due to side effects or lack of efficacy. Side effects data were documented based on unstructured interviews at routine and unscheduled clinical appointments following ASM introduction. Based on patient history and seizure diaries, baseline seizure frequency was calculated as mean number of seizures per month, averaged over the three months prior to making the ASM change. Lack of efficacy was defined as less than a 50% reduction of seizure frequency.

The primary outcome assessed was the proportion of ASM introductions resulting in ≥50% reduction in seizure frequency compared to baseline for 12 months or longer (responders) at any time after introduction of the new ASM and prior to end of follow up, drug cessation or introduction of another ASM or other epilepsy treatment. Seizure outcomes at 3 and 6 months after ASM introduction and sudden unexpected death in epilepsy (SUDEP) and all epilepsy-related mortality rates were also assessed for the study cohort.

3. Potential demographic and clinical confounders

The association of method of ASM introduction with seizure outcome and new ASM retention were potentially confounded by other factors. Patient demographic and other variables assessed were sex, age at ASM introduction, age at epilepsy onset, intellectual disability (measured or estimated intellectual quotient less than 70) and mental health status. Epilepsy-related variables included seizure type/s and electroclinical syndrome, whether epilepsy was refractory from onset (no previous periods greater than six-months seizure free), a prior history of status epilepticus, etiology of epilepsy and type of epileptogenic lesion if known, prior epilepsy surgery and what type, occurrence of seizure clusters in the last year and hospital admissions for seizures in the year prior to ASM introduction.

3. Statistical methodology

Intention-to-treat (ITT) analysis was utilised with assessment starting from the time the new ASM was added or substituted. Equality of proportions was tested with chi-square tests, and equality of means using t-tests.

Multivariable logistic regression models were constructed to identify patient and clinical factors associated with the odds of a) a new ASM being introduced by substitution compared to addition and b) a ≥50% improvement in seizure outcomes for 12 months or longer. The logistic regression models were constructed using population-averaged generalised estimating equations to account for within-patient correlation.

Time to event (survival) analysis was used to assess factors associated with duration on the newly introduced ASM. Kaplan-Meier survivorship functions were constructed assuming independence between multiple ASM failures per patient and equality of survivor functions tested with log rank tests. Multivariable time-to-event analyses were performed using flexible parametric Royston-Parmar models with time-dependent covariates included when non-proportional hazards were present and standard errors adjusted for patient clustering. SUDEP and all epilepsy-related mortality rates were also estimated using censor date for death being 1st May 2019.

For all regression models, plausible interaction terms were assessed for inclusion and robust standard errors estimated. Parsimonious models, where only variables showing a statistical association with the outcome (i.e. $p < 0.05$) or a strong confounding effect on the method of ASM introduction were included. All analyses were performed using Stata 15 (College Station, TX).

RESULTS

436 patients were enrolled and collectively underwent 822 ASM introductions, 816 of which had at least 90 days follow-up and were included in the study. The cohort comprised a highly

refractory group of adults with DRE, with median duration of epilepsy of 21 years and median number of six prior ASMs (Table 1).

Of the 816 ASM introductions 407 (49.9%) were by substitution and 409 (50.1%) were added on. 229 patients had exclusively 1 ASM change during the period of follow-up, 115 patients had 2 ASM changes and 92 patients had 3 or more ASM changes (totalling 357 drug trials). The proportion substituted or added was similar irrespective of whether it was the first, second or third or more ASM introduced. Twenty-five different ASMs were introduced during the study; however most (85.9%) involved one of ten drugs (lacosamide, clobazam, zonisamide, perampanel, levetiracetam, lamotrigine, topiramate, carbamazepine, phenytoin and valproate in decreasing order, see supporting information, figure S1). Of all ASM introductions, 742 (91%) attained the initial planned target dose, and was slightly less frequently achieved when the new ASM was added (87% versus 93%). Of the most frequently introduced ASMs, substitution was most commonly employed for carbamazepine (82%, $p<0.001$), zonisamide (62%, $p=0.010$) and lacosamide (58%, $p= 0.033$) whereas addition was most commonly used for clobazam (74%, $p < 0.001$) (Figure S1 supporting information).

Factors associated with substitution versus addition of new ASM

Cross-tabulation of patient, doctor and temporal variables with mechanism of ASM introduction are shown in table S2 of the supporting information. Multivariable regression analysis adjusting for other covariates found the method of introduction varied significantly between the three treating doctors, with over three times the odds of substitution for one doctor compared to another (Table 2). Other factors significantly associated with increased odds of substitution were increasing number of current ASMs and having an enzyme inducing ASM introduced. Factors associated with new ASM introduction by add-on were the use of a GABA analogue and increasing numbers of previously trialled ASMs.

Patient age at time of ASM change, age at onset of epilepsy, sex, presence of psychiatric issues, intellectual disability, electroclinical syndrome, prior history of status epilepticus or seizure clusters, prior surgery, admission for epilepsy in last 12 months and presence of an epileptogenic lesion were not associated with the decision to add-on or substitute the new ASM after taking other factors into account.

ASM tolerability and retention with method of introduction

The new ASM was stopped in 366 (45%) of all ASM introductions, predominantly due to side effects (n=128; 35%) or lack of efficacy (n=224; 61%) with a small number for other reasons (n=14; 4%, see supporting information table S3). Of the 10 most frequently introduced ASMs, Zonisamide, Perampanel and Topiramate were stopped more frequently for side effects while Lacosamide and Perampanel were most frequently stopped due to lack of efficacy (Table S3 supporting information).

Time to event analysis was used to assess both the timing and occurrence of discontinuing newly introduced ASMs. Overall, the median duration on new ASM was 3.2 years. New ASM retention at 3, 6 and 12 months was 85%, 76% and 60% respectively. When stratified by method of introduction, the median duration on new ASM substituted was 6.5 years compared to 1.8 years for added ASM (figure 1, log rank p-value 0.003). When restricted to discontinued ASM (n=366) and stratified by reason for stopping (figure S2 supporting information), the median duration for ASM stopped due to side effects was 62 (IQR 20-139) days compared to 251 (IQR 133-473) days for ASM stopped due to lack of efficacy (log rank p-value <0.001).

Multivariable survival regression analysis assessed whether the association between method of ASM introduction and duration on ASM remained after taking positive seizure outcome and other factors into account (see supporting information Table S4). After accounting for other covariates, the rate of discontinuation remained 38% (95%CI 11%-69%) higher in ASMs introduced by addition compared to substitution. Tests for interaction terms indicated that association of method of introduction with duration on ASM did not vary by levels of other covariates.

Other factors (Table S4) independently associated with earlier discontinuation of a new ASM were having <50% improvement in seizures, being female, and being commenced on perampanel. Females were more likely to stop the new ASM than males (48% vs 41%) with weak statistical evidence (equality of proportions, chi square p=0.06). Of patients who stopped their ASM due to any reason, females were more likely to discontinue due to side effects (1.6 ORCI 1.0 – 2.4) compared to males, after adjusting for other significant factors. There was no relationship between sex and discontinuation because of lack of efficacy. Introduction of carbamazepine or clonazepam was associated with higher retention rates when compared to all other drugs combined. There was no evidence that number of current ASMs or total ASM load as assessed by PDD/DDD ratio at the time of new ASM introduction was associated with the rate of discontinuation of a new ASM in the multivariable model (see supporting information figures S3 and S4).

For the new ASM introductions that were stopped because of lack of efficacy or side effects (n=352), time-to-event regression models were used to assess whether the method of

introduction modified the association between duration on ASM and reason stopping after taking other covariates into account. Overall, the average rate of discontinuation was 3.3 (95% CI 2.4 – 4.5) times faster for side effects compared to lack of efficacy (see figure S2 supporting information), however this varied by the method of introduction (interaction p-value= 0.035). For all ASM stopped due to lack of efficacy (figure 2), those introduced by add-on were stopped 40% earlier (HR 1.4; 95%CI 1.1-1.8) than ASM introduced by substitution whereas for ASM stopped due to side effects, there was no difference in duration by the method of substitution (HR 0.9; 95%CI 0.6-1.3).

Seizure outcome.

There were 718 ASM introductions with enough follow up to estimate seizure outcomes at 12 months. There was no difference in the proportion of responders (≥50% reduction of seizures over 12 months or more) by method of ASM introduction (p=0.933) (figure 3), with 89 (25.1%) responders amongst all ASM additions and 92 (25.3%) responders amongst all ASM substitutions. Similarly, there was no difference in the proportion of patients with ≥ 50% reduction of seizures for 3 and 6 months by method of introduction (p=0.057 and p=0.668 respectively.

Multivariable analysis showed the lack of association between method of ASM introduction and seizure outcome remained after taking other patient factors into account (Table 3). Sex, age at ASM change and age at onset of epilepsy by either method of ASM introduction did not influence efficacy outcomes. Higher odds of improved seizure outcomes after new ASM introduction were observed for patients who reached the new ASM target dose and those with a prior history of seizure-free periods. Reduced odds of improved seizure outcomes were

observed in patients with an increasing number of previous ASMs tried and for topiramate as the newly introduced ASM.

Worsening of seizures.

63 ASM introductions (8%) were associated with a worsening of seizures within 180 days of commencing a new ASM, with no significant difference between the two groups (36 added and 27 substituted p = 0.245 chi square test).

Mortality

There were 22 (5%) deaths recorded during follow-up, with SUDEP in nine patients (4.4/1000 patient years, 95% CI 2.3-8.4), other epilepsy-related causes in six patients and death from unrelated causes in seven patients. SUDEP occurred in six patients with last ASM change being add-on and in three patients in whom there had been a substitution but the study was insufficiently powered to detect any clinically meaningful difference in death rates by method of ASM introduction.

DISCUSSION

In our study new ASMs were introduced by substitution and addition equally. Comparison of the two strategies showed no difference for efficacy outcomes, with a quarter achieving at least a 12 month period of 50% or greater seizure reduction in both groups, and with 6% achieving seizure freedom for at least 12 months, seizure outcomes comparable to those seen in randomised and observational studies[2-4, 8, 11]. Although physician differences in using one strategy over another were present, these were not associated with any difference in seizure

outcomes, providing reassurance that individual preference of ASM and method of introduction may be less important than previously thought[5-7]. SUDEP rate in the cohort is comparable to previous DRE cohorts[12] and did not seem to differ according to method of new ASM introduction.

Severity of epilepsy as measured by number of prior ASMs was a strong predictor of a poor seizure outcome as consistently shown in prior studies[2-4]. Reaching an optimized target dose significantly improved seizure control, as shown previously in one study where improvements occurred after increasing ASM dose if it was below 50% of DDD[13]. We did not identify any single ASM to be associated with a greater likelihood of a ≥50% reduction in seizures. However, newly introduced Topiramate was associated with a lower likelihood of ≥50% reduction in seizures, in contrast to randomized trials of DRE that demonstrated topiramate efficacy[14] but concordant with a pragmatic open label study showing that topiramate monotherapy was inferior to other ASMs in both focal and generalised epilepsy[15, 16].

In accordance with typical practice in DRE management, the decision how to introduce a new ASM was largely based on patient and ASM factors but was also highly physician dependent[3,5]. We did not find that age and sex influenced the decision to favor substitution over addition despite the potential for the elderly and women of reproductive age to be more prone to adverse effects of polytherapy[5, 17]. Benzodiazepines were preferentially introduced as add-on treatment, consistent with their recommended use[18]. A history of a greater number of prior ASMs was associated with addition rather than substitution of the new ASM, likely reflecting a relative greater severity of epilepsy and lower response rate in these patients as consistently seen in observational studies of DRE[2, 19].

Number of concurrent medications was also associated with method of ASM introduction, substitution being more likely if the patient was on a higher number of concurrent ASMs, but ASM burden as measured by PDD/DDD ratio was not independently associated with increased odds of substitution.

Although one of the strongest predictors for continuing a new ASM is improved seizure control, we found a lower likelihood of early ASM discontinuation with new ASM substitution compared to addition irrespective of seizure outcome. This appears to be independent of both number of concurrent ASMs and dose burden (as determined by PDD/DDD ratio) as shown in an observational study of lacosamide introduction[20]. However whilst the rate of ASM withdrawal was higher in the add-on group, this was not attributable to a difference in the discontinuation rate due to side effects. This finding is congruent with other studies which show that adverse events are more linked to patient susceptibility, type of ASMs used and physician approach including rate of new ASM introduction rather than number of co-prescribed drugs or ASM load[9]. Furthermore it is likely that clinicians have a lower threshold to discontinuing a newly introduced ASM that has been added and is ineffective or is associated with minor side effects because new ASM cessation simply means a return to baseline treatment. In contrast, withdrawal of a new substituted ASM may be less straightforward because, unless the old ASM is recommenced, the patient will be on less than their baseline treatment. This likely explains the apparent higher rate of discontinuation in the add-on group, and is supported by the finding of a much earlier withdrawal of new ASM introduced by addition as compared to substitution. We also found that females had a higher rate of ASM discontinuation than males, concordant with previous prospective observational studies[21-23]. Higher Adverse Event Profile questionnaire scores were reported in females by Canevini et al[9] and the SANAD trial[23] found that females had a significantly higher rate of unacceptable adverse events and associated treatment failure. Furthermore analysis based on

administrative claims data looking at persistence of therapy based on prescription patterns found ASM combinations containing SCB in females to have a higher HR of discontinuation (HR 1.057, p = 0.05) but not GABA analogue combinations[24]. Another study found a hgher rathe of unacceptable cosmetic side effects of ASMs in females which may also contribute to a higher rate of discontinuation [25]. In contrast, we found that age at ASM change was not a predictor of discontinuation, in particular older patients were no more likely to discontinue the new ASM due to side effects, irrespective of how the ASM was introduced. Furthermore neither age or sex predicted seizure outcomes, in line with other prospective and observational studies of DRE [2-4, 13, 26].

The optimal method of new ASM introduction in DRE in clinical practice has not been well studied, with almost all randomized clinical trials on new ASMs utilizing an add-on design as required to assess efficacy and meet regulatory approval guidelines[8]. Trials using substitution have been less commonly employed for drug approvals ('conversion to monotherapy' using placebo, pseudo-placebo or historical-control group comparators)[27-29]. These trial designs, despite their shortcomings, provide evidence of efficacy of a substitution approach in DRE and have led to several ASMs being approved for use as monotherapy. Randomized studies comparing add-on to substitution in relatively newly diagnosed focal epilepsy patients failing initial ASM monotherapy have shown no difference in seizure outcomes[30, 31] but some observational studies suggest substitution is associated with better seizure outcome and retention rate[32]. Prospective observational studies assessing remission in DRE cohorts do not explicitly analyze seizure outcomes by mode of drug introduction[2, 3] but one recent longitudinal cohort study showed no differences in the two approaches[26].

This was a pragmatic observational study without randomized allocation of the method of ASM introduction, but our data suggest that a major difference in the method of new ASM

introduction and seizure outcome is unlikely. A randomized study of add-on versus substitution with systematic evaluation of quality of life, seizure outcomes and adverse effects would be optimal. Other limitations of this study include crossover ASM change analysis rather than single drug changes in individual patients. Whilst the results were similar for those patients having one ASM change compared to multiple ASM changes, 21% of our patients had three or more ASM changes during the study period, consistent with the high rate of severe DRE in the study cohort which could have masked a possible difference in seizure outcome between addition and substitution that may be identified in less drug-resistant patients.

Furthermore although our study documented side effects prospectively at routine and scheduled clinical appointments, this was based on unstructured interviews rather than a structured questionnaire. A systematic and potentially blinded ascertainment of side effects could have altered discontinuation analysis; for example, it is possible that patients with add-on new ASM experienced more side effects or alternatively physicians and patients were biased towards stopping the new add-on ASM even when similar side effects occurred following introduction of a new ASM by substitution. When evaluated systematically adverse effects of ASMs are more likely to be detected[33] and may provide a more inclusive patient experience of polytherapy, although this approach may not improve health outcomes[34].

Conclusions

We have found that the method of introduction of a new ASM in adults with highly refractory DRE is not a major factor in determining seizure outcomes. Our findings support an individualised approach, with decisions to add or substitute a new ASM according to patient characteristics and concurrent ASM therapy.

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Disclosures of Conflicts of Interests:

Dr Lawn has received honoraria and research funds from UCB pharma and Eisai. The research funding is unrelated to this study. The remaining authors have no conflicts of interest.

Ethical publication Statement:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Figure legends

Figure 1. Survivorship function showing duration on ASM stratified by method of introduction (n=816)

Figure 2 Method of introduction and reason for discontinuation in the subset of new ASM stopped (n=352).

Figure 3 Seizure Outcomes at 3, 6 and 12 months.

Supporting information word document

1. Anti-seizure medication (ASM) drug details
    a. Classification of ASMs by mechanism of drug action (TableS1)
    b. Absolute numbers of added or substituted ASMs (Figure S1)
2. Factor associated with substitution versus addition of new ASM (Table S2)
3. Drug discontinuation analysis

    a) New ASMs and reasons for discontinuation (Table S3)
    b) Relative adjusted hazard rate of stopping new ASM by method of introduction (Table S4.)
    c) Survivorship function for ASM discontinuation by method of introduction and reason for discontinuation of new ASM (n=366) (Figure S2)
    d) Drug burden frequency distribution (figure S3) and survivorship function based on PDD/DDD ratio quintiles (Figure S4)

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