



## Treatment-emergent adverse events and antiseizure medication actual drug load

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### ABSTRACT

**Objective:** The correlation between treatment-emergent adverse events (TEAE) and antiseizure medication (ASM) drug load is a controversial topic. Previous studies used daily defined dosage (DDD) to measure drug load. We aim to assess if ASM adjusted to body weight and plasma levels were associated with TEAE.

**Methods:** We analyzed clinical visits of a trial on therapeutic drug monitoring in outpatients with epilepsy. TEAE, treatment, and its changes, as well as ASM plasma levels, were recorded at each visit. Each medication level was stratified according to its position in relation to its proposed reference range (below, in the lower half, upper half, or above).

**Results:** We analyzed 424 visits (151 participants). Treatment-emergent adverse events were reported in 84 (20%) visits. There was no significant difference when comparing visits with TEAE with those without TEAE in terms of ASM drug load (calculated with DDD), corrected for body weight, their changes since the last visit, as well as summed plasma levels compared to reference ranges.

**Significance:** Actual drug load seems not to represent a major determinant of TEAE recorded during routine visits, even when accounting thoroughly for the patient's exposure to the treatment. The use of structured questionnaires and neuropsychometric tests may assess more accurately the potential consequences of drug loads.

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### 1. Introduction

Treatment-emergent adverse events (TEAEs) are a common cause of failure of epilepsy medical treatment. This leads to a significant challenge, as clinicians have to constantly balance efficacy against tolerability. Care providers may choose between many different antiseizure medications (ASMs), which are usually divided into two categories: older and newer generations, sharing similar efficacy [1]. Newer ASMs are generally better tolerated with less TEAEs and drug-drug interactions [2,3].

Antiseizure medications commonly lead to TEAEs; their prevalence is highly dependent on the method used to collect them,

ranging from 10% [4] for spontaneous reporting up to 90% [5] with structured questionnaires. Due to their action on the central nervous system, ASMs are known to cause sedation, fatigue, somnolence, tremor, incoordination, dizziness, headaches, cognition impairment, or sexual disorder [5]. Psychiatric and behavioral side effects are also common, encountered in approximately 17% of patients [6]. Treatment-emergent adverse events are usually dose-dependent. Whether TEAEs in polytherapy can add up and lead to a drug load effect is a matter of debate [7–9]. Clinically, such a question may arise when adding a small dose of a new medication to a polytherapy, leads to unusually severe TEAEs (typically sedation). In such cases, the overall drug load may be responsible for the poor tolerability of the combined treatments, rather than the recently added ASM on its own.

Drug load was mostly studied using overall ASM dosages (expressed in World Health Organization defined daily dosages;

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WHO DDD), which does not fully account for treatment exposure, since the patient’s weight, individual metabolism, and drug interactions are not taken into account. ASMs have moreover extensive variability in their metabolism, making drug level a better reflection of exposure to the treatment [10].

This study aimed to explore if the drug load reflecting the actual patient’s exposure (considering the patient’s weight and ASM plasma levels) could be a predictor of TEAEs.

## 2. Methods

### 2.1. Participants and samples

Data were extracted from a 2019 randomized controlled 2-arm clinical trial comparing systematic versus rescue therapeutic drug monitoring (TDM) in 151 participants [11]. These were consenting adults (>18 years) diagnosed with epilepsy and treated mostly by newer-generation ASMs. They were either starting a treatment or having dosage adjustments. Pregnant women were excluded as they required systematic TDM. Participants were followed in outpatient clinics for 1 year with a delay between visits left to the appreciation of the treating neurologist. At each visit, TEAEs were recorded through a semi-structured interview. This included a recording of reported TEAEs during the routine interview and questioning for common adverse events of the prescribed medications. For instance, psychiatric symptoms were systematically searched in patients on levetiracetam, brivaracetam, topiramate, and zonisamide; dizziness, double vision for lamotrigine, oxcarbazepine, and lacosamide; weight loss, acral paresthesia for topiramate and zonisamide. Intensity of adverse effects (none = 0, minor = 1, moderate = 2, severe = 3) was systematically recorded. Minor TEAEs were defined as events that did not impact the quality of life, moderate ones those that did impact the quality of life, and severe ones those that caused a significant disability or required inpatient admission. Blood samples were taken and plasmatic concentrations of ASM were measured at each visit; the delay between blood samples and the last dosing was at least 6 h. The endpoints of the trial were either the need to stop the studied medication (because of tolerability issues) or treatment failure because of inefficacy with predefined criteria. All details can be found in [11].

### 2.2. Drug load and TEAE analyses

Among TEAE, we analyzed fatigue separately and we also considered TEAE differently if they led to treatment discontinuation.

We analyzed the drug load by different aspects: number of ASM (including benzodiazepines), drug load, drug load adjusted for body weight, and ASM plasma levels. Drug load was calculated using WHO’s daily defined dosages (DDD) summing ASM and benzodiazepines (as proportions of the DDD) using WHO’s DDD index [12]. As DDD does not take into consideration the patient’s weight, we calculated the drug load per weight. To compare ASM plasma levels, we used ILAE proposed reference ranges [13] to categorize the ASMs “plasma level load”. We scored 0 if the level was below the reference range, 1 if in the lower half, 2 if in the upper half, and 3 if it was above the reference range. This scoring is illustrated in Fig. 1 for plasma levels of lamotrigine and levetiracetam. We then summed these categories for every patient’s treatment, to define the ASMs plasma level load.

We excluded other psychoactive drugs such as antidepressants or anxiolytics ( $n = 13$ ) since their prescribed doses were not always recorded in the original study.

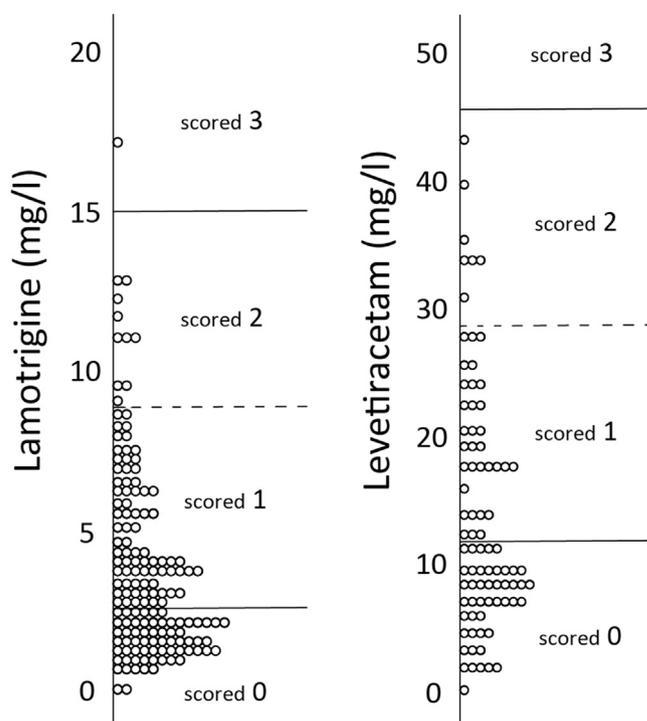


Fig. 1. Distribution of plasma levels of lamotrigine and levetiracetam compared to reference ranges (horizontal lines, dotted line is the middle of reference range) are shown. The figure also illustrates the way the “plasma level drug load” scoring was made.

### 2.3. Statistical analysis

We used the Mann-Whitney U Test to compare patients’ profiles of ASM to the presence or absence of TEAE, and fatigue specifically. The Kruskal-Wallis Test was used for the intensity of TEAEs or their difference in intensity since the last visit. The level of significance was adjusted with Bonferroni correction for multiple testing. A multivariable binary logistic regression was used to adjust for potential confounders associated with TEAEs. The program IBM SPSS Statistic Data Editors version 27 was used for our statistical analysis.

## 3. Results

We analyzed 424 visits; TEAEs were reported in 84 (20%) and plasma levels were available in 293 (69.1%). Demographic and clinical details of the cohort are shown in Table 1. There were no significant demographic differences between patients reporting TEAEs and those who did not. The most common TEAEs are illustrated in Table 2. Antiseizure medications were for the vast majority of newer generation medication (lamotrigine, levetiracetam, oxcarbazepine, topiramate, brivaracetam, zonisamide, or pregabalin), older generations ASMs (valproate and carbamazepine) were reported in 65 visits (15.3%). The frequency of each ASM can be found in Table 3. The distribution of plasma levels of lamotrigine and levetiracetam compared to reference ranges is shown in Fig. 1. Among visits of patients with older generation ASMs, TEAEs were more frequently reported (20/66, 30%) than in visits with newer generation ASMs (64/358, 18%,  $p = 0.017$ , chi-square). Seventeen participants had to stop the treatment because of TEAEs, there was no significant trend toward more treatment discontinuation in visits in which patients were on older ASMs than in visits with only newer ASMs (3% vs 6%,  $p = 0.18$ , chi-square).

**Table 1**  
Demographic data.

|   | All patients<br>(n = 151) | TEAE patients<br>(n = 69) | No TEAE patients<br>(n = 82) | p     | Test used      |
|---|---------------------------|---------------------------|------------------------------|-------|----------------|
| Women                                   | 67                        | 33 (48%)                  | 34 (41%)                     | 0.266 | X <sup>2</sup> |
| Age [years] (median/range)              | 37 (18–82)                | 40 (18–82)                | 35 (18–79)                   | 0.053 | U test         |
| Weight [kg] (median/range)              | 70 (45–109)               | 73 (47–100)               | 68 (45–109)                  | 0.138 | U test         |
| Disease duration [years] (median/range) | 7 (0–47)                  | 4 (0–47)                  | 8 (0–44)                     | 0.058 | U test         |
| Symptomatic epilepsy                    | 79 (52%)                  | 39 (57%)                  | 40 (49%)                     | 0.343 | X <sup>2</sup> |
| Psychiatric history                     | 35 (23%)                  | 16 (23%)                  | 21 (26%)                     | 0.736 | X <sup>2</sup> |
| Number of tried ASM (median/range)      | 1 (0–9)                   | 1 (0–7)                   | 1 (0–9)                      | 0.273 | U test         |
| Number of visits (median/range)         | 3 (1–5)                   | 3 (1–5)                   | 3 (1–5)                      | 0.424 | U test         |

**Table 2**  
Treatment-emergent adverse events.

| TEAE                           |         |
|--------------------------------|---------|
| Fatigue                        | 24 (6%) |
| Irritability and/or depression | 19 (4%) |
| Ataxia/vertigo                 | 12 (3%) |
| Weight gain                    | 8 (1%)  |
| Others                         | 21 (5%) |

**Table 3**  
Frequency of the most common ASM, considering every visit

| ASM               |             |
|-------------------|-------------|
| Lamotrigine       | 200 (31.9%) |
| Levetiracetam     | 124 (19.8%) |
| Zonisamide        | 65 (10.4%)  |
| Topiramate        | 29 (4.6%)   |
| Lacosamide        | 21 (3.4%)   |
| Perampanel        | 11 (1.8%)   |
| Others newer ASMs | 45 (7.2%)   |
| Valproate         | 57 (9.1%)   |
| Carbamazepine     | 20 (3.2%)   |

As detailed in Table 4, there was no significant difference comparing visits in which patients reported TEAEs with those without TEAEs in terms of the number of ASMs, drug load (calculated with DDD), whether crude or adjusted for body weight, changes since the last visit, as well as summed plasma levels compared to reference ranges. The results were not different when analyzing only fatigue as TEAE.

We did not find any significant association with different parameters of drug load analyzing TEAE leading to treatment discontinuation. When considering the reported intensity of TEAEs, drug load (DDD) change since the last visit as well as weight corrected drug load were significant ( $p = 0.012$ ,  $p = 0.015$ , Kruskal-Wallis Test), but did not remain meaningful after correcting for multiple testing. Considering plasma levels of lamotrigine and levetiracetam, we did not find a difference in levels between patients with TEAE compared with those without ( $p = 0.33$  for lamotrigine,  $p = 0.39$  for levetiracetam, Mann-Whitney U test).

**Table 4**  
Main results.

|  | All            | TEAE           | No TEAE        | p     | Test used           |
|--|----------------|----------------|----------------|-------|---------------------|
| Number of ASMs   | 1 (0–4)        | 1 (0–4)        | 1 (0–4)        | 0.235 | Mann-Whitney U Test |
| Drug load (DDD) Median (range)                                   | 1 (0–6)        | 0.83 (0–5.18)  | 1 (0–6)        | 0.594 |                     |
| Drug load (DDD) changes since last visit Median (range)          | 0 (–1.73–2.75) | 0 (–1.73–1)    | 0 (–1.33–2.75) | 0.148 |                     |
| Drug load (DDD)/weight (kg)                                      | 0.01 (0–0.1)   | 0.01 (0–0.1)   | 0.01 (0–0.09)  | 0.723 |                     |
| Drug load (DDD) changes /weight (kg) Median (range)              | 0 (–0.03–0.04) | 0 (–0.03–0.02) | 0 (–0.18–0.04) | 0.136 |                     |
| Summed plasma levels compared to reference ranges Median (range) | 1 (0–6)        | 1 (0–6)        | 1 (0–5)        | 0.938 |                     |

In a multivariable analysis including age, sex, symptomatic epilepsy, psychiatric history, and epilepsy duration, different parameters of drug load were not associated with reporting TEAE.

#### 4. Discussion

Our findings suggest that ASMs drug load, even if considering weight and plasma levels stratified according to reference ranges, is not a major determinant of TEAEs recorded during outpatient visits. Considering specifically fatigue (a symptom that might be related to overall sedation) also did not show any association with the drug load.

This might suggest that TEAEs might be rather related to individual ASMs than the treatment regimen as a whole. Drug load and its relationship to treatment tolerability remain a controversial topic. An early study [9] pooling ASM add-on trials suggested a closer association between TEAEs and calculated drug load using WHO’s daily defined dosage, than counting simply the number of ASMs taken. A more recent study [8] failed to confirm such an association, which might suggest that drug load effects mostly apply to older ASMs. Individual ASM considered in those studies (mostly newer ASMs) may actually have played a role, as older-generation compounds are increasingly replaced by newer ones [14]. A recent Indian study mostly analyzing older generation ASM found indeed an association between TEAEs and the number of ASM [7]. Older-generation ASM is considered to have poorer tolerability (though not unequivocally) [15], and in our study, patients on older ASMs reported more frequently TEAEs. This finding is however not sufficient to demonstrate that a drug load effect occurs predominantly with older ASM: the small sample of older ASM prevented this analysis.

Overall, our results suggest there is little correlation between TEAEs and drug load and there are several potential explanations for these findings. One potential explanation is that pharmacodynamics are more important than pharmacokinetics aspects in the occurrence of TEAEs. Despite our attempts to account as precisely as possible for the patient’s treatment exposure, we did not take into account the pharmacodynamic properties of ASM. Combining ASM with similar mechanisms of action can lead to adverse events that can be addressed by balanced titration. This was typically shown in polytherapies combining several sodium channels block-

ing ASM [16]. Such effect is however difficult to demonstrate in larger patients' samples [17], possibly because it occurs only in a subset of patients. Considering a variety of ASM regimens complicates the detection of such effects, as some medications have multiple mechanisms of action. Another factor potentially explaining the lack of correlation between TEAEs and drug load is the wide interindividual variability in TEAEs reporting rates according to cultural differences, relationships between patients and physicians/nurses, as well as tolerance of discomfort [18–20].

The way adverse events were recorded is a very important point and a limiting factor in our study. We used semi-structured interviews as in routine clinical practice, and our rate of TEAE was only 20% (of visits), which is lower than in studies in a similar setting (33–36%) [8,21], suggesting that underreporting might be an issue. However, throughout the study, almost half (44%) of the patients reported TEAE, which is closer to the results of follow-up studies (61%) [17]. Our study has further limitations. Other psychoactive medications, such as antidepressant or neuroleptic compounds, may participate in drug load effects, but their precise dosages were not available. We did however include benzodiazepines. Blood samples were taken at least 6 h after the last dosing, while this method does not formally provide trough levels, the results are very close [22]. We could not investigate the association between seizure freedom and TEAEs; changes were made to the treatment during the study and the follow-up period was insufficient to fully ascertain that the patients would remain seizure-free. Finally, our participants were consenting adults; this may represent a selection bias since patients with highly disabling causes for epilepsy were not included. Our results suggest TDM may be of little help in assessing the drug load in TEAE. These findings do not obviously imply that TDM is not useful altogether; several situations clearly benefit from TDM, such as compliance assessment, pregnancy, and drug-drug interactions.

Questionnaires might represent a better way to assess the prevalence of TEAEs, although they may not reflect clinical practice, as this approach might compensate for patients' interindividual reporting variability and if adverse events are felt related or not to the treatment. Drug load effects also may have neuropsychological consequences that are better estimated through the use of structured psychometric assessments. It was indeed suggested that reducing the drug load improves executive functions after epilepsy surgery [23]; this effect was even stronger than seizure control. Testing cognition as a correlate of the drug load could therefore provide a better surrogate for a cumulating sedative effect of the treatment as a whole [24,25]. Combining drug levels, as a better account of the treatment load and psychometric measurements may offer a better understanding of the adverse effects of ASMs.

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