Title: Therapeutic drug monitoring newer antiepileptic drugs: a randomised trial for dosage adjustment.

Running head: Antiepileptic drugs therapeutic drug monitoring

Irene Aícua-Rapún. M.D. [1], Pascal André PhD. [2], Andrea O. Rossetti M.D.[1], Philippe Ryvlin M.D. PhD. [1], Andreas F. Hottinger M.D. PhD [1], Laurent A. Decosterd PhD.[3], Thierry Buclin MD [2], Jan Novy M.D. PhD. [1].

Affiliations:

1. Department of Clinical Neurosciences, Neurology service, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland.
2. Service of Clinical Pharmacology, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland;
3. Laboratory of Clinical Pharmacology Laboratory, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland.

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Corresponding author:

Dr Jan Novy

Service de Neurologie BH07

CHUV

Rue du Bugnon 21

1011 Lausanne

Switzerland

Phone: +41 21 314 11 90

Fax: +41 21 314 12 90

Email: jan.novy@chuv.ch

ABSTRACT

Objective: Therapeutic drug monitoring (TDM) of antiepileptic drugs (AEDs) is widely established for older generation AEDs, whereas there is limited evidence about newer AEDs. Our aim is to assess the benefit of newer generation AEDs TDM in epilepsy.

Methods: We performed a randomised, controlled trial comparing *systematic* with *rescue* TDM of lamotrigine, levetiracetam, oxcarbazepine, topiramate, brivaracetam, zonisamide, or pregabalin. Participants were adults with epilepsy, in whom treatment with newer generation AEDs was initiated or needed adjustment. In the *systematic* TDM arm, AED plasma levels were available at each appointment, whereas in the *rescue TDM* arm, levels were known only if a study endpoint was reached (inefficacy or adverse events). The primary outcome was the proportion of participants followed over one year without reaching one of the predefined endpoint.

Results: 151 participants were enrolled; global retention in the study was similar in both arms (56% overall, 58% in the systematic and 53% in rescue TDM arm, p=0.6 Cox regression). There was no difference in term of outcome regarding treatment efficacy or tolerability. Partial adherence of clinicians to TDM (adjusting or not AED dosage based on blood levels) did not explain this lack of benefit.

Interpretation: This study provides Class A evidence that systematic drug level monitoring of newer generation AEDs does not bring tangible benefits in the management of patients with epilepsy. Poor correlation between clinical effects and drug levels likely accounts for this finding. However, TDM is useful in several situations, such as pregnancy, as well as compliance issues.

Key words: efficacy, adverse events, antiepileptic drug blood levels, pharmacokinetic, prospective.

INTRODUCTION:

In clinical practice, therapeutic drug monitoring (TDM) is useful to adjust medication dosages of treatments that have large inter-individual and low intra-individual pharmacokinetic variability, show a good correlation between plasma concentrations and clinical effects, and have a narrow therapeutic index [1,2]. Therapeutic drug monitoring (TDM) of older generation antiepileptic drugs (AEDs) such as phenytoin (PHT), carbamazepine, phenobarbital (PB) or valproate, has been widely implemented since 1960. The relationship between AEDs plasma levels and clinical effect has been well established for those agents, allowing to define reference ranges which are widely accepted [3–8].

The use of older generation AEDs is decreasing as newer generation AEDs are being increasingly prescribed[9], mostly because of their better tolerability profile. In this evolving situation, the International League Against Epilepsy (ILAE) published recommendations for the use of TDM [10]. Evidence about TDM in newer generation AEDs is however very scarce. Observational studies showed a correlation between plasma concentration and clinical response for lamotrigine (LTG) [11–13], levetiracetam (LEV) [14,15] and topiramate (TPM) [16–19], whereas for others (brivaracetam (BRV), lacosamide (LCM), pregabaline (PGB), zonisamide (ZNS), perampanel (PER), oxcarbazepine (OXC)) this relationship remains controversial [2,20–22]. Some of these AEDs, such as LTG, LCM, ZNS, or felbamate, show significant inter-individual pharmacokinetic variability due to interactions or metabolism polymorphisms, as they are substrates of hepatic cytochromes or glucuronyltransferases. Other newer generation AEDs have less pharmacokinetic variability (LEV, TPM, OXC), but still show significant changes in their bioavailability with certain co-medications or under specific physiological modifications, such as pregnancy [23–25]. At times, those pharmacokinetic changes may exert dramatic consequences [26,27].

TDM utility for newer generation AEDs was never assessed in a controlled trial. Its usefulness tends however to be accepted and its use is even recommended in specific situations, such as pregnancy [28].

The aim of this study was to assess whether the systematic monitoring of newer generation AEDs plasma levels provides a tangible benefit in the care of patients with epilepsy.

METHODS:

We set up a randomised controlled two-arm clinical trial comparing *systematic* versus *rescue TDM* (ration 1:1). In the *rescue TDM* arm, medication plasma levels were available only when one of the specific predefined endpoint for failure was reached (status epilepticus, ≥2 seizures with loss of awareness during one year of follow-up, need to add-on a further AED or to discontinue the study drug because of predefined inefficacy or poor tolerability).

The study was approved by the ethical committee of our institution (2015-00079) and it was registered in the clinicalTrials.gov database (NCT02739282). The study was independently monitored, and funded by the Swiss National Scientific Foundation (grant 320030_163430).

Participants

Participants were consenting patients older than 18 years of age, diagnosed with epilepsy and followed in our outpatient clinic. They were treated with newer generation AEDs on mono- or poly-therapy (LTG, LEV, LCM, OXC, TPM, ZNS, BRV, PER), either starting a treatment or requiring dosage adjustment because of inefficacy or adverse events. Pregnant women, in whom systematic TDM is recommended [28], were excluded. The study was presented by JN, AOR, AFH, and PR to the potential participants.

Protocol

Participants were randomized 1:1 (following a predefined randomisation list) either into the *systematic* or *rescue* TDM arm. Allocation was in a list covered with paint, which had to be scratched. The randomisation list was organised in cluster and done by the pharmacists (T.B. and P.A.). Each patient was followed for a studied period of one year with visits set as required clinically, usually 3 to 4 times per year. Participants in both arms had blood samples taken at each visit. Time interval between visits was established by the treating physician according to clinical needs. The participants were instructed

to take their medication at least 6 hours before or after the visit to avoid peak level at the sampling time. All blood samples were collected at steady state after the last dosage adjustment.

A pharmacist specialised in TDM (P.A.) and a neurologist (I.A.R.) assessed all plasma levels to ascertain if concentrations were within the reference ranges, taking into account the time of the last dosing and the medication pharmacokinetics. ILAE recommended reference ranges were used (table 2) [10]. In the *systematic* TDM arm, results were systematically communicated to the clinician in charge of the patient within 24 hours. We did not provide target levels to clinicians in the *systematic* TDM arm, but we compared drug levels (after extrapolation of trough levels when needed) with ILAE recommended reference ranges (table 2) [10]. Clinicians were then free to adjust medication using these results. In the *rescue* TDM arm, drug levels were blinded to the physicians during the study follow-up, AED serum levels were communicated to the treating physician only if a study endpoint (see below) was reached. Otherwise, the results became available only at the end of the follow-up period. Therefore, in systematic TDM arm, drug levels were available for the clinician at each, whereas in the rescue TDM arm, drug levels were available only if the treatment failed and needed to be rescued. The rescue TDM arm assessed therefore the management of patients without drug levels available; once an endpoint was reached, drug levels would be available in that arm at the same time the patient would be excluded from the study (drug levels and dosage adjustment performed thereafter would not be considered as part of the outcome). In both arms, clinicians in charge were free to adjust the treatment dosage based on their clinical judgement (for example, if the patient suffered from adverse events AED doses were decreased or AED was stopped and changed), but, as designed, knowledge of drug level was available only for patients in the *systematic* TDM arm. The inclusion period lasted 18 months and the follow-up 1 year.

At the first visit, demographic data, epilepsy characteristics, current and previous treatments were recorded. At later visits, adverse events and seizure frequency, as well as treatment changes were recorded. The final visit occurred at the end of the 1-year follow-up or when an endpoint was reached.

A combined endpoint (representing treatment failure) was used as the primary outcome of the trial, accounting for both efficacy and adverse events. It was defined by the occurrence of any of: ≥ 2 seizures with impaired awareness (with generalised tonic-clonic seizures), status epilepticus (defined as any seizure lasting >5 minutes), need of an add-on AED, or need to discontinue the studied drug (for either lack of efficacy or adverse reactions); the last two criteria were left to the clinician's judgement. Severe adverse events were defined as hospitalisation or urgent medical visit, death, life-threatening condition, or condition leading to a persistent disability. Upon occurrence of an endpoint, the participant would be taken off study with drug levels being made available to the clinician in charge of the patient. We recorded the retention of participants, defined as time of follow-up in the study without reaching any of the previous endpoints. In the rescue group, once the patient got an endpoint and the AED levels were available, if there was AED levels equal 0 or very low, then the patient was contacted and asked by the compliance. When the compliance was bad the AED doses were maintained, and when the compliance was good we suspected a fast inducer metabolization and the dose was increased.

Determination of plasma AED levels

Plasma levels were determined in the clinical pharmacology laboratory of our institution, which developed an Ultra-performance liquid Chromatography coupled to tandem Mass Spectrometry (UPLC-MS/MS) method, requiring 100 µL of plasma for simultaneous quantification within 7 min of the AEDs [29]. Quality controls/certification in external laboratories were regularly performed.

Statistical analysis

Our inclusion target was 150 participants to have sufficient power to demonstrate a 20% difference in treatment failures.

Retention in the study without reaching a predefined endpoint was assessed using survival analysis. *Systematic TDM* and *rescue TDM* were compared using Cox Regression. The outcome was analysed taking into account all patients included ("intention to monitor") as well as considering only patients who followed the protocol ("per protocol"). Subgroup analysis (drug

resistant epilepsy, focal or generalized epilepsy, patients on monotherapy or polytherapy, patients included due to dosage adjustment or to start of a new AED, patients treated with LTG) were analysed as secondary outcomes. Pearson Chi squared and Mann Whitney U tests were used in univariable analyses. *P* values < 0.05 were considered as significant. All analyses were performed using SPSS version 25 (IBM Inc).

RESULTS

Patients

We enrolled 151 patients between June 2016 and December 2017, the overall flow of the trial is shown in figure 1; demographic details of all participants are shown in table 1. Both groups were comparable with respect to age, sex, origin, type of epilepsy, drug resistant epilepsy, epilepsy duration and number of previously tried AEDs. Most had a focal epilepsy (75.5%) and half of the patients had drug resistant epilepsy, according to ILAE's definition of two adequate AEDs failing to fully control epilepsy [30]. Most prescribed AEDs were LTG (66 participants) and LEV (31), followed by ZNS (21), TPM (9), LCM (6) and OXC (4). Half (55%) of the participants were treated with monotherapy. Considering inclusion criteria, 87 (57%) patients were enrolled because of dosage adjustments and 64 (42%) because of introduction of a new AED, of which 17 (26%) were drug naïve.

Outcome

Global retention rate was 56%: 69 patients completed the one-year follow-up without reaching an endpoint. In the "intention to monitor" analysis, both arms had similar retention rates (58% in the *systematic* TDM arm versus 53% in the *rescue* TDM arm, p=0.6, Cox regression, figure 2). Among the 61 participants with endpoints, 34 (55.7%) had ≥2 seizures with loss of awareness, 18 (29.5%) reported adverse events requiring treatment changes, 8 (13.1%) required treatment changes because of inefficacy, and 1 (0.01%) had focal status epilepticus.

In the "per protocol" analysis (figure 1), the overall retention was 56%, without significant difference between *systematic* (58%) and *rescue* (55%) TDM arms (p= 0.7, Cox Regression). Retention rates between the two arms were not

different in subgroups (systematic vs rescue arm): drug-resistant epilepsy (60% in systematic vs 47% in rescue arm, p=0.3); focal epilepsy (58% in systematic vs 57% in rescue arm, p=0.9); generalized epilepsy (58% in systematic vs 49% in rescue arm, p=0.6); participants on mono-therapy (82% in systematic vs 70% in rescue arm, p=0.3), or polytherapy (36% in systematic vs 35.5% in rescue arm, p=0.9); participants included for dosage adjustment (52% in systematic vs 49% in rescue arm, p=0.7); participants included for starting an AED (73% in systematic vs 65% in rescue arm, p=0.6), drug naïve patients (85% in systematic vs 90.5% in rescue arm, p=0.3); and participants treated with LTG (53% in systematic vs 56% in rescue arm, p=0.7).

Plasma drug levels

All AED blood were measured at least 6 hours after the last dosing, 166 (out of 400, 41.5%) were trough levels.

In the “per protocol” analysis, every participant had at least one AED plasma level. Considering all plasma levels of all AEDs in each participant over the follow-up period, the median proportion of drug levels within the reference ranges per participant was 0.5 (range: 0-1). When stratifying all participants according to their proportion of plasma levels within the reference ranges into high (≥ 50%) or low (<50%), there was no difference of retention between participants with a high proportion of drug levels within the range (52%) versus those with a low proportion (59%) (p=0.5, Cox Regression).

In order to analyse the impact of TDM in the *systematic* TDM arm, we calculated the proportion of prescribed dosage changes for each participant with the aim of bringing serum levels within the reference range (typically, increasing dosage when the drug level was below the reference range), as opposed to when those changes were not prescribed, or when they were not aimed at bringing drug levels within the ranges. Taking into consideration all changes made for all medications over the follow-up period, the median proportion of changes aimed at bringing drug level in the reference ranges was 0.5 (range: 0-1). When comparing retention rate of participants with a high (≥ 50%) proportion of changes targeting the references ranges and those with a low proportion (<50%), there was no significant difference (58% vs 70%, p=0.7)

We assessed the proportion of medication changes prescribed by physicians in each arm. After the initial change which was the inclusion criterion, 43 dosages adjustments were prescribed in the systematic arm during the follow-up in 32 participants (out of 58, 55%) and 38 adjustments were made in the rescue arm in 31 participants (out of 59, 53%). There was no significant difference between both arms (p=0.3 chi squared).

We classified adjustments made at each visits in three of the different categories: treatment increase when medication(s) dosage was only increased; treatment decrease when medication(s) dosage was only decreased and balanced changes when some of the medications dosage were increased whereas others were decreased. In a total 81 changes during the follow-up in both arms: treatment increase accounted for 39.1% of changes in the systematic arm, 40.6% to the rescue arm, treatment decrease for 17.2% in the systematic arm, 11.8% in the rescue arm; balanced changes for 43.1% in the systematic arm and 47.4% in the rescue. There was no difference between both arms (p=0.7, Chi Squared).

The median number of visits (and TDM for systematic arm) was 3 in both arms. The median interval between TDM/visits in both the systematic and the rescue arm was 91.3 days (range 10.5-186 in the systematic arm, range 9.5-130.6 in the rescue arm, p=0.9).

Efficacy

When all inefficacy endpoints were being considered together (occurrence of seizures with loss of awareness, need to change treatment because of insufficient efficacy, occurrence of status epilepticus), there was no retention difference between *systematic* (65%) and *rescue* TDM arms (66%, p= 0.9) in the per protocol analysis. When considering the most commonly prescribed AED (LTG, n=49), last plasma levels in participants who had an inefficacy endpoint (median: 3.5 mg/L, range: 0.8-12.2) were not different to last plasma levels in participants without such endpoints in both arms (2.2 mg/l, 0-17.9, p=0.3, Mann Whitney). Similarly, there was no difference for participants on LEV (n=20; median: 10.9 mg/L, range 0-20.3 vs 7.9 mg/L, 1.2-33.6, p=0.6, Mann Whitney).

Adverse events

In the per protocol analysis, 45% of participants reported an adverse event at least once (leading to an endpoint or not) during the follow-up period. Most common features were tiredness (25%), psychiatric symptoms (depression, aggressiveness, 23%), weight changes (17%), and unsteadiness (13%). The retention in both arms when considering only patients having toxicity endpoints (18) was similar in *systematic* (90%) and in *rescue* TDM (85%) (p=0.4). The occurrence of serious adverse events was also similar in both arms (3.9% in *systematic* vs 1.3% in *rescue* TDM, p= 0.6 Chi Square) over the entire follow-up. There was no difference in last LTG plasma levels in participants who reported adverse events endpoints (median: 1.7 mg/L, range: 0-17.9) when compared with last plasma levels of participants without this endpoint, in both arms (2.7 mg/L, 0.7-12.5, p=0.8, Mann Whitney). There was also no difference between arms for participants on LEV (n=20; 4.4 mg/L, range 1.2-7.7 mg/L vs 8.9, range 0-20.3 mg/L, p=0.2, Mann Whitney).

DISCUSSION

This trial does not show any significant benefit of *systematic* TDM of newer generation AED in an outpatients setting compared to *rescue* TDM, representing TDM as it is widely used in clinical practice. Retention was similar in both groups (59% in the systematic TDM group versus 56%). These results suggest that continuously monitoring drug levels provides at most a modest benefit in the outcome of patient with epilepsy. There was no particular subgroup benefitting of systematic TDM.

Retention in the monotherapy group (76%) and in drug naive participants (90.9%) were greater than the global retention as a favourable outcome (at least in term of seizure control) is more likely in these patients[31], with no difference between both arms. We also failed to find a difference between both arms in participants with drug resistant epilepsy, a group in which one might have expected that finer medication dosage adjustment might have been more useful given the greater prevalence of polytherapy and their risk of drug-drug interactions [32]. There was also no benefit of systematic TDM in term of efficacy or tolerability, respectively.

The overall retention in the study (56%) was comparable with a similar clinical trial assessing the benefit of TDM of older generation AEDs [33], and with retention studies assessing add-on newer generation AEDs [34,35], supporting the generalizability of our observations. Our methodology was comparable to the two previous clinical trial of older generation AED TDM [33,36]. In those studies, however, the treating physician was invited to modify the dosage of patients in the *systematic* TDM arm in order to achieve concentrations within the reference ranges. We chose a more pragmatic approach letting the clinician decide whether to adjust dosages, taking into account the overall context of the patient with the knowledge of drug level compared to the reference range.

Despite the negative results of the previous clinical trials, older generation AEDs TDM is widely established in clinical practice, at least for PHT [3,4,37–39]. TDM usefulness for CBZ and VPA is not clear [5,7,33,36,40]. Several limitations of previous as well as our TDM trial may explain these negative outcomes. The adherence of clinicians to adjust dosage according to AED plasma levels was questioned [41]. Despite being invited to do so, several authors pointed out that a substantial proportion of drug levels fell below or above the reference range in the previous trials [10], suggesting adjustments after TDM may not have been performed systematically. Another retrospective study suggested that modifying dosage (for PHT and PB) according to plasma levels is associated with a better outcome in term of seizure frequency and adverse events [41]; interestingly, TDM adherence (adjusting AED doses based on TDM) by physicians was not a determinant of the outcome when comparing high versus low adherence in our study. Physicians might also have learned from TDM in clinical practice and published studies to anticipate AED pharmacokinetic changes, and they may adjust AED dosage reasonably well without knowing actual drug levels. Another more likely explanation for our negative findings on newer AEDs is the poor correlation between clinical effects and AEDs levels [20,21]. We did indeed not find any differences of drug levels (for LTG and LEV), in participants reporting treatment failure, either in term of efficacy or tolerability. Maximal (ceiling) AED levels associated with remission [42,43] might have provided better references in regards of the endpoints of the trial. It was indeed shown that patients may reach optimal seizure control with AED plasma levels often below reference ranges [44–46]. Individual reference ranges (referring to drug levels associated

with a response in an individual patient) might be also more useful in clinical practice [10,39,47–49], but assessing this aspect went beyond our aims.

Our trial assessed the general systematic use of TDM for dosage adjustment, there are however situations in which TDM might be potentially useful: when toxicity is suspected in patients with intellectual disability in whom assessment of adverse effects is difficult; in lack of efficacy despite appropriate dosages; if compliance issues or drug interactions are suspected; in pregnancy; or in case of renal or hepatic dysfunction. When initiating therapy, individual variability also makes targeting a drug level more desirable than a dosage, there is however that this translates in clinical benefit [10].

Our trial has limitations. Due to regulatory issues, its design excluded patients unable to consent, such as those with intellectual disability or cognitive decline, which might represent important groups for TDM, as those patients are less able to report adverse events[10]. Intervals between visits were also irregular, as we chose to remain as pragmatic as possible to maximise adherence with trial protocol. Reflecting clinical practice, blood samples were drawn during the time the participants spent in clinic, drug levels were therefore not for half of them trough concentrations. Participants were however instructed not to take their medication when coming at the morning clinic, blood samples were drawn at least 6 hours after dosing, and were then interpreted taking into account last dosing and medication pharmacokinetics. The endpoints we chose were also more stringent than those used in the previous trials, particularly occurrence of ≥2 seizures with loss of awareness in patients with drug resistant epilepsy. In previous trials, endpoints were typically the need to switch or to add another AED because of toxicity or inefficacy without clearer criteria [33,36]. The endpoints we chose seem however more likely to reflect on a real benefit in patients' quality of life, such as the return of the ability to drive.

The sample size may also limit the ability to show a small significant difference between both arms; but the intervention effect is likely to be small. The trial included all newer generation AEDs available at the time of study, making it a heterogeneous group of drugs to assess. Some of these compounds are likely to be better candidate for TDM, such as LTG. We did however not find any obvious difference when analysing individually LTG and LEV, although the sample size was not large enough to drive firm conclusions.

We could not analyse specific value of systematic TDM for topiramate, oxcarbazepine or lacosamide, due to the small sample size, so usefulness of TDM of these AEDs is unclear. Another important limitation is that the treating physicians were experienced neurologist specialised in epilepsy, our finding could therefore not be applied to patients treated by general neurologists and primary care physicians. Our study also assessed the usefulness of TDM to prevent treatment failure (as defined by our endpoints), but it did not assessed TDM potential benefit after the treatment failed. Our trial assessed the general systematic use of TDM for dosage adjustment, there are however situations in which TDM might be useful; when toxicity is suspected in patients with intellectual disability in whom assessment of adverse effects is difficult; in lack of efficacy despite appropriate dosages; if compliance issues or drug interactions are suspected; in pregnancy; or in case of renal or hepatic dysfunction. When initiating therapy, individual variability also makes targeting a drug level more desirable than a dosage, there is however no evidence that this translates in clinical benefit.

In summary, systematic TDM of newer generation AEDs in patients with epilepsy appears unlikely to bring any tangible benefit in clinical practice; systematic monitoring of newer generation is therefore not justified. TDM should be reserved for selected situations such as pregnancy/pharmacokinetic changes, drug interactions or renal or hepatic failure, suspicion of non-compliance, suspicion of toxicity, lack of effect in spite of correct dosages[2,10,47,48,50].

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Author contributions:

J.N, A.R., L.D, P.A and T.B. realised the conception and design of the study. J.N., A.R., P.R, A.H and I.A-R contributed to the acquisition of data. I.A-R performed the analysis of data. I.A-R contributed to drafting the text and

preparing the figures and the tables. J.N., A.R., P.R, A.H., P.A, L.D. and T.B edited and approved the final version.

Potential conflict of interest:

The authors have nothing to report relevant for the study.

References:

1. Johannessen SI, Battino D, Berry DJ, et al. Therapeutic drug monitoring of the newer antiepileptic drugs. Therapeutic drug monitoring 2003;25(3):347–363.
2. Patsalos PN, Spencer EP, Berry DJ. Therapeutic Drug Monitoring of Antiepileptic Drugs in Epilepsy. Therapeutic Drug Monitoring 2018;1.
3. Buchthal F, Svenmark O, PJ S. Clinical and electroencephalographic correlations with serum levels of diphenylhydantoin. AMA. Archives of Neurology 1960;2(6):624–630.
4. Lund L. Anticonvulsant Effect of Diphenylhydantoin Relative to Plasma Levels. Arch Neurol 1974;31:289–294.
5. Eichelbaum M, Bertilsson L, Lund L, et al. Plasma levels of carbamazepine and carbamazepine-10,11-epoxide during treatment of epilepsy. European Journal of Clinical Pharmacology 1976;9(5):417–421.
6. Tomson T. Interdosage fluctuations in plasma carbamazepine concentration determine intermittent side effects. Archives of Neurology 1984;41(8):830–834.
7. Schmidt D, Haenel F. Therapeutic plasma levels of phenytoin, phenobarbital, and carbamazepine: individual variation in relation to seizure frequency and type. Neurology 1984;34(9):1252 LP – 1252.
8. Schmidt D, Einicke I, Haenel F. The Influence of Seizure Type on the Efficacy of Plasma Concentrations of Phenytoin, Phenobarbital, and Carbamazepine. Arch Neurol 1986;43:263–265.
9. de Groot MCH, Schuerch M, de Vries F, et al. Antiepileptic drug use in seven electronic health record databases in Europe: A methodologic comparison. Epilepsia 2014;55(5):666–673.
10. Patsalos PN, Berry DJ, Bourgeois BFD, et al. Antiepileptic drugs - Best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49(7):1239–1276.
11. Morris RG, Black AB, Harris AL, et al. Lamotrigine and therapeutic drug monitoring: Retrospective survey following the introduction of a routine service. British Journal of Clinical Pharmacology 1998;46(6):547–551.
12. Besag F, Craven P, Berry DJ, et al. The role of blood-level monitoring in assessing lamotrigine toxicity. Epilepsia 1998;39(Suppl 6):131.
13. Fröscher W.; Keller F., Kramer G. et al. Serum level monitoring in assessing lamotrigine efficacy and toxicity. Epilepsia 1999;40(suppl 2):253.
14. Leppik IE, Rarick JO, Walczak TS, et al. Effective levetiracetam doses and serum concentrations: age effects. Epilepsia 2002;43(Suppl 7):240.

15. Sheinberg R, Heyman E, Dagan Z, Youngster I. Correlation Between Efficacy of Levetiracetam and Serum Levels Among Children With Refractory Epilepsy. Pediatric Neurology 2015;52(6):624–628.
16. Penovich P, Schroeder M, Gates J, Morriatry G. Clinical experience with topiramate: correlation of serum levels with efficacy and adverse effects. Epilepsia 1997;38(S8):181.
17. Lhatoo SD, Wong ICK, Sander JWAS. Prognostic factors affecting long-term retention of topiramate in patients with chronic epilepsy. Epilepsia 2000;41(3):338–341.
18. Stephen LJ, Sills GJ, Brodie MJ. Topiramate in Refractory Epilepsy: A Prospective Observational Study. Epilepsia 2000;41(8):977–980.
19. Fröscher W, Schier KR, Hoffmann M, et al. Topiramate: A prospective study on the relationship between concentration, dosage and adverse events in epileptic patients on combination therapy. Epileptic Disorders 2005;7(3):237–248.
20. Krasowski MD. Therapeutic drug monitoring of the newer anti-epilepsy medications. Pharmaceuticals 2010;3(6):1909–1935.
21. Glauser TA, Pippenger CE. Controversies in blood-level monitoring: reexamining its role in the treatment of epilepsy. Epilepsia 2000;41 Suppl 8(s8):S6-15.
22. Krasowski MD, McMillin GA. Advances in anti-epileptic drug testing. Clinica Chimica Acta 2014;436:224–236.
23. Naik GS, Kodagali R, Mathew BS, et al. Therapeutic Drug Monitoring of Levetiracetam and Lamotrigine: Is There a Need? Therapeutic Drug Monitoring 2015;37(4):437–444.
24. Westin AA, Nakken KO, Johannessen SI, et al. Serum concentration/dose ratio of topiramate during pregnancy. Epilepsia 2009;50(3):480–485.
25. Wegner I, Edelbroek P, De Haan G-J, et al. Drug monitoring of lamotrigine and oxcarbazepine combination during pregnancy. Epilepsia 2010;51(12):2500–2502.
26. Novy J, Hubschmid M, Michel P, Rossetti AO. Impending status epilepticus and anxiety in a pregnant woman treated with levetiracetam. Epilepsy and Behavior 2008;13(3):564–566.
27. Cappellari AM, Cattaneo D, Clementi E, Kustermann A. Increased levetiracetam clearance and breakthrough seizure in a pregnant patient successfully handled by intensive therapeutic drug monitoring. Therapeutic Drug Monitoring 2015;37(3):285–287.
28. Harden CL, Pennell PB, Koppel BS, et al. Practice Parameter update: Management issues for women with epilepsy - Focus on pregnancy (an evidence-based review): Vitamin K, folic acid, blood levels, and breastfeeding. Neurology 2009;73:142–149.
29. Decosterd LA, Mercier T, André P, et al. Multiplex Mass Spectrometry Analysis of Latest-Generation Antiepileptic Drugs : A Clinically Useful Laboratory Tool for Improved Real-Time Patients ' Care. Epileptologie 2015;32:85–89.
30. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;1069–1077.
31. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. Epilepsia

2001;42(10):1255–1260.
32. Alexandre Jr V, Capovilla G, Fattore C, et al. Characteristics of a large population of patients with refractory epilepsy attending tertiary referral centers in Italy. Epilepsia 2010;51(5):921–925.
33. Jannuzzi G, Cian P, Fattore C, et al. A multicenter randomized controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy. The Italian TDM Study Group in Epilepsy. Epilepsia 2000;41(2):222–230.
34. Wehner T, Chinnasami S, Novy J, et al. Long term retention of retigabine in a cohort of people with drug resistant epilepsy. Seizure 2014;23(10):878–881.
35. Novy J, Bartolini E, Bell GS, et al. Long-term retention of lacosamide in a large cohort of people with medically refractory epilepsy: A single centre evaluation. Epilepsy Research 2013;106(1–2):250–256.
36. Fröscher W, Eichelbaum M, Gugler R, et al. A prospective randomised trial on the effect of monitoring plasma anticonvulsant levels in epilepsy. Neurology 1981;224:193–201.
37. Andre P, Novy J, Decosterd LA, Buclin T R LE. Therapeutic Drug Monitoring of Antiepileptic Drugs in the 21st century. Epileptologie 2015;32:78–84.
38. Koch-Weser J. Serum drug concentrations in clinical perspective. Therapeutic drug monitoring 1981;3(1):3—16.
39. Johannessen Landmark C, Johannessen SI, Tomson T. Dosing strategies for antiepileptic drugs: from a standard dose for all to individualised treatment by implementation of therapeutic drug monitoring. Epileptic Disorders 2016;18(4):367–383.
40. Bentué-Ferrer D, Tribut O, Verdier M-C. Therapeutic drug monitoring of valproate. Therapie 2010;65(3):233–240.
41. Beardsley RS, Freeman JM, Appel FA. Anticonvulsant Serum Levels Are Useful Only If the Physician Appropriately Uses Them: An Assessment of the Impact of Providing Serum Level Data to Physicians. Epilepsia 1983;24(4):430–430.
42. D'Anto J, Wnuk W, Rossetti AO, et al. Lamotrigine serum levels: Ceiling effect in people with epilepsy in remission? Epilepsy and Behavior 2017;74:41–44.
43. Malerba A, Ciampa C, De Fazio S, et al. Patterns of prescription of antiepileptic drugs in patients with refractory epilepsy at tertiary referral centres in Italy. Epilepsy Research 2010;91(2–3):273–282.
44. Shorvon SD, Chadwick D, Galbraith AW, Reynolds EH. One drug for epilepsy. British Medical Journal 1978;1(6111):474 LP – 476.
45. Feldman RG, Pippenger CE. The Relation of Anticonvulsant Drug Levels to Complete Seizure Control. The Journal of Clinical Pharmacology 1976;16(1):51–59.
46. Woo E, Chan YM, Yu YL, et al. If a Well-Stabilized Epileptic Patient Has a Subtherapeutic Antiepileptic Drug Level, Should the Dose Be Increased? A Randomized Prospective Study. Epilepsia 1988;29(2):129–139.
47. Stepanova D, Beran RG. Measurement of levetiracetam drug levels to assist with seizure control and monitoring of drug interactions with other anti-epileptic medications (AEMs). Seizure 2014;23(5):371–376.
48. Jacob S, Nair AB. An Updated Overview on Therapeutic Drug Monitoring of Recent Antiepileptic Drugs. Drugs in R and D 2016;16(4):303–316.
49. Perucca E. Is There a Role for Therapeutic Drug Monitoring of New

Anticonvulsants? Clin Pharmacokinet 2000;38(3):191–204.
50. Gross AS. Best practice in therapeutic drug monitoring. Br J Clin Pharmacol 1998;46:95–99.

Figure legends:

Figure 1: Flow diagram of the study. The single death was not related to the study (brain tumour progression).

Figure 2: Overall retention in both arms ("intention to monitor" analysis). There was no difference between the *systematic* TDM arm (58%) and the *rescue* TDM arm (53%, p= 0.5 Cox regression).

Table 1: Demographic characteristics of participants according to their randomization. *Combination of all inefficacy endpoints: patients (≥2) with loss of awareness, status epilepticus and need to add a treatment because of inefficacy.

	Total (151)	*Systematic* TDM arm (76)	*Rescue* TDM arm (75)	P value	Test used
Sex (female)	55.6%	55.3%	56%	0.9	Pearson's Chi Square
Age, median, (range)	37(18-82)	38 (18-82)	36 (18-76)	0.5	U Mann Whitney
Focal epilepsy	75.5%	76.3%	74.7%	0.8	Pearson's Chi Square
Drug-resistant epilepsy	48.7%	46.7%	50.7%	0.6	Pearson's Chi Square
Epilepsy duration-years median, (range)	7 (0-47)	8 (0-44)	7 (0-47)	0.7	U Mann Whitney
Number of previously tried AEDs median, (range)	1 (0-9)	1 (0-7)	1 (0-9)	0.3	U Mann Whitney
All inefficacy endpoints*	43 (28.5%)	24 (31.6%)	19 (25.3%)	0.4	Pearson's Chi Square
Adverse event endpoints	18 (12%)	7 (9.2%)	11(14.6%)	0.6	Pearson's Chi Square

Table 2: AED and ILAE recommended reference ranges (Patsalos, Epilepsia 2008, Patsalos Seeizure 2014, Patsalos Therapeutic drug monitoring 2018)

Antiepileptic drug	Reference range
Brivaracetam (BRV)	0.4-1.2 mg/L
Lacosamide (LCM)	10-20 mg/L
Lamotrigine (LTG)	2.5-15 mg/L
Levetiracetam (LEV)	12-46 mg/L
Oxcarbazepine (OXC)	3-35 mg/L
Perampanel (PER)	180-980 µg/L
Pregabaline (PGB)	2.8-10 mg/L
Topiramate (TPM)	5-20 mg/L
Zonisamide (ZNS)	10-40 mg/L

FIGURES:

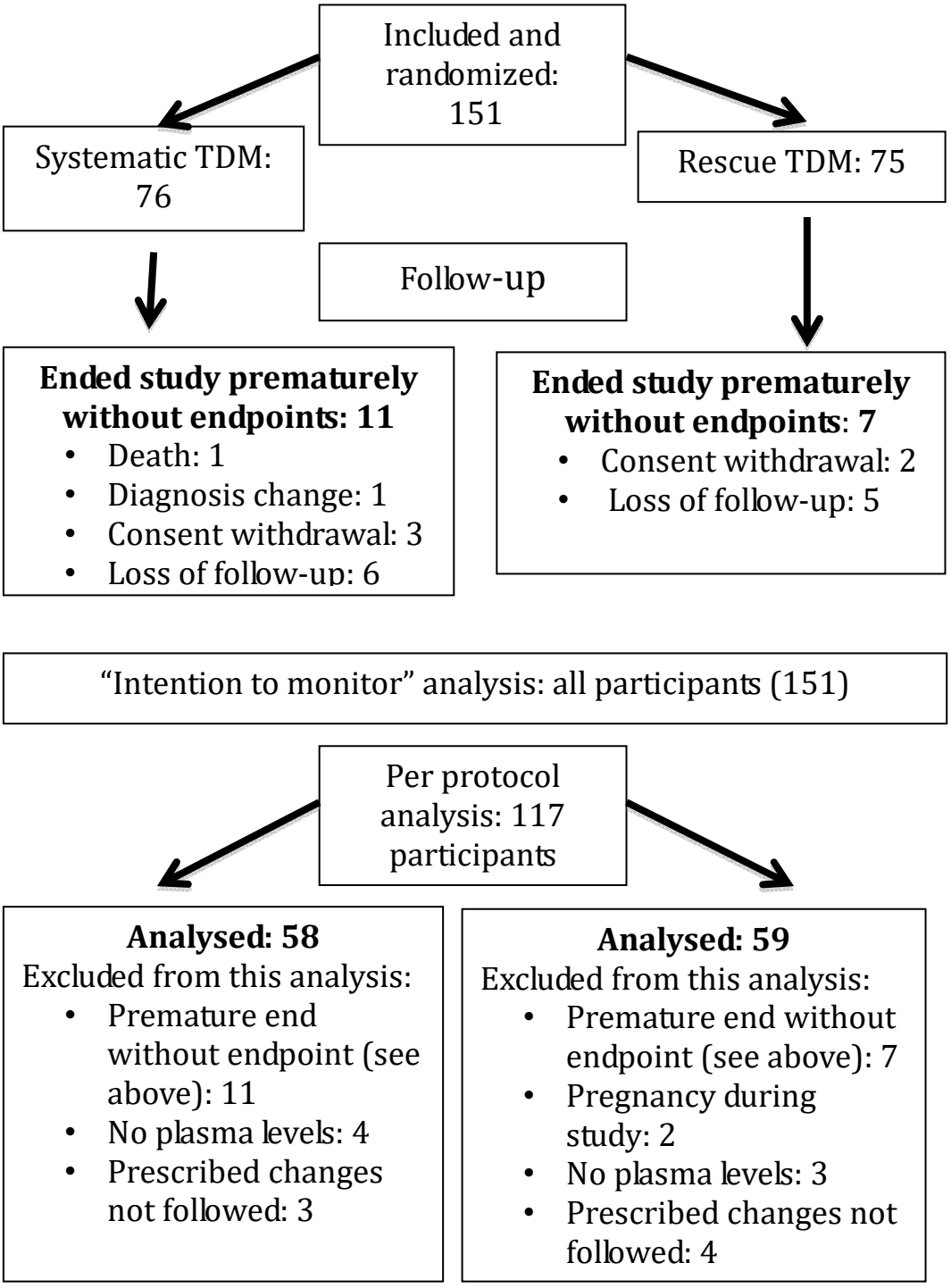

Figure 1: Flow-diagram of the study. The single death was not related to the study (brain tumour progression).

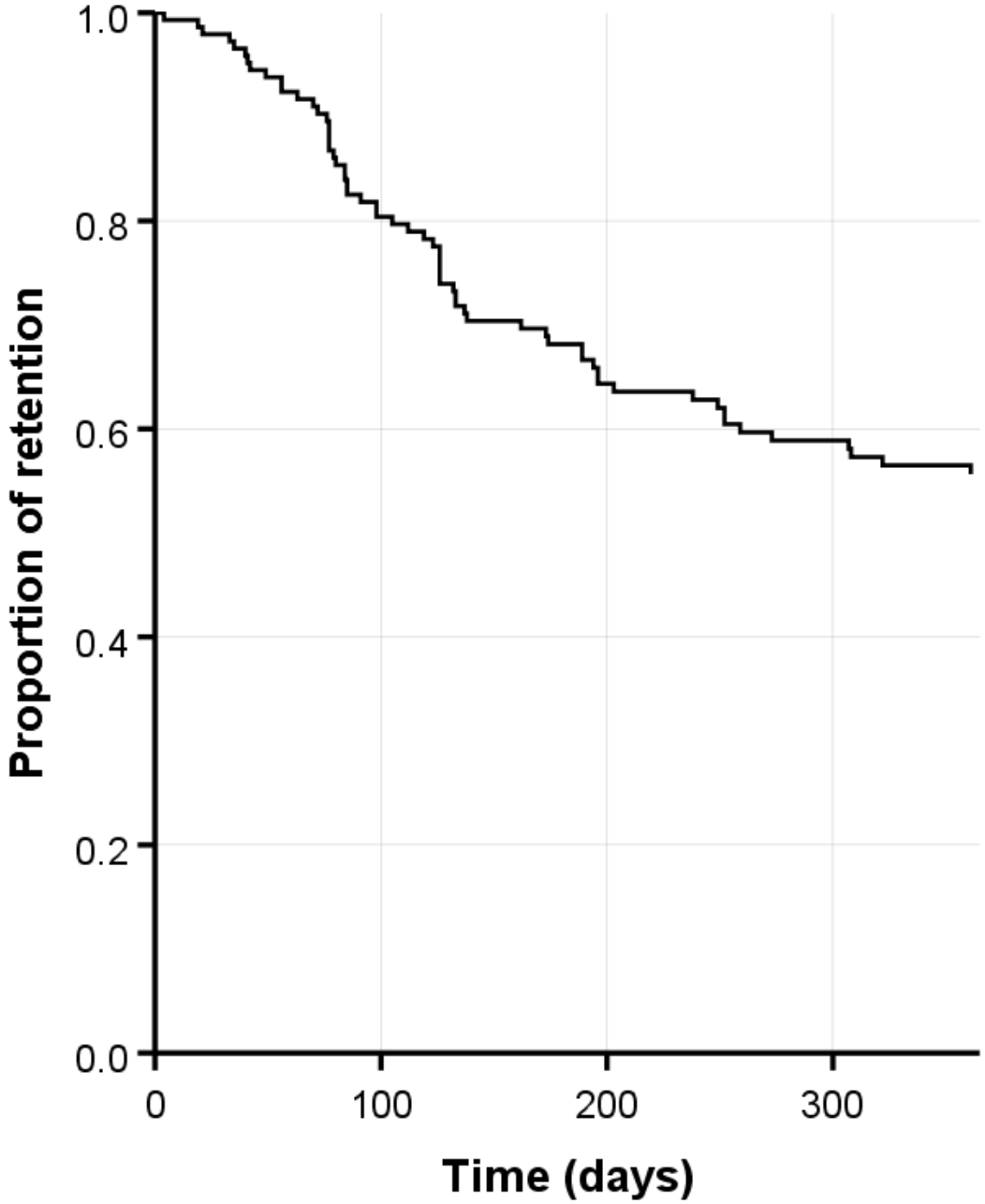

Figure 2: Retention (56%) without endpoints, taking into account all participants ("intention to monitor" analysis).

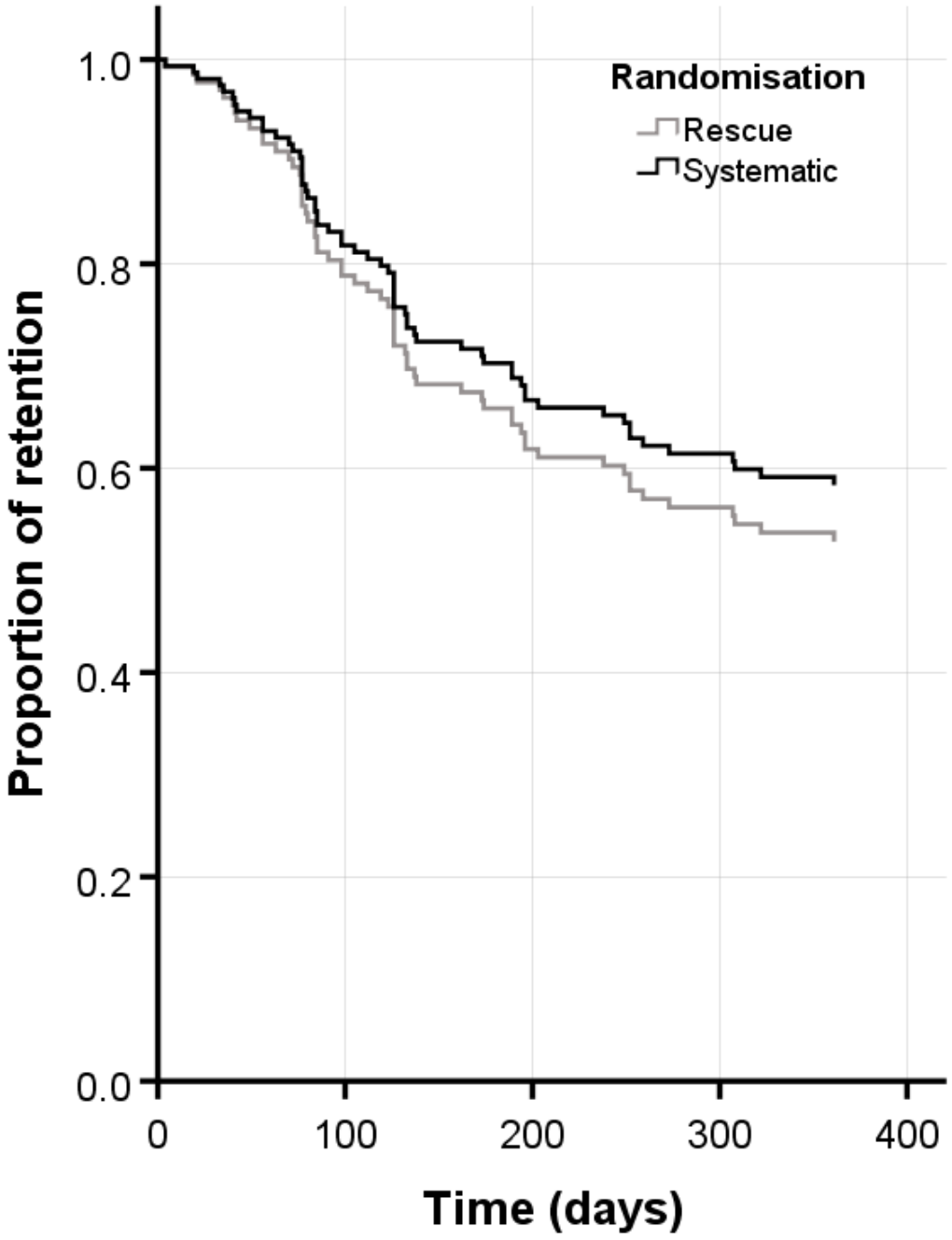

Figure 3: Overall retention in both arms ("intention to monitor" analysis). There was no difference between the *systematic* TDM arm (58%) and the *rescue* TDM arm (53%, p= 0.5 Cox regression).