HHS Public Access

Author manuscript

Ann Neurol. Author manuscript; available in PMC 2026 January 09.

Published in final edited form as:

Ann Neurol. 2026 April ; 99(4): 1076–1082. doi:10.1002/ana.78134.

Does missing medication acutely change seizure risk? A prospective study

Daniel M. Goldenholz, MD PhD[1,2], **Joshua C. Cheng, MD, PhD**[1,2], **Chi-Yuan Chang, PhD**[1,2], **Robert Moss**[3], **M. Brandon Westover, MD, PhD**[1,2]

[1]Department of Neurology, Harvard Medical School, Boston, MA

[2]Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA

[3]Seizure Tracker LLC, Springfield VA

Abstract

Objective: To determine whether missing individual doses of anti-seizure medications (ASMs) elevates short-term seizure risk in people with drug-resistant epilepsy.

Methods: In a prospective, community-based cohort, adults with drug-resistant epilepsy (≥3 seizures/month) or their caregivers recorded seizures and ASM intake with smartphone applications for 10 months each. Individual level analysis modelled the relationships between ASM adherence with seizure occurrence, as well as with a simplified seizure forecast via a 90-day moving average ("Napkin method"). Group-level analysis with a mixed-effects model was performed to examine the relationship between ASM adherence and simplified forecasts, while controlling for differences in individual seizure frequency via random effects.

Results: 27 participants (median age 29 years) contributed 7,853 person-days. Individual analysis showed that only a small ($n = 2$) number of participants had a weak relationship between ASM adherence with seizure occurrence. Group-level analysis showed that seizure occurrence was highly linked to the Napkin method, but not ASM adherence.

Interpretation: Among individuals with frequent, drug-resistant epilepsy, occasional missed ASM doses did not measurably raise immediate seizure risk. While sustained non-adherence remains a clinical concern, clinicians may reassure patients that infrequent brief lapses are unlikely to trigger seizures acutely, yet they should continue emphasizing overall adherence for long-term seizure control.

Corresponding author: daniel.goldenholz@bidmc.harvard.edu, 330 Brookline Ave, Baker 5, Boston MA 02215.
Co-first authors
Daniel M. Goldenholz
Joshua C. Cheng

Author contributions:
DMG, MBW contributed to the conception and design of the study; RM, CYC, JC contributed to the acquisition and analysis of data; DMG and JC contributed to drafting the text or preparing the figures.

POTENTIAL CONFLICTS OF INTERST
R.M. is the cofounder/owner of Seizure Tracker, LLC (used in this study), which has received funding from Courtagen, Engage Therapeutics, Epitel, Greenwich Biosciences, Neurelis, Neuropace, UCB, Xenon Pharmaceuticals, and grants from Tuberous Sclerosis Alliance. The remaining authors have no nothing to report.

Keywords

seizure; forecast; medication adherence; prospective

INTRODUCTION

Protection against seizures is the number one concern for people with epilepsy. The mainstay of treatment is anti-seizure medication (ASM)[1]. The standard message to patients is that proper adherence to the ASM regimen is very important, because missing doses may precipitate seizures[2], status epilepticus[3] or death[4].

But the scientific evidence supporting this standard message is scant. Specifically, there may be a difference between prolonged non-adherence and missing a dose or two occasionally. A recent review from our lab[5] concluded that although short-term ASM nonadherence might increase seizure risk, there was insufficient evidence for a definite conclusion. In the literature, one study looking at ASM levels following hospitalization for breakthrough seizures found that the percentage of patients who were definitively non-adherent varied by age (from 10% for age > 60 to 37% in age < 30)[6]. However, this was likely due to *prolonged* non-adherence rather than *intermittent* missed doses. Another study which found a relationship between breakthrough seizures and missed ASMs was done in a cross-sectional manner[7], however it is critical to have access to the comprehensive longitudinal data to establish these correlations. Anecdotally, our clinical practice has numerous patients who admit to missing an occasional medicine with no subsequent seizure.

Our lab has demonstrated in several contexts that low-quality seizure forecasting can be achieved[8,9] using a 90-day moving window average (MA) which calculates the number of seizure days over the past 90 days and divides by 90 to arrive at a predicted daily risk. This can colloquially be referred to as the ”Napkin Method”, given its ease of calculation such that it can be performed on the back of a napkin. Using this approach, it has been shown to perform equal to or better than a chance forecaster which uses permuted forecasts in simulation, in self-reported diaries and in wearable device-based diaries[9]. For this reason, we see the Napkin method as a minimum bar for any clinically meaningful seizure forecasting[10].

Therefore, we set out to obtain prospective data on a cohort of adults with drug resistant epilepsy, looking for evidence that missing a single dose of ASM can increase the risk of seizures. If missing a dose does have a significant impact on seizure risk, we hypothesize that forecasting with ASM adherence data will improve beyond the Napkin method.

METHODS

Following an IRB approved protocol (BIDMC 2022P000548). Targeted recruitment emails were sent to 1341 users of SeizureTracker.com. Additional recruitment emails were sent out via BuildClinical.com (distribution size was not disclosed to us). Informed consent was obtained from each subject. Patients were screened for eligibility based on a diagnosis of drug-resistant epilepsy, a seizure rate of 3/month or more. Adult patients or adult caregivers

of pediatric patients were encouraged to enroll. Of note, participation in the research study had no impact on their treatment decisions or care. The study lasted for 10 months for each participant. Enrolled participants (or caregivers when appropriate) signed up with two free online services: Seizure Tracker and Medisafe. Both services provided an app on Android or iOS for mobile phone access. Seizure Tracker was used for 10 months of seizure diary recording. Medisafe was used for documenting every dose of ASM taken (or missed). Medisafe has optional medicine alarms as well as mobile alerts to document adherence for each dose. Once a week, the Medisafe app requested the answers to an online survey to confirm that the seizure diary is complete. Participants who did not complete the survey were contacted by study staff, and when possible, completeness of data was confirmed. A de-identified data-table was generated based on the seizure dairies as well as the medication adherence data.

Calculation of MA, ASM adherence and seizure occurrence

To calculate MA, the number of seizure days was summed over a 90-day period and then divided by 90. A seizure day was defined as a 24-hour day (midnight to midnight) where 1 or more seizures occurred. This 90-day sliding window was then advanced iteratively by one-day increments and re-calculated until the end of the window reached the last timepoint. To calculate ASM adherence, the number of missed administration periods (i.e., AM and/or PM dosing) was summated for each day. The output for each day and participant was a range from 0–2, where 0 = no missed ASMs, 1 = 1 missed administration period (either AM or PM), or 2 = 2 missed administration periods (both AM and PM). For the response variable of seizure occurrence, the output for each day was binarized as 1 = at least 1 seizure occurred that day, or 0 = no seizures occurred that day.

Individual Analysis

The relationship between ASM adherence and seizure occurrence was examined on an individual level using Pearson’s correlations. As there was likely a delayed effect of missed ASMs on seizure risk, the correlation was done with a one-day lag between seizure occurrence and missed ASMs the day prior. Implementing this lag was also important as it prevented missed ASMs occurring on the same day but after a seizure happened from erroneously used as a predictor

However, there may also be longer temporal dependencies between missed ASMs and seizure occurrence beyond one day. To better account for these potential longer delays, we performed a logistic regression between ASM adherence and seizure occurrence, while also including additional lag terms up to 1 week prior for ASM adherence (see Appendix).

Using a similar overall approach of correlational and regression analyses, we also looked at the relationship between ASM adherence and MA on an individual level to determine if they were separate constructs (see Appendix).

Group-Level Analysis

To examine the relationship between ASM adherence and MA with seizure occurrence on a group level, a mixed-effects logistic regression model was used (see Appendix) The use

of a mixed-effects model was important as the data from seizure diaries were repeatedly sampled over time from the same participants, leading to non-independence of the data points across subjects. In the context of this study, random effects were used to account for different baseline seizure frequencies across participants when examining the relationship between seizure occurrence with MA and ASM adherence. This was done by modelling a random intercept for each participant as a predictor to help adjust for different baseline seizure frequencies. For the fixed effects component, MA and ASM adherence were used as the independent variables, with seizure occurrence used as the dependent variable. As the MA and missed ASM doses may have different ranges of values, feature scaling for each variable was performed using a Z-score transformation prior to model fitting. Furthermore, to account for potential delayed impacts of missed ASMs on seizure risk, the model was iteratively assessed while progressively including lag terms for ASM adherence from 1 to 7 days prior. Feature scaling was similarly used for all lag terms for ASM adherence. Overall statistical significance of the models was determined by comparing the deviance of the model to a null model (fixed and random intercepts only) to generate a chi-squared test statistic (significance $p < 0.05$).

As an alternative approach to assess delayed effects of missed ASMs on seizure occurrence, a simplified analysis was conducted to account for ASM half-lives. Specifically, for each ASM, the maximum reported half-life for that medication was assumed. Furthermore, we assumed that if an ASM had reached at least one half-life due to consecutively missed doses, then that ASM was no longer “optimal” for that individual, even if still potentially therapeutic for them. To do this methodologically, a binary variable was created for each individual. The variable was assigned 0 for each timepoint until the number of consecutively missed doses of an ASM for a participant exceeded the maximum half-life for that ASM, after which the subsequent time points were marked with a 1 as an indicator of increased seizure risk. This trail of 1’s would then continue until that medication was re-dosed, after which the timepoints would be a given a value of 0. Of note, one additional advantage of using this approach is the lack of *a priori* selection of window/lag length. Using this approach, the group mixed-effects logistic regression analysis was repeated using MA (feature-scaled) and ASM adherence (via the half-life method) as the predictor variables, and seizure occurrence as the outcome variable. Statistical significance testing of the overall model was performed by taking the difference of the deviance of the model with the null model (fixed and random intercepts only) to derive a chi-square test statistic. Significance was set at $p < 0.05$.

Lastly, the power of the mixed-effects logistic regression analysis in detecting a possible relationship between seizures and missed ASM doses was examined. To do this, a simulated timeseries of seizures was generated for each participant based on their ASM dosing history. More specifically, in the day immediately following a missed ASM administration, the possibility of a seizure was generated with probability p. As such, if p was closer to 0, then the likelihood of a seizure the day after a missed ASM dose would be low, whereas if p was closer to 1, then seizure likelihood would be high. The rationale here was that if the mixed-effects analysis was sensitive at detecting a relationship between missed ASM doses and seizures, then missed ASM doses would be a statistically significant predictor of seizure occurrence even when probability p was small (i.e., the effect of missed ASM

doses on seizures was small). The mixed-effects analysis with MA and ASM adherence the day prior as predictor variables was repeated at different values of probability *p*. Similar to previous analysis, a subject specific random intercept was used to account for variations in seizure frequency across subjects. Feature scaling via z-transform of the predictor variables was performed prior to model fitting. Given the probabilistic nature of this analysis when simulating seizure timeseries, the mixed effects analysis was iterated 500 times at a broad range of seizure probability *p* (0.01, 0.05, 0.1, 0.25, 0.5, and 0.75). The proportion of iterations where MA or ASM adherence was statistically ($p < 0.05$) related to seizure occurrence was assessed, and the mean regression coefficients calculated across all the iterations.

Our open-source analysis code is available at Github: https://github.com/GoldenholzLab/AdherenceStudy.git

RESULTS

A total of 27 participants were recruited and followed through the 10-month study. Basic information about seizure frequency, gender, and medications are available in the Appendix. With regards to ASM adherence, 4 patients did not miss any doses of ASMs. Mean ± SD of ASM adherence across all patients during the study was 93.04% ± 13.62%. However, despite good ASM adherence, breakthrough seizures were common, with mean ± SD seizure days during the study being 21.17% ± 23.70% across the group.

In 2 patients, there was a weak relationship between ASM adherence and seizure occurrence

There was a weak positive correlation between ASM adherence and seizure occurrence in two individuals ($r = 0.14$, 95% CI[1.12×10^{-4}, 0.28], $p = 0.0499$; $r = 0.21$, 95% CI[0.06, 0.34], $p = 0.004$), suggesting that more missed ASMs was weakly related to increased seizure occurrence. Similarly, using the logistic regression with lag terms approach, there was a weak relationship between ASM adherence and seizure occurrence in two individuals ($p < 0.05$; see Appendix and Table S2). Across the statistically significant predictors, more missed ASMs were related to higher seizure occurrence. However, only one of the two individuals had a weak significant relationship between missed ASMs and seizure occurrence across both the correlational and regression approach (Fig. 1).

In a small subset of individuals, there was a weak relationship between ASM adherence and MA

Using a correlational approach, there was a weak correlation between ASM adherence and the MA in four individuals ($r = -0.19$, 95% CI[−0.32, −0.05], $p = 0.009$; $r = 0.16$, 95% CI[0.02, 0.30], $p = 0.027$; $r = -0.24$, 95% CI[−0.37, −0.10], $p = 7.23 \times 10^{-4}$; $r = -0.20$, 95% CI[−0.33, −0.06], $p = 0.006$), with a mix of the direction of the relationship. However, when more appropriately accounting for temporal dependencies using the linear regression with lag terms approach, there was a weak relationship between MA and ASM adherence in only two individuals (see Appendix and Table S3). Overall, this suggests that MA and ASM adherence were likely capturing separate constructs across the majority of individuals.

On a group level, the moving average but not missed ASM doses was statistically significantly related to seizure occurrence.

From group level analysis, the overall mixed-effects logistic regression using MA and ASM adherence (1-day lag) as predictors for seizure occurrence was statistically significant ($p < 0.05$). However, only MA was a statistically significant predictor ($p < 0.05$), with a positive regression coefficient ($\beta = 1.29$). This suggests that across participants, a higher MA as an estimate of prior seizure history was positively associated with seizure occurrence. In contrast, missed ASM doses the day prior was not related to seizure occurrence ($p = 0.55$). See Fig. 1 for an illustration of how individual and group level seizure occurrence is generally not higher for a missed versus no missed ASM dose aside from one subject mentioned earlier.

When the analysis was repeated progressively including lag terms for ASM adherence up to one week prior, MA but not ASM adherence remained related to seizure occurrence for all models. Specifically, MA was always positively related to seizure occurrence such that a higher seizure history over the past 90 days was related to a higher subsequent seizure occurrence (see Appendix and Tables S4 and S5).

Even when accounting for ASM half-lives, ASM dosing was not a predictor of seizure occurrence.

The analysis was then modified to account for ASM half-lives. Using this approach, the MA remained related to seizure occurrence ($\beta = 1.86$, 95% CI[0.98, 2.74], $p = 3.34 \times 10^{-5}$). However, missed ASM doses were not related to seizure occurrence ($\beta = 0.06$, 95% CI[−0.48, 0.59], $p = 0.84$).

The lack of relationship between missed ASMs and seizure occurrence was not due to poor sensitivity of the mixed-effects analysis approach.

To determine whether the lack of relationship between missed ASMs and seizure occurrence was due to limitations in sensitivity of the mixed-effects approach, a simulated power analysis was performed whereby different seizure probabilities following missed ASM doses was generated. Even when simulated seizure probability following missed ASM doses was low (1%), the mixed effects analysis was able to detect a relationship between missed ASM doses and seizure occurrence on a majority of iterations (see Appendix and Table S6). Similarly, the MA was related to seizure occurrence for the majority of iterations despite variations of seizure probability following missed ASM doses.

DISCUSSION

This study found evidence that in the large majority of patients, intermittent missed ASM doses were not related to increased seizure occurrence. Rather, seizure occurrence was linked to past seizure history. More specifically, group level analysis showed that higher recent seizure history estimated by MA was associated with a greater seizure occurrence. To confirm that this finding was meaningful, we conducted a simulated power analysis that found that even small impacts on seizure risk would have been identified due to the

longitudinal nature of our dataset. We therefore suspect that more broadly, the short-term impact of missed medication is unlikely to have a dramatic impact on seizure risk.

For the one individual who had a weak positive relationship between missed ASM doses and seizure occurrence across both statistical (correlational and regression) techniques, it is uncertain why this relationship exists in this particular person. However, this individual was on levetiracetam, carbamazepine, and lacosamide, with various missed combinations of these ASMs. Interestingly, animal models investigating the link between ASM non-adherence and breakthrough seizures have shown this relationship to be present with both levetiracetam[11] as well as carbamazepine[12].

As to why the majority of the individuals in this study did not have a relationship between ASM adherence and seizure occurrence, one plausible reason was that the ASMs were well above the optimal dose for the individual such that missed doses did not result in seizure occurrence. Another plausible reason was due to the drug-resistant nature of these individuals, the ASMs were ineffective for them and so there was little effect of missed ASM doses. Although some research has been done on “catch-up” dosing[13], the findings from this cohort suggests that this may not be beneficial.

The overarching conclusion of the study does not contradict other studies which explored the long-term impact of frequently missing medications[5]. In that case, it has been shown that poor medication adherence can increase seizures[2], ED visits[4], injuries[4], status epilepticus[3] and mortality[4]. Additionally, standard practice in epilepsy monitoring units (EMU) is to taper anti-seizure medications with the specific intention of changing seizure risk[14]. The fact that this standard practice is often successful further augments the clinical intuition that long-term medication adherence challenges increase seizure recurrence risk. Conversely, it is well known among those who regularly work in EMU settings that the first missed ASM dose typically does not bring out seizures in most patients, supporting the findings here.

Hypothetically, missing a medication dose at “the wrong time” could have significant consequences. Specifically, it has been shown that there are daily and multi-day seizure risk cycles[15–17]. If a medication were missed during a period of higher seizure risk, perhaps this could represent “the perfect storm” and result in a seizure. It remains an effort for future studies to determine if this hypothesis is correct.

There are practical implications for this study. Many patients will miss doses of ASMs occasionally, though this is often minimized if not asked in a permissive way[18]. It is recommended that patients be given psychological permission to admit missed doses[19], and we have anecdotally found that asking “In an average month, how often do you miss a dose” results in very different answers (usually: “one or two”) compared with “Are you taking all your meds?” (usually: yes). It is generally good practice to gently remind patients about the safety afforded by proper ASM adherence. However, the present study raises the possibility that “one or two” missed doses may be a reasonably acceptable answer to the adherence question.

There are several limitations to the present study. First, our primary data come from self-reported seizures and self-reported ASM adherence. Both were obtained in a curated

manner- that is, involving weekly check-ins and oversight from the study team. However, it is well documented that self-reported outcomes such as these can suffer from over-reporting and under-reporting[20,21], thus decreasing the certainty of the results. As such, it is unclear whether these results generalize to electrographically recorded seizures. However, our prior work[17,20,22–32] suggests that there is often signal (biologically relevant data) despite the noise (distractors such as over- and under-reporting), and that self-reported data can be thought of as lower signal-to-noise ratio data compared with intracranial EEG.

It is possible that there may be a subtle selection bias based on our recruited sample of patients. Although the true number of recruitment messages sent out was undisclosed by one of our vendors, we know our total recruitment was <2% of the emails that were sent out by SeizureTracker alone. The recruitment materials mentioned that we were studying seizure forecasting, including the influence of medication on seizure risk. Perhaps those who chose to participate were different in a systematic way from the broader drug-resistant epilepsy population. Without detailed information about non-participants, this remains speculative.

Another limitation was that because our cohort included patients with drug-resistant epilepsy, this may not generalize to those with non-drug-resistant epilepsy. It remains to be determined whether missed intermittent ASM increases seizure occurrence in this population. Given that drug-resistant epilepsy is such a widespread disease – 0.5% of the US[33,34], it remains unknown if this modest sample of patients can adequately represent the much broader population. Much larger studies would be needed to validate these findings.

Additionally, our study included a relatively small number of patients. The small sample size limits the generalizability of our results. We mitigated the small sample size somewhat using a long duration observation period of 10 months.

Lastly, seizure forecasting is well-known to be very challenging[10]. In this study, a relatively simple mixed-effects regression was used to capture the essence of the Napkin method, while trying to disentangle the impact of ASM adherence on seizure risk. We acknowledge that many other forecasting models are possible. Future work with larger datasets may explore more advanced models. However, we would note that it has been shown that the MA forecast, while underwhelming, does provide a better than chance forecast of seizure risk across many patients in multiple contexts[9].

In conclusion, despite the limitations above, we show evidence that short-term impact of missed ASMs does not appear to have a significant impact on short-term seizure risk. Despite this result, we emphasize that there are numerous reports that long-term impacts of medication non-adherence are dangerous and would always recommend medication adherence whenever possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS:

Dr. Westover's laboratory received support from grants from the NIH (R01NS102190, R01NS102574, R01NS107291, RF1AG064312, RF1NS120947, R01AG073410, R01HL161253, R01NS126282, R01AG073598) and NSF (2014431). Dr. Goldenholz was funded by the NIH (K23NS124656).

DATA AVAILABILITY

Data available on request from the authors.

REFERENCES

1. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet 2019;393(10172):689–701. [PubMed: 30686584]
2. Li J, Si Y, Hu J, et al. Enhancing medical compliance of patients with convulsive epilepsy in rural community: a randomized intervention trial. Epilepsia 2013;54(11):1988–1996. [PubMed: 24117425]
3. Magdy R, Kishk NA, Fouad AM, Alsayyad E. Risk estimation of SUDEP during COVID-19 pandemic era in a tertiary referral center. Epilepsy Res 2021;173:106625. [PubMed: 33819756]
4. Faught E, Duh MS, Weiner JR, et al. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. Neurology 2008;71(20):1572–1578. [PubMed: 18565827]
5. Eccleston CA, Goldenholz SR, Goldenholz DM. Exercise, medication adherence, and the menstrual cycle: How much do these change seizure risk? Epilepsy Res 2022;188:107052. [PubMed: 36403515]
6. Samsonsen C, Reimers A, Bråthen G, et al. Nonadherence to treatment causing acute hospitalizations in people with epilepsy: An observational, prospective study. Epilepsia 2014;55(11):e125–e128. [PubMed: 25252007]
7. Suzuki H, Mikuni N, Ohnishi H, et al. Forgetting to take antiseizure medications is associated with focal to bilateral tonic-clonic seizures, as revealed by a cross-sectional study. PLoS One 2020;15(10):e0240082. [PubMed: 33002061]
8. Goldenholz DM, Eccleston C, Moss R, Westover MB. Prospective validation of a seizure diary forecasting falls short. Epilepsia 2024;65(6):1730–1736. [PubMed: 38606580]
9. Chang C-Y, Zhang B, Moss R, et al. Necessary for seizure forecasting outcome metrics: Seizure frequency and benchmark model. Epilepsy Res 2024;208:107474. [PubMed: 39522392]
10. Cheng JC, Goldenholz DM. Seizure prediction and forecasting: a scoping review. Curr Opin Neurol 2025;38(2):135–139. [PubMed: 39831588]
11. Guignet M, Vuong J, Martinez A, et al. Temporal relationship between levetiracetam nonadherence and breakthrough seizures in a preclinical model of temporal lobe epilepsy. Epilepsia 2024;65(2):497–510. [PubMed: 38031477]
12. Thomson KE, Modi AC, Glauser TA, et al. The impact of nonadherence to antiseizure drugs on seizure outcomes in an animal model of epilepsy. Epilepsia 2017;58(6):1054–1062. [PubMed: 28401980]
13. Li Z-R, Wang C-Y, Lin W-W, et al. Handling Delayed or Missed Dose of Antiseizure Medications: A Model-Informed Individual Remedial Dosing. Neurology 2023;100(9):e921–e931. [PubMed: 36450606]
14. Lado FA, Ahrens SM, Riker E, et al. Guidelines for Specialized Epilepsy Centers: Executive Summary of the Report of the National Association of Epilepsy Centers Guideline Panel. Neurology 2024;102(4):e208087. [PubMed: 38306606]
15. Baud MO, Ghestem A, Benoliel J-J, et al. Endogenous multidien rhythm of epilepsy in rats. Exp Neurol 2019;315:82–87. [PubMed: 30776337]
16. Baud MO, Kleen JK, Mirro EA, et al. Multi-day rhythms modulate seizure risk in epilepsy. Nat Commun 2018;9(1):88. [PubMed: 29311566]
17. Karoly PJ, Goldenholz DM, Freestone DR, et al. Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. Lancet Neurol 2018;17(11):977–985. [PubMed: 30219655]

18. Cabral AC, Moura-Ramos M, Castel-Branco M, et al. Influence of the mode of administration on the results of medication adherence questionnaires. J Eval Clin Pract 2017;23(6):1252–1257. [PubMed: 28714551]
19. Carey RM, Calhoun DA, Bakris GL, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertension 2018;72(5):e53–e90. [PubMed: 30354828]
20. Goldenholz D, Brinkmann BH, Westover MB. How accurate do self-reported seizures need to be for effective medication management in epilepsy? Epilepsia 2024;65(7):e104–e112. [PubMed: 38776216]
21. Halliday AJ, Gillinder L, Lai A, et al. The UMPIRE study: A first-in-human multicenter trial of bilateral subscalp monitoring for epileptic seizure detection. Epilepsia 2025;66(9):3426–3439. [PubMed: 40445205]
22. Goldenholz DM, Goldenholz EB, Kaptchuk TJ. Quantifying and controlling the impact of regression to the mean on randomized controlled trials in epilepsy. Epilepsia 2023;64(10):2635–2643. [PubMed: 37505116]
23. Goldenholz DM, Westover MB. Flexible realistic simulation of seizure occurrence recapitulating statistical properties of seizure diaries. Epilepsia 2023;64(2):396–405. [PubMed: 36401798]
24. Karoly P, Goldenholz DM, Cook M. Are the days of counting seizures numbered? Curr Opin Neurol 2018;31(2):162–168. [PubMed: 29369115]
25. Oliveira A, Romero JM, Goldenholz DM. Comparing the efficacy, exposure, and cost of clinical trial analysis methods. Epilepsia 2019;60(12):e128–e132. [PubMed: 31724165]
26. Karoly PJ, Romero J, Cook MJ, et al. When can we trust responders? Serious concerns when using 50% response rate to assess clinical trials. Epilepsia 2019;60(9):e99–e103. [PubMed: 31471901]
27. Variations-in-the-natural-history-of-epilepsy-and-epilepsy-subgroups [Internet]. Default [date unknown];[cited 2025 Sep 15] Available from: https://aesnet.org/abstractslisting/variations-in-the-natural-history-of-epilepsy-and-epilepsy-subgroups
28. Goldenholz DM, Moss R, Scott J, et al. Confusing Placebo Effect with Natural History in Epilepsy: A Big Data Approach. Ann Neurol 2015;78(3):329–336. [PubMed: 26150090]
29. Goldenholz DM, Strashny A, Cook M, et al. A multi-dataset time-reversal approach to clinical trial placebo response and the relationship to natural variability in epilepsy. Seizure 2017;53:31–36. [PubMed: 29102709]
30. Goldenholz DM, Goldenholz SR, Moss R, et al. Is seizure frequency variance a predictable quantity? Ann Clin Transl Neurol 2018;5(2):201–207. [PubMed: 29468180]
31. Ferastraoaru V, Goldenholz DM, Chiang S, et al. Characteristics of large patient-reported outcomes: Where can one million seizures get us? Epilepsia Open 2018;3(3):364–373. [PubMed: 30187007]
32. Simulating clinical trials with and without intracranial EEG data - Goldenholz - 2017 - Epilepsia Open - Wiley Online Library [Internet]. [date unknown]; [cited 2025 Sep 15] Available from: https://onlinelibrary.wiley.com/doi/10.1002/epi4.12038?msockid=082e2bc4613a671a11b53f9b608d663b
33. CDC. Epilepsy Facts and Stats [Internet]. Epilepsy 2024;[cited 2025 Oct 5] Available from: https://www.cdc.gov/epilepsy/data-research/facts-stats/index.html
34. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. JAMA Neurol 2018;75(3):279–286. [PubMed: 29279892]

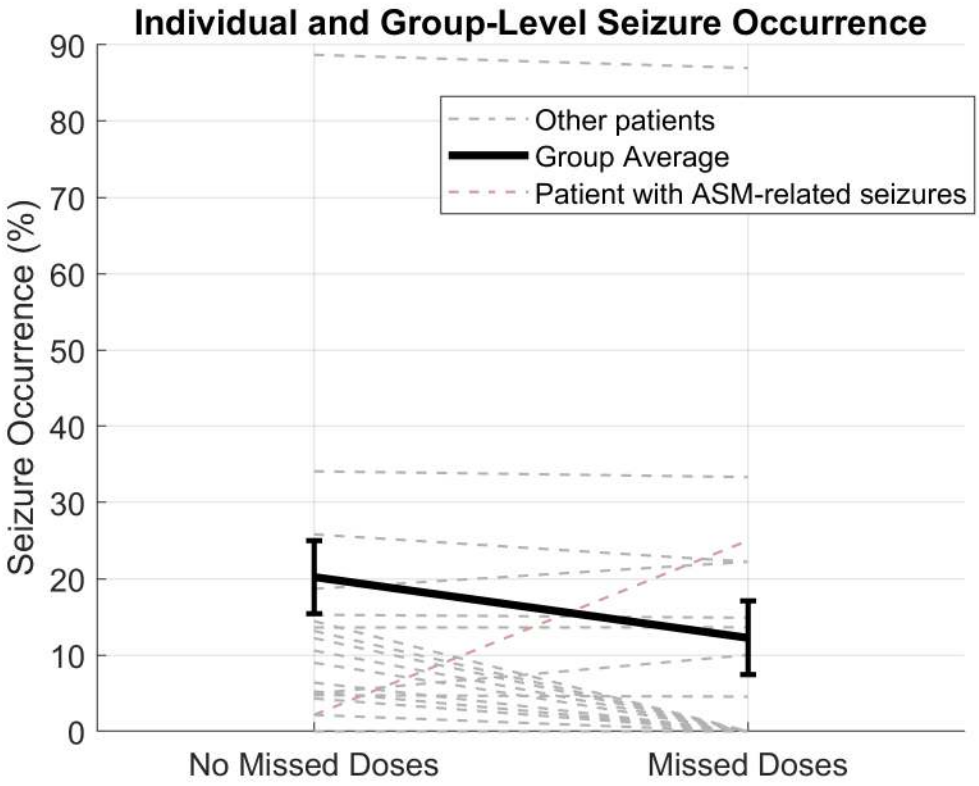

Fig 1.

Individual and group level plots of seizure occurrence (%) following missed versus no missed ASMs. One subject (highlighted in red) appears to have a higher seizure fraction on days after missed doses of medication. The group (highlighted in thick black) generally speaking has a nonsignificant decrease in seizure fraction on the day after missed medication dose. Other individuals follow a similar pattern to the group.