

# Prevalence and clinical correlates of antiseizure medication polytherapy among children and adolescents attending a specialist paediatric neurology clinic in Uganda

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## Research Article

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# Abstract

## Background

Antiseizure medication (ASM) monotherapy is generally preferred for childhood epilepsy, but some children require two or more ASMs because of persistent seizures, epilepsy syndrome, treatment transition or greater clinical complexity. Contemporary Ugandan data on the frequency and clinical correlates of paediatric ASM polytherapy are limited.

## Objective

To determine the prevalence of current ASM polytherapy and identify clinical factors associated with polytherapy among children and adolescents attending a specialist paediatric neurology clinic in Uganda.

## Methods

We conducted a cross-sectional analysis of retrospectively abstracted clinical data from 496 children and adolescents aged 1–18 years with epilepsy attending the Paediatric Neurology Clinic at St. Francis Hospital Nsambya, Kampala, Uganda. Current ASM regimen was classified as monotherapy or polytherapy. Modified Poisson regression with robust standard errors was used to estimate crude and adjusted prevalence ratios (PRs) with 95% confidence intervals (CIs).

## Results

Seventy-eight of 496 participants were recorded as receiving polytherapy, giving a prevalence of 15.7% (95% CI 12.8–19.2). In the primary adjusted model, generalized epilepsy was associated with a higher prevalence of recorded polytherapy than focal epilepsy (aPR 2.62, 95% CI 1.70–4.04;  $p < 0.001$ ), while any documented comorbid condition was associated with approximately twice the prevalence (aPR 2.01, 95% CI 1.25–3.23;  $p = 0.004$ ). Medication-name review classified 64/496 (12.9%) as receiving at least two recognizable ASMs; agreement with the recorded regimen classification was 92.7% (Cohen's kappa 0.70). In this sensitivity analysis, the association with comorbidity remained strong (aPR 2.65;  $p < 0.001$ ), whereas the generalized-epilepsy association attenuated to borderline statistical significance (aPR 1.60;  $p = 0.050$ ).

## Conclusion

Approximately one in six children and adolescents were recorded as receiving ASM polytherapy. Comorbidity was the most robust clinical correlate across outcome definitions. The association with

generalized epilepsy was sensitive to how polytherapy was classified, highlighting the importance of standardized medication reconciliation in retrospective epilepsy research.

## Introduction

Epilepsy is a common chronic neurological disorder in childhood and may affect development, schooling, psychosocial functioning and family wellbeing. Antiseizure medications remain the mainstay of treatment. When possible, treatment is usually initiated with a single appropriately selected ASM because monotherapy reduces regimen complexity, drug–drug interactions and cumulative adverse effects while simplifying medication administration and monitoring.<sup>1,2</sup>

Polytherapy becomes necessary for some children when seizures remain inadequately controlled, when particular epilepsy syndromes require combination treatment, or during periods of medication transition. Current use of two or more ASMs, however, should not be equated automatically with drug-resistant epilepsy. The International League Against Epilepsy definition of drug resistance requires failure of adequate trials of two tolerated, appropriately chosen and used ASM schedules to achieve sustained seizure freedom.<sup>2</sup> Cross-sectional medication counts cannot reconstruct this treatment history.

Evidence from African paediatric epilepsy services shows considerable variation in ASM regimens. At Mulago Hospital in Uganda, Atugonza and colleagues reported multiple-AED use in 32.4% of 139 children in 2013; poor seizure control and focal neurological deficits were independently associated with multiple-drug use.<sup>3</sup> More recent Ethiopian studies have reported monotherapy proportions ranging from 64.3% to 78.6%, illustrating variation across referral populations and treatment settings.<sup>4,5</sup> Direct comparison is difficult because study periods, eligibility criteria, available medicines, outcome definitions and clinical case mix differ.

Ugandan evidence on ASM polytherapy in children is still limited. The main specialist-clinic study was conducted more than a decade ago, before some of the changes in medicine availability and paediatric neurology practice seen today. We therefore sought to establish how common polytherapy is in a contemporary specialist clinic and which clinical characteristics are associated with its use among children and adolescents with epilepsy.

## Materials and Methods

### Study design and analytical framework

We conducted a cross-sectional analysis of retrospectively abstracted clinical data from children and adolescents with epilepsy attending the Paediatric Neurology Clinic at St. Francis Hospital Nsambya, Kampala, Uganda. The analysis focused on current ASM regimen and its clinical correlates.

### Setting and source population

The Paediatric Neurology Clinic at St. Francis Hospital Nsambya is a specialist outpatient service providing follow-up care for children and adolescents with epilepsy and other neurological disorders. Clinical information was obtained from existing electronic and available paper medical records.

## **Eligibility for the analysis**

Eligible participants were children and adolescents aged 1–18 years with a documented diagnosis of epilepsy, a documented current ASM regimen, and the clinical information required for the present analysis. A total of 496 participants met these analytic criteria.

## **Primary outcome: current ASM polytherapy**

The outcome was current ASM regimen, categorized as monotherapy or polytherapy from the recorded treatment-regimen field. Polytherapy was defined as current treatment with two or more ASMs. The outcome was treated as a measure of current treatment complexity and not as a diagnosis of drug-resistant epilepsy.

## **Candidate explanatory variables**

Explanatory variables were selected a priori on the basis of clinical plausibility and availability in the clinical records. They included current age, sex, age at epilepsy onset, duration of epilepsy, epilepsy type, documented neurodevelopmental problems, and documented comorbid conditions.

## **Variables intentionally excluded from the primary model**

Seizure-freedom, post-treatment seizure reduction, clinician-documented treatment response, and variables describing medication switching or add-on treatment were not included in the primary model because they could occur after treatment escalation and introduce reverse-causation or overadjustment.

## **Data quality and medication-name sensitivity analysis**

The recorded regimen field was used as the primary outcome because it directly represented the documented current treatment classification. Free-text medication-name fields contained spelling variants, brand names, and occasional non-ASM medicines. Recognizable ASM names and common brand-name variants were standardized for a sensitivity analysis in which documentation of two or more recognizable ASMs was classified as polytherapy.

## **Statistical analysis**

Categorical variables were summarized using frequencies and percentages. The prevalence of polytherapy was reported with a 95% confidence interval (CI). Modified Poisson regression with a log link and robust standard errors was used to estimate crude prevalence ratios (cPRs) and adjusted prevalence ratios (aPRs) with 95% CIs. The multivariable model included current age, sex, age at epilepsy onset, epilepsy duration, epilepsy type, documented neurodevelopmental problems, and documented comorbidity. Statistical significance was set at  $p < 0.05$ . Because treatment regimen is clinically determined, all associations were interpreted as non-causal and with consideration of potential confounding by indication.

## **Sensitivity and robustness analyses**

Two robustness checks were incorporated. First, percentage agreement and Cohen's kappa were calculated between the recorded regimen classification and the medication-name-derived classification. Second, the complete adjusted modified Poisson model was repeated using the medication-name-derived polytherapy outcome. A clinical correlate was considered more robust when the direction and magnitude of association were reasonably consistent across the two outcome definitions. The sensitivity analysis was not used to overwrite the primary analysis because free-text medication documentation could itself be incomplete.

## **Missing data and bias**

The current-regimen outcome was complete for all 496 participants. Analyses used available documented values for explanatory variables. Where a clinical field was blank, results are described as 'none documented' rather than assuming definitive absence of the condition. The retrospective design may have introduced information bias, and confounding by indication was considered when interpreting associations.

## **Ethical considerations**

### **Ethical approval**

for the retrospective review of existing clinical records was obtained from the St. Francis Hospital Nsambya Institutional Review Board (NH/ADDCS/RESCH/148/26), with waiver of individual informed consent. Only de-identified data were used for analysis.

## **Reporting**

The manuscript was prepared with reference to the STROBE recommendations for reporting observational studies.

## **Results**

### **Prevalence of recorded polytherapy**

All 496 participants had a recorded current ASM regimen. Of these, 418 (84.3%) were classified as receiving monotherapy and 78 (15.7%; 95% CI 12.8–19.2) as receiving polytherapy.

**Table 1. Current antiseizure medication regimen among participants (N=496)**

| Current recorded ASM regimen | N   | %    |
|------------------------------|-----|------|
| Monotherapy                  | 418 | 84.3 |
| Polytherapy                  | 78  | 15.7 |

## Medication documentation and concordance

Medication names were available as free-text entries for all 496 participants, but documentation was not fully standardized. After harmonizing recognizable generic and brand names, 64 participants (12.9%) had at least two recognizable ASMs documented. The recorded-regimen and medication-name-derived classifications agreed for 460/496 participants (92.7%), with a Cohen's kappa of 0.70, indicating substantial but incomplete agreement. Eleven participants recorded as receiving monotherapy had at least two recognizable ASMs in the medication-name field, while 25 recorded as receiving polytherapy had fewer than two recognizable ASMs identified from the standardized name list. These discrepancies motivated the sensitivity analysis.

## Factors associated with recorded polytherapy

**Table 2. Factors associated with current antiseizure medication polytherapy (N=496)**

| Variable                   | Category                 | cPR (95% CI)     | aPR (95% CI)     | Adjusted p |
|----------------------------|--------------------------|------------------|------------------|------------|
| Current age                | 1–4 years                | Reference        | Reference        | —          |
|                            | 5–9 years                | 1.25 (0.67–2.31) | 1.06 (0.56–2.01) | 0.867      |
|                            | 10–14 years              | 1.20 (0.62–2.33) | 0.94 (0.42–2.10) | 0.883      |
|                            | 15–18 years              | 0.57 (0.13–2.39) | 0.35 (0.08–1.51) | 0.158      |
| Sex                        | Female                   | Reference        | Reference        | —          |
|                            | Male                     | 1.12 (0.74–1.68) | 1.02 (0.67–1.56) | 0.922      |
| Age at epilepsy onset      | <1 year                  | Reference        | Reference        | —          |
|                            | 1–4 years                | 1.24 (0.59–2.59) | 1.38 (0.66–2.92) | 0.392      |
|                            | ≥5 years                 | 1.42 (0.70–2.87) | 1.81 (0.87–3.77) | 0.115      |
| Epilepsy duration          | <2 years                 | Reference        | Reference        | —          |
|                            | 2–4 years                | 0.59 (0.31–1.14) | 0.71 (0.37–1.36) | 0.303      |
|                            | ≥5 years                 | 0.92 (0.44–1.94) | 1.16 (0.56–2.37) | 0.691      |
| Epilepsy type              | Focal                    | Reference        | Reference        | —          |
|                            | Generalized              | 2.57 (1.67–3.96) | 2.62 (1.70–4.04) | <0.001     |
|                            | Mixed/other              | 2.37 (1.08–5.19) | 2.25 (0.98–5.13) | 0.055      |
| Neurodevelopmental problem | None documented          | Reference        | Reference        | —          |
|                            | Any documented problem   | 1.34 (0.89–2.01) | 1.06 (0.71–1.58) | 0.772      |
| Comorbid condition         | None documented          | Reference        | Reference        | —          |
|                            | Any documented condition | 2.21 (1.42–3.45) | 2.01 (1.25–3.23) | 0.004      |

Abbreviations: ASM, antiseizure medication; cPR, crude prevalence ratio; aPR, adjusted prevalence ratio; CI, confidence interval. The adjusted model included current age, sex, age at epilepsy onset, epilepsy duration, epilepsy type, documented neurodevelopmental problems, and documented comorbidity.

In the primary adjusted analysis, generalized epilepsy was associated with a higher prevalence of recorded polytherapy than focal epilepsy (aPR 2.62, 95% CI 1.70–4.04;  $p < 0.001$ ). Any documented comorbid condition was also associated with polytherapy (aPR 2.01, 95% CI 1.25–3.23;  $p = 0.004$ ). Mixed/other epilepsy showed borderline evidence of association (aPR 2.25, 95% CI 0.98–5.13;  $p = 0.055$ ). Current age, sex, age at epilepsy onset, epilepsy duration and neurodevelopmental problems were not independently associated with the recorded regimen.

## Sensitivity analysis

When polytherapy was redefined as documentation of at least two recognizable ASM names, the prevalence was 12.9% rather than 15.7%. Comorbidity remained strongly associated with polytherapy (aPR 2.65;  $p < 0.001$ ). The generalized-epilepsy association attenuated to borderline statistical significance (aPR 1.60;  $p = 0.050$ ), indicating that this finding was less robust to outcome classification than the comorbidity association.

## Discussion

This analysis found that 15.7% of children and adolescents were recorded as receiving ASM polytherapy. The principal finding was that documented comorbidity was consistently associated with polytherapy across both the primary and sensitivity definitions. Generalized epilepsy was strongly associated with the recorded regimen classification, but this association weakened when polytherapy was reconstructed from standardized medication names. The sensitivity analysis therefore materially refines the interpretation of the primary model.

The recorded polytherapy prevalence was lower than the 32.4% reported by Atugonza and colleagues at Mulago Hospital in 2013.<sup>3</sup> It was also lower than the approximately 35.7% polytherapy implied by a 2025 Ethiopian paediatric epilepsy study in which 64.3% received monotherapy,<sup>4</sup> and somewhat lower than the 21.4% polytherapy implied by a more recent Ethiopian cohort reporting 78.6% monotherapy.<sup>5</sup> These differences should not be interpreted as evidence that one service is superior. Referral patterns, epilepsy severity, treatment duration, medicine availability, prescribing culture and study methods differ substantially across settings and periods.

The robust association between comorbidity and polytherapy is clinically plausible. Children with additional neurological or systemic conditions may have more complex underlying brain disease, multiple seizure phenotypes, interacting treatments or a greater need for specialist review. However, the broad comorbidity variable cannot identify the mechanism. It is better regarded as a marker of clinical complexity rather than a causal determinant of treatment escalation.

The association between generalized epilepsy and recorded polytherapy requires greater caution. In the primary analysis, generalized epilepsy was associated with more than twice the prevalence of polytherapy compared with focal epilepsy. Yet the estimate attenuated substantially when the outcome was reconstructed from medication names. This suggests that some of the apparent relationship may

depend on how treatment regimen was recorded. In addition, the dataset did not consistently capture specific epilepsy syndromes or aetiology, which are more informative for treatment selection than the broad focal/generalized classification alone.

The medication-documentation discrepancies are themselves informative. Although the two polytherapy classifications agreed in more than 90% of participants, several records contained combinations of recognizable ASMs despite being labelled monotherapy, while some records labelled polytherapy did not contain two recognizable ASM names. These discrepancies may reflect transitional prescribing, incomplete free-text entry, brand-name variation, non-ASM co-medication, or data-entry inconsistency. They reinforce the importance of structured medication reconciliation in both clinical care and retrospective research.

Polytherapy should not be interpreted as harmful treatment or as synonymous with drug resistance. Clinicians commonly add or switch medicines because of persistent seizures, adverse effects, syndrome-specific treatment needs or planned cross-titration. Confounding by indication is therefore unavoidable in this observational analysis. Formal drug-resistant epilepsy requires evidence that two appropriately selected and adequately used ASM schedules have failed, information that cannot be reconstructed reliably from the current cross-sectional regimen variable alone.<sup>2</sup>

## Strengths and Limitations

A strength of this study is the inclusion of 496 children and adolescents receiving specialist epilepsy care, providing a useful contemporary picture of polytherapy in a Ugandan paediatric neurology clinic. The outcome was straightforward—whether a child was currently receiving one ASM or more than one—and the analysis used prevalence ratios, which are easy to interpret for an outcome of this frequency. We were also able to examine several relevant clinical characteristics in the same adjusted model.

There are important limitations. Because the study relied on routine clinical records, the analysis was only as complete as the documentation available, and some variables may have been misclassified. Records did not consistently provide detailed epilepsy syndromes or aetiology, seizure severity, the adequacy of previous ASM trials, dose and treatment duration, reasons for changing treatment, or adverse effects.

Current polytherapy does not necessarily indicate drug-resistant epilepsy. Some children may have been receiving multiple ASMs because of persistent seizures, syndrome-specific treatment, treatment optimization, or temporary cross-titration. The available records did not permit reliable reconstruction of the sequence and adequacy of previous ASM trials required to establish drug-resistant epilepsy.

Confounding by indication is another concern: children with more severe or difficult-to-control epilepsy are also the children most likely to have another ASM added. The associations reported here therefore cannot be taken as causal, and unmeasured differences in epilepsy severity, syndrome, or aetiology may

still influence the estimates. In addition, the study was conducted in one specialist clinic, so the findings may not reflect treatment patterns in general hospitals, lower-level facilities, or community settings.

## Recommendations

For children receiving polytherapy, regular medication review should confirm why each ASM is being used, whether the dose remains appropriate, whether adverse effects or important drug interactions are present, and whether combination treatment is still needed.

Children with comorbid conditions deserve particular attention because they were more likely to be receiving polytherapy in this cohort. Where feasible, coordinated review across the relevant paediatric services may help balance seizure treatment with the child's wider neurological and medical needs.

Better treatment documentation would also be valuable. Recording epilepsy classification, current and previous ASMs, doses, treatment duration, reasons for medication changes, response to previous regimens, and adverse effects would improve continuity of care and make it easier to distinguish long-term combination therapy from temporary treatment transitions or possible drug-resistant epilepsy.

Future prospective studies involving more than one centre should follow treatment sequences over time and use more detailed epilepsy syndrome and aetiological classification. This would help clarify why children move from monotherapy to polytherapy and how different treatment patterns relate to seizure control, adverse effects, treatment burden, and quality of life.

## Conclusion

Polytherapy was recorded in approximately one in six children and adolescents attending this specialist paediatric neurology clinic, while most participants were managed with a single ASM. Generalized epilepsy and documented comorbidity were associated with a higher prevalence of polytherapy, although these findings are best interpreted as markers of clinical complexity and treatment burden rather than causal effects. Children receiving multiple ASMs, particularly those with additional comorbidities, may benefit from structured medication review and careful reassessment of epilepsy classification, previous treatment trials, and the continuing indication for each medicine. Prospective studies with detailed syndrome classification and longitudinal treatment histories are needed to better characterize treatment escalation and appropriate combination therapy.

## Declarations

Ethics approval and consent to participate: Ethical approval for the retrospective review of existing clinical records was obtained from the St. Francis Hospital Nsambya Institutional Review Board (NH/ADDCS/RESCH/148/26), with waiver of individual informed consent. Only de-identified data were used for analysis.

Consent for publication: Not applicable.

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