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Brief Communication

Quality of life in adults with epilepsy is associated with anticonvulsant polypharmacy independent of seizure status

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ABSTRACT

Rationale: Polypharmacy, sometimes necessary to control epilepsy, can result in adverse effects that may affect quality of life (QOL). Our purpose was to determine the association of polypharmacy with QOL.
Methods: Two hundred seven patients with epilepsy were surveyed on characteristics within the last 4 weeks: QOL Quality of Life in Epilepsy-Patient-Weighted (QOLIE-10-P) and seizure status (seizure-free or not), demographics, epilepsy characteristics, insomnia, sleepiness, mood, sleep–wake timing, healthcare use, and employment. Those on polypharmacy (antiepileptic drug (AED) > 1) were compared with controls (AED = 1) with univariate comparisons and subsequent multivariate regression.
Results: Patients on polypharmacy had worse QOL scores (mean 33.3 ± 6.9 versus 36.7 ± 5.7), were less likely to be seizure-free (39 (44%) versus 82 (68%)), had more evening-weighted wakefulness, and were more likely unemployed (74% versus 49%). Polypharmacy was associated with worse QOL (odds ratio 1.068 and 95th CI 1.018–1.121) even after controlling for seizure status. Covariates offered no improvement to the model.
Conclusion: Polypharmacy was associated with worse QOL in patients with epilepsy despite seizure control. Further investigation into specific etiology of polypharmacy's influence on QOL is warranted in order to develop paradigms for optimal treatment.

1. Introduction

Quality of life (QOL) both supplements and correlates with seizure occurrence [1–3] as a measure of epilepsy treatment [4]. The QOL is useful in assessing the relative "costs" of treatments, since antiepileptic drugs (AEDs) and other treatments may affect QOL [5–7]. Particular adverse events of AED include tiredness/fatigue, sleepiness, memory problems, difficulty concentrating, and nervousness/agitation [2]. These may occur independently from seizure status [5]. In a recent survey by the International Bureau for Epilepsy (IBE), "sleepiness/tiredness" was the most common (and least desired) adverse event (59–63%) [8,9].

Two studies have looked specifically at the association between polypharmacy and QOL. One recent retrospective study demonstrated improvement in QOL when transitioning from polypharmacy to monopharmacy in patients with medically refractory epilepsy [7]. However, these findings are confounded by a coincident decrease in seizure frequency in 66% of the study patients. A prospective study demonstrated similar findings of improved patient satisfaction with polypharmacy reduction in adults, with minimal change in seizure frequency, but did not directly compare polypharmacy with monopharmacy [10]. Therefore, seizure control remains a confounder in evaluating the effects of polypharmacy on QOL.

Our objective was to evaluate the effects of AED polypharmacy on QOL while accounting for seizure status and other potential covariates.

2. Material and methods

This was an observational case–control study approved by the University of Virginia's IRB. All participants signed an informed consent document. A convenience sample of the approximately 1020 unique patients presenting to the Comprehensive Epilepsy Program clinic from September 2014 to March 2015 were surveyed regarding the prior 4 weeks. Based on patient eligibility and staff availability, 212 patients were asked to participate. Four patients declined, and one did not complete the survey due to seizure. Patients >17 years of age had to have >1 unprovoked seizure over the course of their history and be currently treated with at least 1 AED. Patients with psychogenic nonepileptic spells, those not on any AED treatment for the past 1 month, and those who were cognitively unable to complete the survey were excluded.

Abbreviations: QOL, quality of life; AED, antiepileptic drug; MEQ, Horne–Östberg Morning–Eveningness Questionnaire; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; CES-D, Center for Epidemiological Studies Depression Scale.

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Patients were divided into two groups: polypharmacy (N AED > 1) and a monopharmacy (AED = 1) control group. To accurately record AEDs, patients were given a complete list of all AEDs from which they selected all the AEDs they were currently taking. The AEDs with potential dual uses (such as gabapentin for chronic pain) were counted as an AED since the principal intention of use could not be reliably determined. This list, along with the prevalence of each medication in our sample, is provided in Supporting information (Supplemental Table 1) ("PRN" medications were excluded). All patients were surveyed on QOL Quality of Life in Epilepsy-Patient-Weighted (QOLIE-10-P) [11]. Other data included seizure status (seizure-free or not within the prior 4 weeks), age, sex, age of onset and duration of epilepsy, type of epilepsy (partial versus generalized), chronotype via the Horne–Östberg Morning–Eveningness Questionnaire (MEQ) [12], the Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS) [13], and mood via the Center for Epidemiological Studies Depression Scale (CES-D) [14]. Unexpected healthcare use was assessed as positive or negative depending on the unscheduled visit of a healthcare provider within the last 4 weeks. Unemployment status (unemployed/disability versus part- or full-time employment) was also obtained.

Univariate comparisons of variables against treatment group were performed with Student's *t*-tests or Fisher's exact tests. Cohen's d was used to calculate effect size for continuous variables. Significant variables ($P < 0.05$), in addition to seizure status and QOL, were then evaluated against polypharmacy status via binomial regression models.

3. Results

Of the 207 patients who completed questionnaires, 88 (43%) were on polypharmacy and 119 (57%) patients were on monopharmacy (Table 1). Those on polypharmacy were almost twice as likely to have continuing seizures than monotherapy patients. Patients on polypharmacy also had worse QOL scores, most prominently in the epilepsy (memory, physical effects, mental effects) and role functioning (seizure worry, work, driving, and social) domains. Age, sex, and duration or type of epilepsy did not differ between the two groups, but younger age of onset was associated with polypharmacy. Patients on polypharmacy had more evening-weighted sleep–wake preferences as per the MEQ, meaning they preferred a relatively later bedtime and wake time than those on monopharmacy. There were no significant associations with polypharmacy and insomnia, sleepiness, depression, or unexpected healthcare use. Patients who were unemployed were more likely to be in the polypharmacy group.

Table 1
Univariate analysis of variables in polypharmacy versus monopharmacy.

Variables	Polypharmacy N = 88 (43%)	Monopharmacy N = 119 (57%)	Effect size	P value
QOLIE-10-P (mean ± SD)	33.3 ± 6.9	36.7 ± 5.7	−0.54	0.005*
QOLIE/epilepsy domain	9.9 ± 3.5	11.9 ± 3.1	−0.61	0.001*
QOLIE/mental health domain	10.3 ± 1.5	9.9 ± 1.7	0.25	0.11
QOLIE/role functioning	13.2 ± 4.4	14.9 ± 3.9	−0.41	0.002*
Seizure-free (n (%))	39 (44%)	82 (68%)		0.001*
Age (mean ± SD years)	39.5 ± 13.7	41.4 ± 16.7	−0.12	0.398
Sex (M:F, n(%))	43:45 (49:51%)	52:67 (44:56%)		0.483
Age onset (mean ± SD years)	18.3 ± 15.6	23.1 ± 16.3	−0.30	0.035*
Duration of epilepsy (mean ± SD years)	21.2 ± 13.4	18.3 ± 15.8	0.20	0.163
Epilepsy syndrome (generalized, partial, n(%))	19:69 (22:78%)	38:81 (32:68%)		0.116
MEQ (mean ± SD)	52.1 ± 9.6	55.6 ± 11.0	−0.34	0.017*
ISI (mean ± SD)	9.0 ± 6.5	8.2 ± 7.0	0.12	0.210
ESS (mean ± SD)	8.5 ± 4.4	8.4 ± 4.7	0.02	0.210
CES-D (mean ± SD)	18.0 ± 11.0	15.6 ± 10.5	0.22	0.452
Healthcare use (Y:N, n(%))	16:72 (19:81%)	24:95 (20:80%)		0.860
Unemployment (Y:N, n(%))	65:23 (74:26%)	60:59 (51:49%)		0.001*

* Statistically significant.

Patients were treated with a mean ± standard deviation 1.7 ± 0.9 AED. Seven AED were prescribed in 10% or more of cases: levetiracetam (37%), lamotrigine (34%), zonisamide (16%), lacosamide (14%), carbamazepine (12%), topiramate (12%), and oxcarbazepine (12%). Only lacosamide had a statistically significant association with worse QOL ($P = 0.002$); however, no patients were on lacosamide monopharmacy to provide a valid comparison.

Polypharmacy was associated with worse QOL even after controlling for seizure status (Table 2). The association between polypharmacy and worse QOL remained after additions of significant covariates (age of onset, MEQ, and unemployment) to the binomial model. Unemployment status among covariates remained significant in the model with unemployment associated with polypharmacy with an odds ratio = 2.66 (1.40–5.00, $P = 0.003$).

4. Discussion

In this study, worse QOL in epilepsy was associated with AED polypharmacy when compared with monopharmacy, even after controlling for seizure status. The absence of associations between polypharmacy and factors such as sleepiness [9], depression [3,6], and insomnia [15] suggests that other factors may mediate this association.

Our study supports earlier findings that the number of AED may influence QOL [7,10]. In these studies, QOL improved after reduction of AED. The present study differed in design and findings from a previous study that determined that QOL and the number of AED were not related [6]. In contrast to the previous study, our sample defined seizure status in terms of the presence or absence of seizures within the most recent 4 weeks; thus, our sample contains those with well-controlled as well as poorly controlled epilepsy in which the statistical model evaluated seizure status as a covariate. A comparison of the two studies suggests that seizure-free status attained by polypharmacy may have a cost in QOL.

The exact mediator of impaired QOL associated with polypharmacy was not determined in our study. Potential mediators such as mood, sleep disorder, and daytime sleepiness were evaluated, but none had a significant association with polypharmacy. We can only speculate as to what these factors may be. Based on the available literature regarding QOL in epilepsy, possible mediators that we did not evaluate include a host of potential medication side effects, socioeconomic factors such as stigma or cost, or other unmeasured aspects of the epileptic condition such as seizure severity or type (beyond "partial" or "generalized" syndrome evaluated here).

The covariates of young age at onset, evening chronotype, and unemployment were all significantly associated with polypharmacy. Childhood onset epilepsy has been shown to have significant psychosocial and societal impacts that could affect QOL [16]. Our study would indicate that polypharmacy may also have a role in this relationship.

In an earlier study of patients with epilepsy selected for an absence of psychiatric comorbidities, QOL as well as chronotype and sleep

Table 2
Binomial regressions of polypharmacy versus quality of life with addition of seizure status and other significant covariates.

Polypharmacy and QOL	Odds ratio	L 95% CI	U 95% CI	P value
Model: basic QOL	0.919	0.879	0.962	<0.0001[a]
Model: QOL adjusted for seizure status	0.936	0.892	0.982	0.007[a]
Model: QOL adjusted for seizure status and covariates	0.950	0.903	0.999	0.045[a]

These data are obtained from the QOLIE-10-P with additions of seizure status and significant covariates determined from univariate analysis (age, chronotype, unemployment status) to iterative statistical models. The odds ratio can be interpreted that for every additional point in the quality of life scale, the likelihood of being in the polypharmacy group and not being in the monopharmacy group decreases by a factor of 92–95% depending on the statistical model.

[a] Statistically significant.