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## Adherence to Treatment in Patients with Juvenile Myoclonic Epilepsy: Correlation with Quality of Life and Adverse Effects of Medication

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### ABSTRACT

**Purpose:** To study the adherence to clinical treatment in patients with Juvenile Myoclonic Epilepsy (JME) and its correlation to Quality of Life (QOL) scores, and antiepileptic drugs (AEDs) adverse effects. **Methods:** Forty-three JME (ILAE, 1989) outpatients in regular treatment were evaluated by clinical anamnesis and EEG/video-EEG at Hospital São Paulo, UNIFESP, Brazil. They answered a self-report questionnaire assessing adherence to treatment (scores 0 to 100), with higher scores meaning poorer adherence; Quality of Life in Epilepsy-31 (QOLIE-31) Brazilian validated version (scores 0 to 100), and the Adverse Events Profile (AEP), scores 19 to 76, in which scores  $\geq 45$  indicate toxicity; values less than 0.05 were considered statistically significant. **Results:** Sixteen patients (37,2%) were on monotherapy, while 26 (60,4%) on polytherapy. Twenty-two (48%) had experienced a seizure in the preceding three months of the survey. Mean adherence to treatment score was 68.5. AEP scores  $\leq 45$  were observed in 38 (88,3%), and 29 (67,4%) reported spontaneous adverse effects with AEDs. The most common adverse effects were sleepiness in 11 (13,8%), and restlessness in 7 (8,8%). QOLIE-31 highest mean score was 79.0 (Social Function), and the lowest 33.0 (Seizure Worry). Adherence to treatment presented good correlation to better QOL scores (Pearson  $< 0.05$ ), while higher AEP scores indicated poorer adherence (Pearson  $< 0.05$ ). **Conclusions:** Adherence to treatment showed high correlation to better QOL. The presence of adverse effects was negatively associated with adherence. **Key-words:** Adherence to treatment, antiepileptic drugs; adverse effects of medication, quality of life, juvenile myoclonic epilepsy.

### RESUMO

**Adesão ao tratamento em pacientes com Epilepsia Mioclônica Juvenil: correlação com qualidade de vida e efeitos adversos da medicação**

**Objetivos:** Este estudo teve como objetivo avaliar a adesão ao tratamento com drogas antiepilépticas (DAEs) em pacientes com Epilepsia Mioclônica Juvenil (EMJ) e correlacionar com a Qualidade de Vida (QV) e com os efeitos adversos à medicação. **Metodologia:** A amostra foi composta de 43 pacientes com diagnóstico clínico e eletrográfico (EEG/Vídeo-EEG) de EMJ (ILAE, 1989), em tratamento regular no Hospital São Paulo, UNIFESP, Brasil. Todos os pacientes responderam a um questionário de adesão ao tratamento (escores de 0-100), em que escores mais elevados evidenciavam uma pobre adesão ao tratamento. Para avaliar a QV foi utilizada a versão brasileira validada do *Quality of Life in Epilepsy Inventory 31* (QOLIE-31); os efeitos adversos das DAEs

foram avaliados através do *Adverse Events Profile* (AEP), escores de 19 a 76, no qual escores  $\geq 45$  indicam toxicidade. Foram considerados significantes os valores de  $p < 0,05$ . **Resultados:** Dezesesseis pacientes (37,2%) estavam em monoterapia e 26 (60,4%), em politerapia; 22 (48%) tiveram uma crise nos últimos três meses antes da entrevista. A média de adesão ao tratamento foi 68,5. Foram observados escores  $\leq 45$  em 38 (88,3%) no AEP e 29 (67,4%) apresentaram queixas espontâneas em relação ao uso das DAEs. Os efeitos adversos mais comuns foram sonolência em 11 (13,8%) e inquietação em 7 (8,8%). A maior média do QOLIE-31 foi 79,0 (Funcionamento Social), e a mais baixa 33,0 (Preocupação com as Crises). A adesão ao tratamento apresentou correlação estatística com valores melhores na QV enquanto valores elevados no AEP indicaram pior adesão (Pearson  $< 0,05$ ). **Conclusão:** A adesão ao tratamento mostrou alta correlação com uma melhor QV. A presença de efeitos adversos foi negativamente associada com a adesão ao tratamento.

**Unitermos:** Adesão ao tratamento, drogas antiepilépticas, efeitos adversos à medicação, qualidade de vida, epilepsia mioclônica juvenil.

## INTRODUCTION

Medication adherence can be defined as the act of follow the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking.<sup>6</sup>

Epilepsy is a chronic condition in which non-adherence is considered to be a significant problem faced during clinical treatment.<sup>23</sup> Poor adherence to treatment is one of many reasons for pharmacological treatment failure and seizure recurrence. Stanaway et al. (1985) found that 31% of seizures were precipitated by non-adherence to medication treatment.<sup>26</sup> The behavior of adherence depends on specific clinical situation, nature of the illness, and treatment program.<sup>1</sup>

Estimates suggest that between 30% and 50% of epilepsy patients do not adhere with their drug regimens.<sup>20,21</sup> Many factors contribute to medication non-adherence, including memory problems, age, complexity of their medication regimen,<sup>27</sup> discomfort resulting from treatment, expense of treatment and decisions based on personal judgment about the effectiveness of the proposed treatment.<sup>1,2</sup>

Adherence to treatment can be measured in various ways, including self-report measures, pills count, appointment attendance, medication refills, drug levels, and seizure frequency. Most of studies have attempted either to identify predictors or to measure the incidence of non-adherence,<sup>3</sup> but there is not a validated scale for measuring epilepsy patient adherence to treatment. The lack of these measurements provides difficulties to assess the impact of specific factors in adherence to treatment.<sup>24</sup>

Recent data shows that non-adherence is strongly related to low scores in quality of life (QOL) measurements, and decrease in work productivity.<sup>17</sup>

Behavior problems that could influence the medical treatment were reported in 1957 by Janz and Christian in JME patients: "*They will declare that they adhere to all prescriptions, but in fact they forget to attend control visits and to take their medication regularly...*".<sup>18,19</sup> This syndrome

is a well-defined primary generalized epileptic syndrome characterized by myoclonic jerks and generalized tonic-clonic seizures (GTCS).<sup>4</sup> Five to eleven percent of patients with epilepsy have JME.<sup>9</sup>

The purpose of this study was to evaluate the frequency of adherence to treatment in a homogeneous series of patients with a specific epilepsy, the JME syndrome. We also intended to verify some aspects in the behavior to adherence, adverse effects of medication and QOL. To perform this pilot study we elaborated a self-report questionnaire, because it is the most commonly method used to assess the adherence and it is easily adaptable.

## METHODS

### Subjects

All patients were evaluated between May 2008 and October 2008 in the Outpatient Epilepsy Clinic of Hospital São Paulo of the UNIFESP, Brazil. The inclusion criteria was the presence of electroclinical diagnosis of JME based on ILAE classification<sup>4</sup> and a regular treatment in our unit for at least 6 months with stable doses of antiepileptic drugs (AEDs). Patients with other medical conditions besides epilepsy were excluded.

### Procedures

A working group specialized in epilepsy composed by epileptologist, pharmacist and QOL psychologist expert designed the survey and the questionnaire based on a literature review on adherence measurements.<sup>3,5,13,22</sup> Pre-test was performed with a semi-structured questionnaire composed of 27 questions. This questionnaire evaluated the following aspects in treatment: self-perception and complaints about the adverse effects of AEDs; problems to acquire the medicines; conduct facing "forgetting"; strategies used to remember taking the AEDs; expectations of seizure control by the medication; satisfaction with the current treatment; and finally, interferences of treatment in daily activities and relationships. Each answer ranged

**Table 1.** Adherence to treatment questionnaire, questions and answers of patients, higher scores (3 to 5) were considered YES.

Questions	YES	NO
Do you feel any adverse effect of the medication as a result of its use?	29 (67.4%)	14 (32.6%)
Are you afraid of becoming addicted to your medicine?	27 (62.9%)	16 (37.2%)
Do you become out of medication if it is hard to find it?	13 (30.2%)	30 (69.8%)
Have you ever forgotten to take your medicine?	28 (65.2%)	15 (34.9%)
Do you believe that the medications can control your seizures?	36 (83.7%)	7 (16.3%)
Do you have seizures when you forget to take your medications?	24 (55.8%)	19 (44.2%)
Do you think that taking medications affects your daily life?	12 (27.9%)	31 (72.1%)
Do you care about taking your medicine in public places (school, work, in front of your friends or in meetings)?	18 (41.8%)	25 (58.1%)
Do you feel like quitting your treatment?	20 (46.6%)	23 (53.5%)
Are you satisfied with your current treatment?	40 (93%)	3 (7%)
Which strategy do you use to remember to take your medication?	40 (93%)	3 (7%)
Do you use any alternative treatment?	17 (43.5%)	26 (56.5%)

from “never” to “frequently” in a scale from 0 to 5 and by definition, higher scores were established as poorer adherence evidence.

QOL in epilepsy was measured using the Brazilian version of QOLIE-31,<sup>8</sup> which includes 31 items organized into seven subscales, and the scores being transformed in a scale 0 to 100, with higher values reflecting better QOL. The AEP was used to assess the most common negative adverse effects reported by patients taking AEDs. This instrument contains 19 brief items and the frequency of a different adverse effect is reported in a scale of 1 to 4, with 4 indicating more frequent occurrences. A score in AEP ranging from 19 to 76 may be calculated to measure total adverse effect burden of a medication regimen.<sup>12</sup>

Patients had to complete a questionnaire regarding clinical and sociodemographic information such as, gender, age, schooling, duration of epilepsy, type and frequency of seizures, and drug treatment. All questionnaires were administered in face-to-face interviews to check the comprehensibility of the measurements.

### Statistical analyses

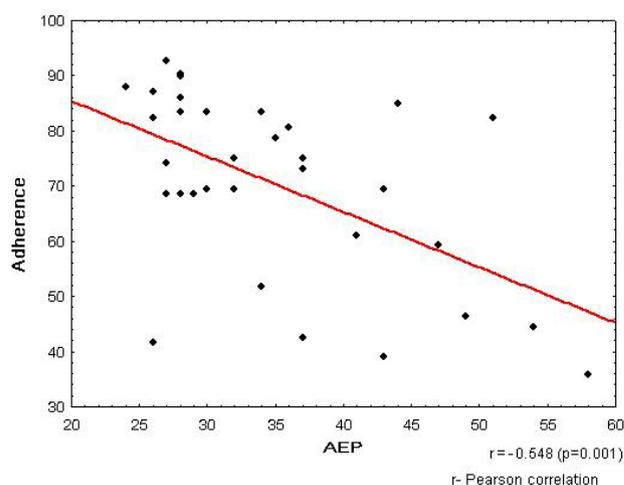
Pearson coefficient was used to investigate the correlation between adherence results, QOLIE-31 domains and AEP scores. For statistical analysis, p values < 0.05 were considered statistically significant.

## RESULTS

Forty-three patients were interviewed with mean age of 27.1 yrs. (range 15-66). Twenty four (55.8%) were male, 34 (79.1%) were single, with mean age of 27.1 yrs. (range 15-66), and 27 (62.8%) had 9 to 11 yrs. of education. Fourteen patients (32.6%) were fulltime employed, seven (16.3%) unemployed, and 12 (27.9%) were studying only.

Mean duration of epilepsy was 15.2 yrs.: 16 patients (38.1%) had had epilepsy for less than 10 years, and 12 (28.6%) between 11 to 20 years. Nearly half of the sample 22 patients (51%) experienced a seizure in the preceding three months of the survey. Sixteen patients (37.2%) were taking only one AED at the time of the study, while 26 (60.4%) were on polytherapy and the most common drug prescribed was valproate (VPA) in 32 patients, followed by topiramate (TPM) in 12, and lamotrigine (LTG) in 12. Twenty-four (57.2%) had been taking AED for more than 10 yrs.

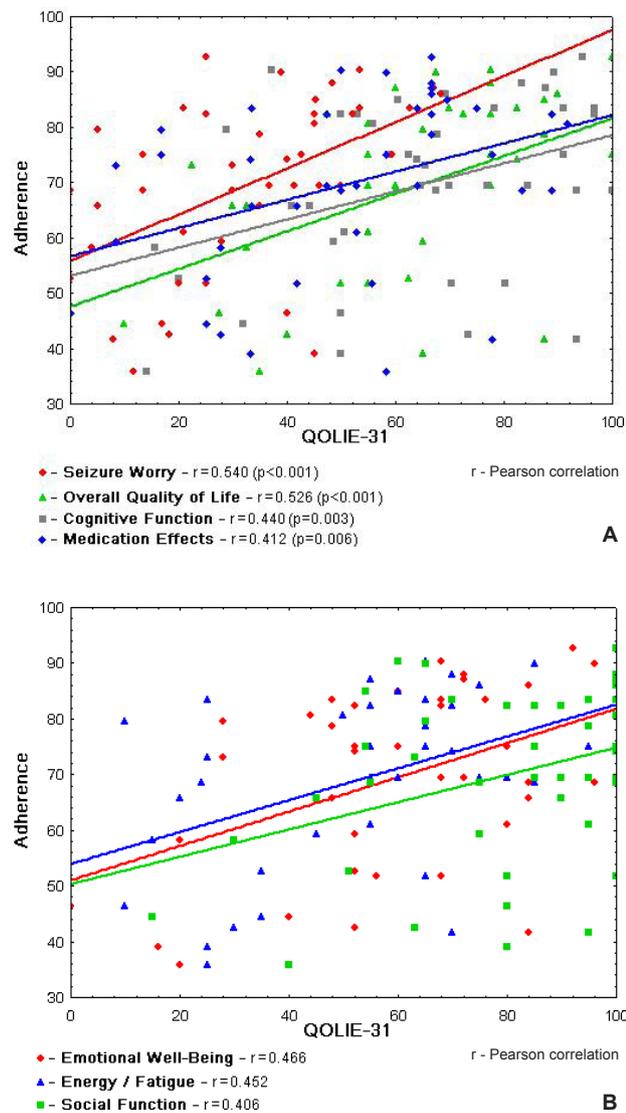
In this study, problems related with AEDs were reported by 29 patients (67.4%). The most common adverse effects were sleepiness in 11 (13.8%) and restlessness in seven (8.8%). AEP scores below 45 were observed in 38 patients (88.3%). The correlation between AEP scores and adherence revealed that higher AEP scores were correlated to poorer adherence (Pearson coefficient < 0.05), as seen in Figure 1.



**Figure 1.** Graphic showing correlation of adherence and AEP scores.

Adherence to treatment mean score was 68.5, indicating poor adherence to medication regimen. Twenty-seven (62.9%) of 43 patients declare to be afraid of becoming addicted by the medicine, 29 patients (67.4%) felt any adverse effect of the medication and 28 patients (65.2%) forgot to take the medicine.

The results of QOLIE-31 were correlated with adherence scores. QOLIE-31 domains mean scores were as follows: 79.0 for *Social Function*; 65.1 for *Cognitive Function*; 64.9 for *Overall Quality of Life*; 60.6 for *Emotional Well-Being*; 55.0 for *Energy/Fatigue*; 51.0 for *Medication Effects* and 33.0 for *Seizure Worry*. Statistical analysis revealed that adherence to treatment scores showed a strong correlation with all QOLIE-31 domains (Pearson coefficient <0.05), indicating better QOL in patients with good adherence to medical regimen, as showed in Figure 2 (A and B).



**Figure 2 (A and B).** Correlation between QOL domains and adherence scores

Statistical correlations were identified between AEP scores and QOLIE-31 ( $p < 0.05$ ) in all domains, except Seizure Worry ( $p = 0.09$ ) subscales. Better QOL was associated with lower AEP scores.

## DISCUSSION

In our study we found that non-adherence to treatment is common in JME. Our mean score of the questionnaire was 68.5%, indicating poor adherence. These results are consistent with findings from previous studies of self-report data suggesting that between 30 and 60% of patients with epilepsy are non-adherent with their AED regimens.<sup>14,20,21</sup>

Our study relies on patient self-report and demonstrates many of the advantages of this method. We have been able to gather a great deal of information about the behavior of adherence that would have been difficult to obtain by other means. This, in turn, has enabled us to examine relations among patient attitudes, medication problems, mental health, and QOL.<sup>7</sup>

Although patient self-report can be a useful instrument, there are some limitations. Some patients declare their usual attitudes in daily life and their statements usually can be accepted as definitive, while others may provide less reliable information.

We also assessed some aspects of the behavior of the patients regarding adherence, adverse effects of medication and QOL measurements. Non-adherence was found to be statistically significant and associated with complaints of adverse effects to medication. AEP higher values had a strong association with decrease in adherence to medication treatment. This fact is similar to the results of other studies, which have demonstrated that patients who take more medications have lower adherence and an increase in adverse effects.<sup>11</sup>

In our sample, perception of adverse effects also showed a strong correlation with QOLIE-31 decrease in almost all domains. However, many of the complaints that were reported by patients reflected in the domain *Medication Effects*. Another study showed that patients probably do not report problems with adherence and they overestimate the adverse effects.<sup>10,16</sup> The mechanisms which may be involved in the pathogenesis of these adverse effects are pharmacodynamic problems associated with polytherapy, dosage-related toxic effects, dosage unrelated idiosyncratic effects in predisposed patients, and effects related to efficacy of treatment, like forced normalization and drug withdrawal.<sup>25</sup>

The correlation with the adherence and the global impact on JME patients lives, we documented in QOLIE-31 results. The dimensions related to *Seizure Worry* (33.0), *Medication Effects* (51.0) and *Energy/Fatigue* (55.0) showed the greatest impact in QOL. Da Silva et al. (2007)

reported score 53.8 in the domain *Medication Effects* of QOLIE-31, which showed similar results comparing with other studies done with the same type of epilepsy syndrome.<sup>8</sup> Grudzinski et al. (1998) and Gilliam et al. (1998) found that problems of cognition, energy level, school performance, childbearing, coordination, and sexual function were the most commonly mentioned adverse effects that influence negatively patients' QOL.<sup>12,15</sup>

We observed that the Social Function (79.0) did not represent impact in this epilepsy syndrome. This was expected since these patients, when compared with temporal lobe epilepsy patients with mesial temporal sclerosis, have fewer cognitive complaints, are younger, with higher education, and good employment rates.<sup>8</sup>

In conclusion, we confirm that adverse effects of medication impact in QOL and adherence to treatment. Further studies are necessary combining patient report and other direct measures of adherence to assess the degree a patient adheres to a pharmacological treatment and the importance of poor adherence to seizure control.

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