Epilepsy & Behavior 98 (2019) 110–116

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Treatment and challenges with antiepileptic drugs in patients with juvenile myoclonic epilepsy

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ARTICLE INFO

Article history:
Received 27 April 2019
Revised 13 May 2019
Accepted 17 May 2019
Available online xxxx

Keywords:
Adherence
Antiepileptic drugs
Juvenile myoclonic epilepsy
Treatment challenges

ABSTRACT

Background: Patients with juvenile myoclonic epilepsy (JME) may have uncontrolled seizures. The purpose of this study was to investigate the use and challenges with antiepileptic drugs (AEDs) and the patients' view of these challenges.
Method: A questionnaire about the use of AEDs, adherence to therapy, and quality of life was given to patients with JME recruited from Drammen Hospital. Data regarding AEDs were confirmed from medical records at Drammen Hospital, Norway (2007–2018). Additional clinical interviews were performed, and a mixed method approach was applied.
Results: Ninety patients with defined JME diagnosis, 54/36 women/men aged 14–39 (mean: 25) years, were included. Only 29 (33%) were seizure-free. Within the last year, 21% experienced generalized tonic–clonic seizures (GTCS), and 68% had myoclonic jerks. Seventy-six (84%) used AEDs, 78% in monotherapy. A total of 10 AEDs were used;: most commonly valproate (n = 33), lamotrigine (n = 27), and levetiracetam (n = 21). Two-thirds of valproate users were men while all other AEDs were used more in females than in men. Valproate and levetiracetam displayed better efficacy against GTCS than lamotrigine. One-third often/sometimes forgot their medication nonintentionally while 14% had intentional poor adherence. The majority reported good quality of life (76%). No significant correlations between the use of AEDs, use of valproate, poor adherence, quality of life score, and seizure freedom were demonstrated. Half of the patients had serum concentrations measured every year, and two-thirds thought this was important. Qualitative interviews elucidated treatment challenges in JME;, adverse effect burden, adherence, and activities of daily life.
Conclusion: Despite the use of AEDs in the majority of patients, only one-third were seizure-free. Other challenges included polypharmacy, the use of valproate in women, and variable adherence. This points to a need for closer follow-up in patients with JME.

1. Introduction

Juvenile myoclonic epilepsy (JME) is the most common epilepsy type that affects adolescents. It is characterized by myoclonic jerks, predominantly after awakening, and may be aggravated by sleep deprivation and stress [1,2]. The majority of patients experience occasional generalized tonic–clonic seizures (GTCS), and about one-third have absence seizures. They, therefore, often use antiepileptic drugs (AEDs) their whole life [3–5]. Life-long treatment from young age may result in a considerable burden of AEDs, including various adverse effects that may affect adherence and quality of life.

Treatment with AEDs is challenging because of extensive pharmacokinetic variability and the risk of clinically relevant interactions [6–8]. According to clinical studies and evidence-based guidelines from the UK, initially valproate, then lamotrigine, levetiracetam, or topiramate are the main AEDs of choice in JME, even if the evidence is limited [9,10]. The choice of proper treatment in women is challenging because of restrictions in the use of valproate due to dose-dependent teratogenic effects and long-term effects on cognitive development in the offspring [11–13]. Another challenge is that patients with JME might have difficulties with treatment adherence as a possible consequence of executive dysfunction and impulsive decision-making [14–18]. The use of

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https://doi.org/10.1016/j.yebeh.2019.05.021

therapeutic drug monitoring (TDM) is considered the best way to measure adherence and is useful to individualize AED treatment and could therefore be used as a tool for improved treatment follow-up [7,19,20].

The aim of the present study was to investigate the use and challenges with AEDs and the patients' view of these challenges in a large group of patients with a confirmed JME diagnosis.

2. Methods

2.1. Included patients

Recruitment of patients was based on a search of medical records containing an International Classification of Diseases, 10th Revision (ICD-10) code of epilepsy (G40) at Drammen Hospital during 1999–2013. Drammen Hospital serves all patients with epilepsy in Buskerud County, covering 9% of the Norwegian population. The only electroencephalography (EEG) laboratory in the county is located at Drammen Hospital, and EEG is a part of standard work-up when diagnosing epilepsy in Norway. We included patients who would most likely be diagnosed with JME within the period of the medical record search, i.e., those younger than 40 years and older than 14 years. All patients diagnosed with genetic generalized epilepsy (GGE) were invited to participate, where 69% accepted, and those with a confirmed diagnosis of JME were included in the present study [2,17,18].

The study was approved by the Regional Committee for Medical Research Ethics, South East Norway (ethical agreement no. 2013/1027) and by the data protection officer at Drammen Hospital. Written informed consent was obtained from all study participants.

2.2. Questionnaires and interviews

A mixed method approach was used by combining a quantitative questionnaire with a qualitative additional clinical interview in a subset of the patients. A semistructured questionnaire designed for the purpose of this study was used with questions about current and previous use of AEDs, intentional and nonintentional poor adherence, and the patients' view of using TDM as part of their follow-up. The questions in the survey are included in the supplementary file. Each participant's hospital record was thoroughly reviewed in order to confirm information concerning medical history, including previous AED use. Information about current quality of life, treatment adherence, current AED use, seizure outcome, and impact of TDM was obtained directly from the patient. Adherence was measured using a 4-point Likert scale, which is widely utilized. Adherence was considered poor if the patient sometimes/often deviated from the dosing schedule, nonintentionally or intentionally, as in a recent nationwide study [21]. As a measure of quality of life, a 10.0-cm visual analogue scale (VAS) was used, and the results were measured manually. A VAS score of ≥5.5 was characterized as good quality of life whereas scores below 5.0 were regarded as reduced quality of life. The clinical interviews were conducted between November 2016 and August 2018 at Drammen Hospital or in the patient's home, and they were based on the content of the questionnaire. In a random selection of patients (n = 10), relevant topics were further explored in a qualitative approach through a conversation between the patient, the neurologist, and the participating pharmacologist. Comments and citations were noted manually.

2.3. Data collection and analysis

Data in use of various AEDs, quality of life measure, and intentional and nonintentional adherence were further analyzed in a spreadsheet. The qualitative part was analyzed according to the principles of systematic text condensation, a four-step process that we have also applied in a similar study [22]. From the transcripts, recurring themes were identified (adherence, adverse effects, poor adherence, and other challenges related to JME), and transcripts were further condensed with quotes and rechecked with the original notes [23].

2.4. Statistical methods

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software, version 23. Independent Student's t-tests were used for comparison of continuous variables where the groups had a normal distribution. Chi-Square tests were used for comparison of categorical variables, Yate's Continuity Correction for 2×2 tables. If the expected cell count was less than five in any cell, Fisher's Exact Probability test was used. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated for the three most commonly used drugs and the occurrence or not of GTCS during the last year. Direct logistic regression was performed to assess the impact of the three most commonly used drugs on the likelihood of experiencing GTCS within the last year. Independent variables in the model were current use of levetiracetam, current use of valproate, current use of lamotrigine, gender, and age. Independent variables were checked for collinearity, and all had tolerance values exceeding 0.5. The dependent variable was being without GTCS for more than one year (yes or no). p-Values <0.05 were considered statistically significant. Sample size was based on the maximum number of participants we were able to identify and recruit, as opposed to a priori power calculations. This approach was chosen in order to obtain a highly representative sample, aiming at including all patients with JME in our region and given age group [2,17,18].

3. Results

3.1. Patient characteristics

Ninety patients were classified as having JME and included. Nine of them (10%) had JME evolving from childhood absence epilepsy (CAE). Mean age was 26 years, 60% were women. Only one-third were seizure-free, as 68% had experienced myoclonic jerks and 21% GTCS within the last year (Table 1).

3.2. Use of AEDs and other drugs

Eighty-four percent of the patients used 1–3 AEDs as their current therapy (Table 2). Most of the patients who were seizure-free used one AED (n = 24/40%). Only two seizure-free patients used 2–3 AEDs concomitantly. The total use of each of the three most common AEDs in women and men (mono- or polytherapy) is depicted in Fig. 1a. Valproate was most commonly used (n = 33), and two-thirds of the users were men. There were more female users of lamotrigine and levetiracetam and all other drugs listed, 10 different AEDs in total. Sixteen

Table 1
Patient characteristics.

Patients and seizures	Patients (n = 90)
Gender, n (%)	
Women	54 (60)
Men	36 (40)
Age, years	
Mean (SD)	26 (±7)
Median (range)	26 (14–39)
Epilepsy debut, age, years	
Mean (SD)	15 (±3)
Median (range)	14 (6–23)
Seizure types last year, n (%)	
Seizure-free	29 (32)
Myoclonia	61 (68)
Generalized tonic–clonic seizures	19 (21)

Mean (standard deviation SD)

Table 2
Use of antiepileptic drugs (AEDs) in women and men (n = 90).

AEDs	Women (n)	Men (n)	Total (n)[a]	Seizure-free, n (%)
Monotherapy				
Valproate	7	15	22	7
Lamotrigine	8	4	12	5
Levetiracetam	12	5	17	11
Other monotherapies	5	1	6	1
In total	32	25	57	24 (30)
Polytherapy				
Valproate + lamotrigine	3	4	7	1
Valproate + levetiracetam	0	2	2	0
Levetiracetam + lamotrigine	2	0	2	0
Other polytherapies	6	2	8	1
In total, 2/3 AEDs			17/2	2 (2)
No AEDs in use	11	3	14 (16)	3 (21)

[a] In total, 84% of the patients used 1–3 AEDs. There were no statistically significant differences between categorical variables as valproate, lamotrigine, or levetiracetam as part of the treatment, or mono-or polytherapy in relation to seizure freedom or not, tested by chi-square test, Yate's continuity correction or Fischer's exact probability (for cell counts <5).

patients used polytherapy (17%), where lamotrigine and valproate were the most commonly occurring AEDs used in combination. Based on data from the medical records, sixteen patients (17%) had used AEDs that are not considered appropriate for treatment of GGE; e.g., one patient tried both carbamazepine and oxcarbazepine. Additional drugs were also used by the included patients; 14 women used oral contraceptives, eight with estrogen content, and three of them used lamotrigine. Four used antipsychotics or antidepressants, and one used medication for attention-deficit hyperactivity disorder (ADHD). Other drug classes included treatment for asthma, allergies, pain, heart and circulation disorders.

3.3. Use of antiepileptic drugs in relation to seizure situation

Of those who had not suffered GTCS in the last year, 28 were using valproate, 17 lamotrigine, and 18 levetiracetam (some in combinations), as shown according to gender in Fig. 1b. In patients using valproate, 85% (9 women/19 men) had not experienced GTCS in the last year. In total, 70% of those who were seizure-free from GTCS used valproate. Of those who did not experience GTCS in the last year, 59% were women and 86% men. Direct logistic regression demonstrated that valproate and levetiracetam were superior to lamotrigine on the likelihood of experiencing GTCS within the last year (Table 3). Fig. 1c illustrates the three most commonly used drugs according to seizure situation. No statistically significant relationships were, however, found between mono- or polytherapy, or the use of valproate, lamotrigine, or levetiracetam, or valproate in mono- or polytherapy in relation to seizure freedom or not. Of the 14 patients who reported not to use AEDs, three were seizure-free, nine had myoclonic jerks, and two had experienced GTCS in the last year.

3.4. Patients' view of adverse effects, adherence, use of TDM, and quality of life

In the questionnaire, the patients were asked about common adverse effects from the three most widely used AEDs. Fifty-six of the patients had a history of valproate use, where 12 (21%) reported troublesome weight gain. Of the 42 patients who had used levetiracetam, 18 (43%) reported irritability, aggression, or severe mood change while of the 61 patients who had been treated with lamotrigine, 7 (12%) had developed a rash. Twenty-nine (48%) had no effect of lamotrigine, or experienced aggravation of myoclonic jerks. All patients were asked about intentional and nonintentional poor adherence to AED therapy. According to Fig. 2, most participants reported good adherence, but one-third said that they sometimes or often forgot to take their medication at time while 14% reported to take their AEDs differently than agreed upon with their treating physician, i.e., intentional poor adherence sometimes/often. Poor adherence was not significantly associated with gender or differences in seizure status. The majority (66%) appreciated the use of TDM as part of their follow-up. Half of the patients noted that serum concentration measurements were performed at least once a year. Most patients reported good quality of life with a mean score of 7.1 out of 10 (n = 85). There was a trend to lower scores in women (6.8) than men (7.6), but it was not significant. There were 65 patients with a VAS score ≥5.5, characterized as good quality of life, while 20 patients (24%) (14 women/6 men) scored below 5.0, regarded as reduced quality of life. Scoring of quality of life was not significantly associated with gender or seizure situation.

3.5. Challenges in the treatment of JME

The qualitative part included patients' comments regarding their experience and challenges related to living with JME and treatment with AEDs. The clinical interviews lasted for 30–60 min and included six women and four men age 14–35 years. The main categories of issues discussed included adherence, adverse effects, and other challenges related to JME. The patients expressed uncertainty regarding proper use of AEDs and which effects and/or adverse effects that could be attributed to the drugs. All patients had used valproate, lamotrigine, and/or levetiracetam and reported that they presently or previously experienced adverse effects because of these drugs. This seemed to substantially affect quality of life and adherence. Several of the patients admitted that they had withdrawn AEDs without consulting a physician, often due to adverse effects, even when knowing that it could result in more seizures. Various quotes from five of the patients, reflecting their view regarding these challenges, are summarized in Table 4; concerns about adverse effects, seizure situation, changes in medication, reasons for poor adherence in this regard, and that these challenges affected their daily life.

4. Discussion

In the present study of patients with JME, the use of AEDs in patients with JME is characterized. The most commonly used AEDs included valproate, lamotrigine, and levetiracetam. Only one-third of the patients were seizure-free while one-fifth experienced GTCS during the last year. There were clear gender and drug differences regarding the absence of GTCS. The patients' perception of challenges related to their treatment was explored, including adherence and adverse effects affecting their subjective quality of life.

4.1. Use of AEDs in JME and seizure situation

Valproate was the most commonly used AED (two-thirds of users were male) followed by lamotrigine and levetiracetam with most female users. This might be a consequence of the recent restrictions of the use of valproate in women of childbearing age [13]. According to the regression model, lamotrigine had significantly less effect on GTCS than valproate and levetiracetam while gender differences were not significant because of small subgroups. Still, other unidentified factors may also contribute to GTCS status. The evidence is limited for appropriate drug choice in JME with only valproate and topiramate with class D evidence in recent guidelines [9]. A small randomized, open-label study comparing valproate and topiramate in 28 patients over 26 weeks found similar efficacy of seizure freedom in 57–67% of patients [24]. Polypharmacy with 2–3 AEDs carries a risk of interactions and increased burden of adverse effects [22,25]. In addition, several women included in our study used estrogen-containing oral contraceptives that decrease serum concentrations of lamotrigine and, to some extent,

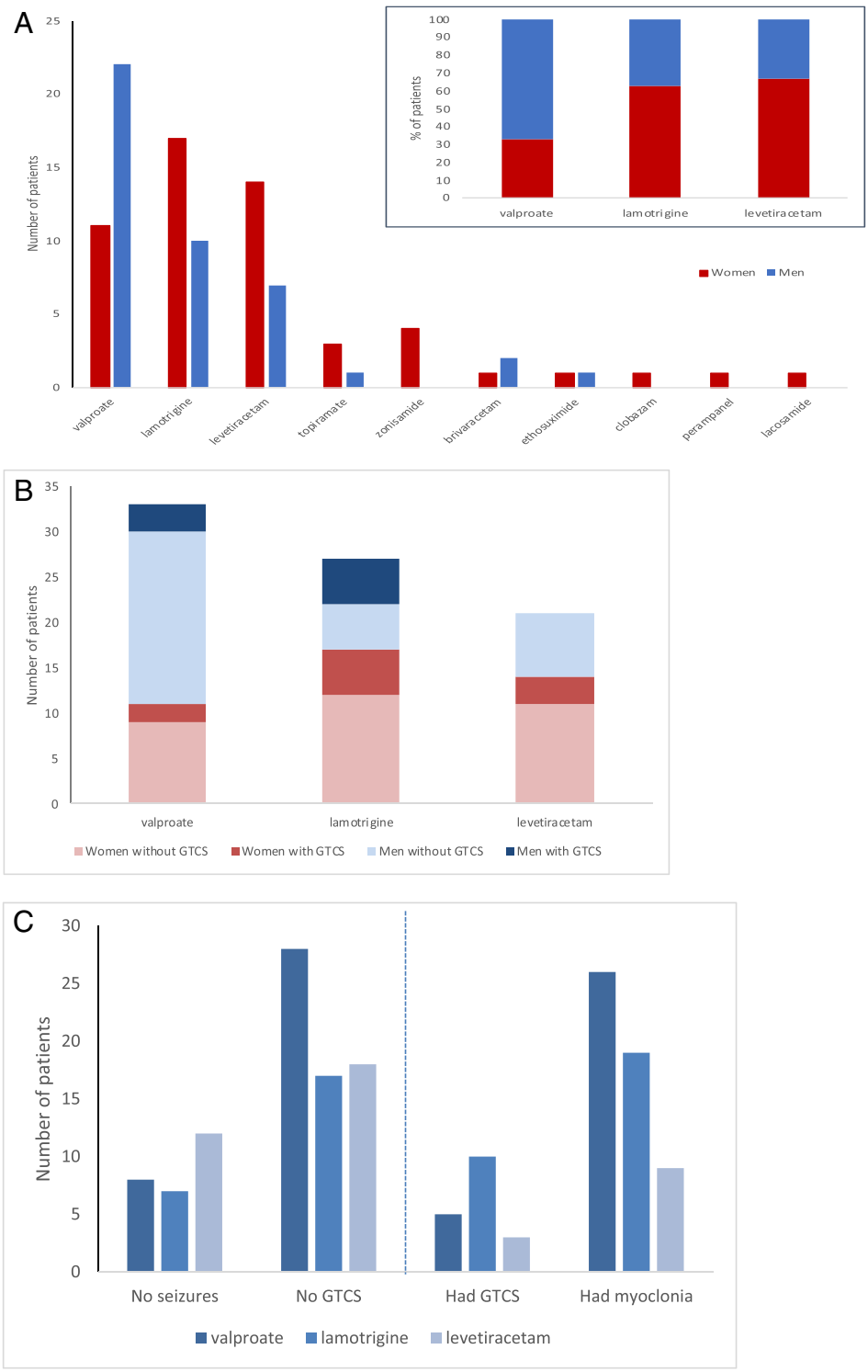

Fig. 1. a) Total use of antiepileptic drug (AEDs) in patients with juvenile myoclonic epilepsy (JME), women (red) and men (blue) (n = 90), and percentage of patients using the three most common AEDs according to gender distribution shown in the upper right figure. b) Distribution of women and men who used the three most common AEDs, valproate, lamotrigine, and levetiracetam and relation to occurrence of generalized tonic–clonic seizures (GTCS) or not during the last year. c) Distribution of the use of the three most common AEDs, valproate, lamotrigine, and levetiracetam involved in the treatment (in mono- or polytherapy) according to number of patients who were seizure-free, all or GTCS, or who experienced seizures, GTCS, or myoclonic jerks last year. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

other AEDs. Furthermore, various psychotropic drugs may result in pharmacokinetic interactions in combinations with AEDs [26]. Knowledge of all drugs in use is, thus, of importance for evaluation of the efficacy of AEDs.

Only 1/3 of the patients in the present study were seizure-free. As a consequence of our population-based recruitment approach [2,17,18], we do not expect the included sample of patients to be biased towards difficult-to-treat epilepsy. The results are comparable with a recent study from Portugal, where half of the patients have seizures regarded as being refractory to treatment. Patients with treatment-refractory and nonrefractory seizures, 25% and 71% respectively, were seizure-free in the last year, and 57% and 13%, respectively did not experience

Table 3
The impact of antiepileptic drug use on occurrence of GTCS.

	β	SE	Wald	df	p	OR	95% CI for OR
Age	0.082	0.045	3.364	1	0.067	1.085	0.994–1.185
Gender	−0.275	0.600	0.209	1	0.647	0.760	0.234–2.463
Current use of lamotrigine	**−1.679**	**0.592**	**8.033**	**1**	**0.005**	**0.187**	**0.058–0.596**
Current use of levetiracetam	0.359	0.768	0.219	1	0.640	1.432	0.318–6.450
Current use of valproate	0.353	0.649	0.296	1	0.586	1.424	0.399–5.086

Details of the regression model are given in the Methods.
Bold values indicates significance at 0.05.
SE: standard error

GTCS [27]. We noted, however, that the rate of people free from GTCS (79%) was much higher than the rate of people free from myoclonic jerks (32%). Thus, the present study demonstrates that in a regular clinical setting, a large proportion of people with JME continue to experience occasional myoclonic jerks. When asked about seizure outcome, however, it could be that patients (and physicians) focus on GTCS only and omit myoclonic jerks. As when diagnosing GGE/JME [2], it is important to ask specifically about myoclonic jerks when recording seizure outcome and prognosis.

4.2. Patients' view of adverse effects, adherence, use of TDM, and quality of life

In the present study, we inquired about adverse effects considered relevant to the AEDs most commonly used in the treatment of JME, i.e., weight gain (valproate), irritability and aggression (levetiracetam), and rash (lamotrigine) in the questionnaire. It is noteworthy that more than 40% of the patients using levetiracetam experienced substantial irritability, aggression, or mood change, considering it is one of few treatment alternatives for JME in females of childbearing age [28]. These adverse effects may be particularly challenging in combination with the frontal lobe dysfunction and impulsivity now described in JME [14–16,28]. Moreover, nearly half of the patients using lamotrigine, which is the other treatment option in JME for females of childbearing age, reported little or no effect, or even aggravation of myoclonic jerks. Troublesome adverse effects like weight gain might be a cause of withdrawal against medical advice, as reported by some of the patients during the interviews and recently shown in a larger sample [18]. Adverse effects are linked to nonadherence and may influence quality of life [22,29]. Despite up to half of the patients experiencing adverse effects with the most commonly used AEDs, and only one-third of the patients being seizure-free, the majority of patients regarded their quality of life as good. When it comes to adherence, two-thirds of the patients reported good adherence and only a minority admitted to intentionally taking their AEDs differently than prescribed, in line with recent findings

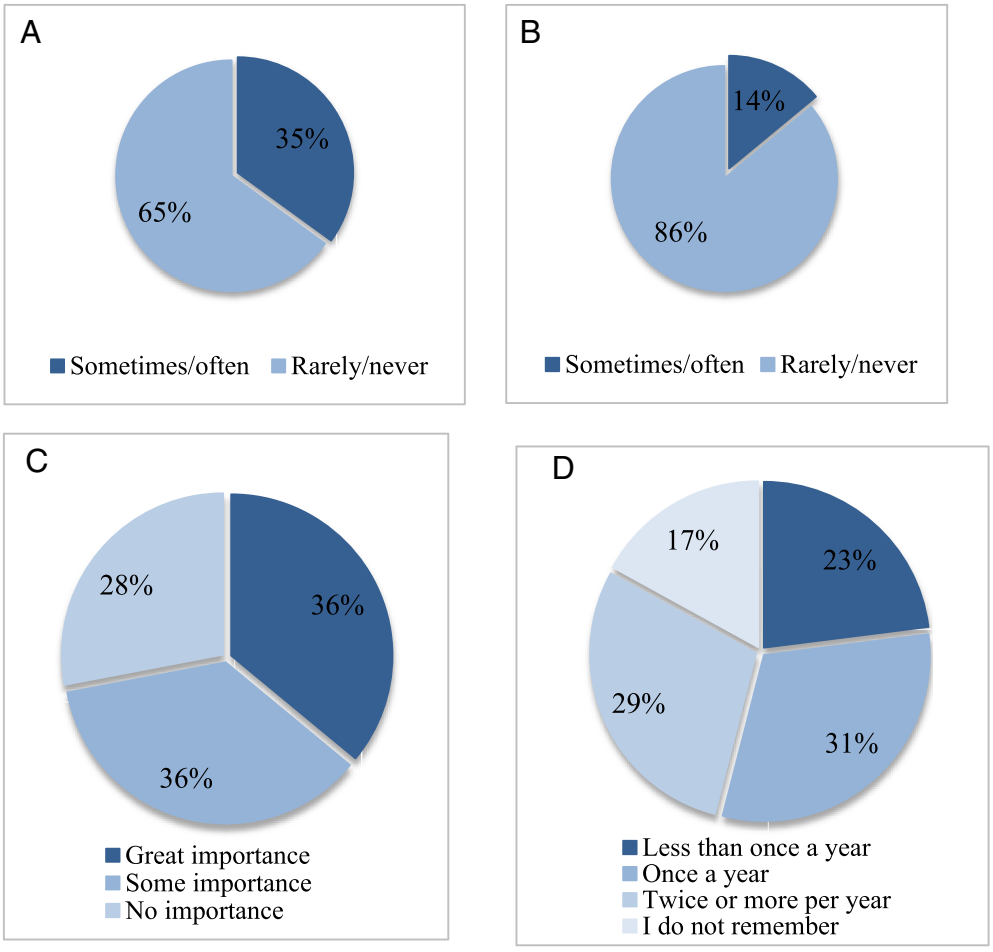

Fig. 2. Adherence in juvenile myoclonic epilepsy (JME) and the patients' view of the importance of using therapeutic drug monitoring (TDM) as part of their follow-up: "Does it happen that you forget to take your antiepileptic drugs (AEDs) at the correct time?" Nonintentional poor adherence (a) to the left and "Does it happen that you take your AEDs intentionally differently than prescribed?" Intentional poor adherence (b) to the right (n = 75). Light: Rarely, never, Dark: Often/sometimes What impact does the use of measurements of the amounts of drugs in the blood have to you? (c) and How often are blood samples taken? (d).

Table 4
Examples of citations from patients regarding treatment challenges.

Patient	Use of AEDs	Comments
Woman, 30s	No AEDs in use today	*"I used lamotrigine previously but had to withdraw it due to many adverse effects. I was indifferent to everything, my emotional life was flat, and even my friends noticed it. When I stopped everything, I was normal again."*
Woman, 30s	Valproate, topiramate	*"I gained a lot of weight with valproate alone, but with the addition of topiramate, which may lead to a decrease in body weight this is unstable and goes up and down."*
Woman, 20s	Lamotrigine, topiramate	*"I have been seizure free for some months with lamotrigine and topiramate. But I am troubled with nausea and cannot eat a meal with my family which affects my daily social life… I gained weight with valproate and lost weight with topiramate."*
Man, 20s	Valproate	*"I am struggling with anxiety and cannot look people in the eyes. I feel like I lost my spark I used to have and suspect it might be due to the medication. I have tried to skip the daily dose every other day, but I did not feel better."*
Man, 20s	Valproate	*"I was very annoyed when I used levetiracetam but feel better now as I use valproate, even if I feel blue periodically. I experience seizures from time to time, but usually this happens only when I have not taken my medication for some days."*

[29–31]. It should be noted that patients considering their adherence as good had subtherapeutic serum concentrations in another study, pointing to nonintentional poor adherence [30]. This finding supports the view of the patients that the use of TDM has impact as part of their follow-up. Communication about lifestyle, seizure-aggravating factors, adherence, polypharmacy, and closer follow-up is of great importance. The use of TDM could improve challenges with poor adherence, as recently elucidated [20].

4.3. Clinical implications

At present, optimal treatment in young women may be challenging because of recent restrictions due to dose-dependent teratogenic effects and long-term effects on cognitive development in the offspring caused by valproate [11–13,32]. The majority of those who used valproate were men, and the majority of valproate users did not experience GTCS during the last year. If levetiracetam is not tolerated, lamotrigine has little effect, and valproate should be avoided in women of childbearing age; limited possibilities are left in JME. A consequence might be that women are prescribed other new AEDs with limited experience and evidence in JME, as perampanel, lacosamide, and brivaracetam in this study. This could give an increased risk of uncontrolled GTCS in general or due to withdrawal or switch of valproate during the first trimester of pregnancy. The risk of sudden unexpected death in epilepsy (SUDEP) is increased in those with GTCS, and the risk of maternal death is increased 10-fold in those with GTCS during pregnancy [33,34]. This has to be considered against the risk of unplanned pregnancy or possible risks of malformations or cognitive outcomes.

4.4. Methodological considerations

The present cohort represents a large and well-defined group of patients with JME [2,17,18]. Still, the subgroups of patients are small when impact of gender and use of specific AEDs are evaluated and correlated to seizure freedom, adherence, and quality of life. Thus, the absence of statistical significance does not rule out differences between groups. A limitation of the present study is that validated and systematic tools for the assessment of adverse effects were not used. Still, the present results point to major issues regarding treatment of a group of young patients with epilepsy and appropriate use of AEDs, as reported by the patients themselves. This study was based on clinical interviews and descriptive data from the medical records, with limitations including bias of the patients' answers in the clinical situation. A combination of a quantitative and qualitative mixed method approach seems to be suitable to evaluate challenges in the AED treatment and particularly give insight into the patients' perspective.

4.5. Conclusions

The present study demonstrates that the vast majority of patients with JME use AEDs and that only one-third of the patients in this cohort were seizure-free. Valproate, lamotrigine, and levetiracetam were the most commonly used AEDs. Gender differences with more men using valproate and more women using lamotrigine and levetiracetam were demonstrated, and valproate and levetiracetam had significantly better efficacy against GTCS than lamotrigine. Variable adherence is a challenge in a number of patients, and the majority appreciates the use of TDM as part of the follow-up. Patients' concerns about challenges with their treatment include a burden of adverse effects and persisting seizures, affecting their daily life. Improved knowledge, understanding of treatment, and closer follow-up might improve the seizure outcome in patients with JME.

Declaration of Competing Interest

None.

Acknowledgment

We are grateful to Professor Torbjörn Tomson, Karolinska Institutet, Sweden and Drs. Oliver Henning and Margrete L. Burns at the National Center for Epilepsy for constructive discussions.

Authors' note

Marte Syvertsen, Cecilie Johannessen Landmark, and Jeanette Koht designed the study. Marte Syvertsen (neurologist) was responsible for the clinical interviews, while Ida Fløgstad (pharmacologist) attended in a selection of the cases and Jeanette Koht and Cecilie Johannessen Landmark in one case. Ida Fløgstad had a major role in the acquisition and analysis of the data together with Arton Baftiu. Cecilie Johannessen Landmark and Svein I. Johannessen developed the first draft of the manuscript. Marte Syvertsen and Ulla Enger contributed in the patient recruitment and data collection. All authors contributed to the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.05.021.

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