# Refractory juvenile myoclonic epilepsy: A meta-analysis of prevalence and risk factors

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**ABSTRACT**

*Background:* Juvenile myoclonic epilepsy (JME) is a common epilepsy syndrome for which treatment response is generally assumed to be good. We aimed to determine the prevalence and prognostic risk factors for refractoriness of JME.

*Methods*: We systematically searched PubMed and Embase and included 43 eligible studies, reporting seizure outcome after anti-epileptic drug treatment in JME cohorts. We defined refractory JME as persistence of any seizure despite AED treatment and performed a random-effects meta-analysis to assess the prevalence of refractory JME and of seizure-recurrence after AED withdrawal in individuals with well-controlled seizures. Studies reporting potential prognostic risk factors in relation to seizure outcome were included for subsequent meta-analysis of risk factors for refractoriness.

*Results:* Overall 35% (95%CI: 29 – 41%) of individuals (n=3311) were refractory. There was marked heterogeneity between studies. Seizures recurred in 78% (95%-CI: 52-94%) of individuals who attempted to withdraw treatment after a period of seizure-freedom (n=246). Seizure outcome by publication year suggests that prognosis has not improved over time. Meta-analysis suggested six variables as prognostic factors for refractoriness: having three seizure types, absence seizures, psychiatric comorbidities, earlier age at seizure onset, history of childhood absence epilepsy, and having praxis-induced seizures.

*Conclusion:* A third of people with JME were refractory, which is more prevalent than expected. Risk factors were identified and can be used to guide treatment and counselling of people with JME.

## INTRODUCTION

Juvenile myoclonic epilepsy (JME) is the most common form of genetic generalised epilepsy, affecting 5-10% of all people with epilepsy, with prevalence of 0.1-0.2/100,000 [1]. JME typically manifests during adolescence and is characterised by arrhythmic myoclonic seizures, particularly occurring on awakening, and electroencephalography (EEG) that shows generalised spike- and polyspike-waves [2]. Although not required for diagnosis, often people with JME also experience generalised tonic-clonic seizures (GTCS) and, less often, absence seizures [2]. According to its definition "response to appropriate drugs is good" [2]. This could lead to optimistic counselling by physicians. Seizures, however, continue despite adequate treatment with anti-epileptic drugs (AED) in a proportion of individuals and this impacts on quality of life [3,4]. Once an individual becomes seizure-free on AEDs, it is usually recommended to continue life-long therapy, given the high risk of relapse following drug withdrawal [5,6]. Some studies have suggested that a subset of individuals remains seizure-free after drug withdrawal [7,8]. Establishing how often individuals are refractory, and how frequently AED can be safely withdrawn is important to allow reliable prognostic counselling.

Several studies have explored risk factors for refractory JME but individual studies are limited by relatively small sample sizes and there are inconsistencies between studies. Prediction of refractoriness is of value for individualized management, for example by considering higher drug doses, polytherapy, experimental AEDs, or non-pharmacological treatment options earlier in those at risk [9–12].

We aimed to provide a systematic overview of refractory JME and its prognostic risk factors. By meta-analysing available studies, we estimated the proportion of refractory JME and – at the other end of the spectrum – the proportion of individuals remaining seizure-free after drug withdrawal. Lastly, we assessed which clinical variables may predict refractory JME.

## METHODS

### Search strategy and study selection

Procedures were consistent with PRISMA guidelines [13]. A literature search in PubMed and Embase identified articles describing treatment outcome in people with JME (see **Tables e-1 and e-2** for search terms). We have not adopted a registered pre-specified protocol.

We included all retrospective and prospective studies reporting seizure outcome after AED treatment in observational cohorts of individuals with a diagnosis of JME, regardless of the diagnostic criteria used by the study (see **Table e-3** for an overview**)**, which may vary [14]. We excluded articles which specifically recruited refractory individuals or those in remission. Drug-trial reports were not included as they could be biased towards individuals with a refractory condition. We contacted authors of articles describing multiple generalised epilepsy syndromes to provide stratified data of individuals with JME, if not available in the publication. We only included articles describing seizure-freedom of all seizure types and excluded those with ambiguous definitions (e.g. 'Good outcome') without specifying seizure-freedom. When the same cohort was included in multiple reports, we included the most recent, except in cases where an older article provided data on potential risk factors of refractory JME. Articles in English, Dutch and German were included.

Definitions of seizure-freedom and refractory JME varied articles, primarily regarding the length of the seizure-free follow-up period. Only two articles used the definition of drug-resistant epilepsy proposed by the ILAE in 2010 [15]. We defined refractory JME as persistence of any seizure (i.e. myoclonic, absence or GTCS) despite AED treatment, regardless of the length of the seizure-free follow-up period. We assessed one year seizure-

freedom when multiple time points were described within the same study. Where possible, individual cases of 'pseudo-refractory' individuals (i.e. those who had seizures due to non-compliance, inadequate treatment or other factors not related to therapy) were excluded. Studies reporting potential prognostic risk factors stratified by seizure outcome were included for subsequent meta-analysis of risk factors for refractoriness.

All search results were reviewed based on title and abstract, full-text was reviewed in potentially eligible articles. Reference lists were checked for additional eligible articles..

**Data extraction**

Study selection and data extraction was performed by RS. A standardised data extraction form was created containing: number of individuals seizure-free and those refractory, seizure outcome after drug withdrawal, mean follow-up duration, country, prospective or retrospective design, type of AED used, and definition of seizure-freedom.

Data of prognostic risk factors from articles reporting clinical variables stratified by seizure outcome were also extracted. To reduce publication bias, raw data of potential risk factors was extracted from all articles, regardless of whether the variable was tested for association with seizure-outcome. We analysed only potential risk factors reported in at least two articles, regardless of whether it was significantly associated with outcome.

**Statistical analyses**

A random-effects meta-analysis was performed using the R-package *Metafor (v2.0-0)* to assess the prevalence of refractoriness. The $I^2$–statistic was assessed as a measure to quantify heterogeneity, where values between 50-75% are considered to represent moderate and >75% high heterogeneity [16]. We used a random-effects model to account for heterogeneity between studies [17]. Secondary analyses stratified by definition of refractory JME and by

study design (prospective or retrospective) were performed to assess whether this increased homogeneity. Differences between 1, 2 and 5 year seizure-freedom were assessed with a mixed effects meta-regression, using *Metafor*. A random-effects meta-analysis was performed using *Metafor* to assess the prevalence of individuals who remained seizure-free after AED withdrawal.

Random-effects meta-analyses of potential risk factors were performed using Review Manager (v5.3) for all potential risk factors reported in at least 2 articles. We assessed the odds-ratio as outcome measure for dichotomous variables and the mean difference for continuous variables.

The Newcastle Ottawa Quality assessment scale for cohort studies was used to assess the methodological quality of all studies included in the meta-analysis of risk factors [18]. This scale is used to assess three major components: cohort selection, comparability and assessment of outcome, and ranges from 0-9, where studies are considered to have a high quality when scoring 5 or higher and a low quality when scoring below 5.

Funnel plots were generated as a measure to assess potential publication bias and were visually inspected for asymmetry [19]. Considering the small number of studies included per risk factor, we did not perform statistical tests for asymmetry of the funnel plot, as it is only recommended when including >10 studies per analysis [19].

## RESULTS

The literature search was last performed on 1 March 2018 and yielded 1362 articles (see **Figure 1** for flow-chart). After removing duplicates and applying inclusion and exclusion

criteria, 43 articles were included, describing treatment outcome for a total of 3311 subjects (**Table e-4**).

**Prevalence of refractory JME**

Meta-analysis showed that 35% (95%CI: 29 – 41%) of individuals with JME were refractory to treatment (**Figure 2**). The proportion of refractory subjects varied between 7 and 75% and heterogeneity between studies was high ($I^2$=91%). As the definition of seizure-freedom varied between studies, we also performed analyses stratified by definition, which made little difference on the estimate of refractory JME or the amount of heterogeneity (**Figure 3**). A meta-regression analysis showed no significant difference between 1, 2 or 5 year seizure-freedom (p=0.41). The proportion of refractory individuals was comparable between prospective (36%, 95% CI: 18 – 56%) and retrospective studies (35%; 95%CI: 29 – 42%). We next assessed whether the proportion of seizure-free individuals has changed over time (**Figure 4**). A meta-regression analysis showed no significant association between publication year and percentage of refractoriness (mixed-effects meta-regression: p=0.61).

**Seizure-recurrence after AED withdrawal**

Eleven articles described a subset of 246 subjects who attempted AED withdrawal. Some studies had specific criteria for subjects to withdraw (e.g. at least 3 years seizure-freedom), however, most did not. Meta-analysis showed that seizures recurred in 78% (95% CI: 58 – 94%) after withdrawal. (**Figure 5**), although estimates varied widely and heterogeneity was high ($I^2$=84%).

**Risk factors for refractory JME**

Twenty-one studies reported seizure outcome in relation to potential risk factors for refractory JME. Univariate meta-analyses were performed for 10 risk factors (**Table 1;** see **Figures e1-10** for forest plots). Having three seizure types, absence seizures, psychiatric comorbidities, a history of childhood absence epilepsy (CAE) progressing to JME, praxis induced seizures (seizures and epileptiform EEG discharges precipitated by complex, cognition-guided tasks, such as playing chess, writing or drawing) and early age at epilepsy onset, each were significant risk factors for refractory JME. Heterogeneity between studies was mild to moderate. Scores on the Newcastle-Ottawa quality assessment scale (**Table e-5**) ranged between 2 and 7 (mean 4.1), 13 studies were assessed as low (score ≤4) and 8 as high quality (score ≥5). Funnel plots, inspected as a measure of publication bias, did not show asymmetry (**Figures e1-10**).

## DISCUSSION

One third of people with JME described were refractory (**Figure 2**). The estimates of refractoriness were comparable when assessing 1, 2 and 5 year seizure-freedom ( **Figure 3**), suggesting that people who are seizure-free for at least 1 year are likely to remain so. This is consistent with studies that reported 1 and 2, or 1 and 5 year seizure-freedom in the same subjects, which showed minor differences between outcomes at different follow-up intervals [20,21].

We found no evidence for a decrease in the proportion of refractory JME over the last decades. Valproate, marketed as an AED since 1967, is still considered the most effective drug for people with JME [9,22,23]. Thus, there is still much room for improvement.

In contrast to the ILAE definition (1989) of JME, describing the treatment response to "appropriate drugs" as "good", our results suggest that the proportion of refractoriness is not much different than the overall proportion of refractoriness in people with epilepsy, which is estimated between 16 and 37% [24–26]. Physicians should be careful when counselling

people with JME that their prognosis is particularly good. It is possible, however, that we overestimated refractoriness in JME. Individuals in the included studies were mainly treated at tertiary centres, who are likely to have more severe or difficult to treat epilepsy than those at secondary care. Conversely, it has been shown that seizure control improves after referral to tertiary care [27]. It is also possible that some were misdiagnosed, as other conditions may mimic JME [28]. There is also the possibility of selection bias and selective-loss to follow-up of people with a more benign course, who might be less inclined to return to the clinic or agree to inclusion in a study. Our estimate, however, could be an underestimation of refractoriness of myoclonic seizures, which are difficult to objectify and can be underreported. Another limitation is that study selection and data extraction was done by a single author. Statistical heterogeneity between studies was substantial, but definition of seizure-freedom, publication year or retrospective vs prospective study design did not seem to play a major role for heterogeneity. Other potential causes of heterogeneity could not be assessed, such as ethnic origins, different treatment regimens and different diagnostic criteria. Determining seizure-freedom is subjective and a recent study established that inter-observer variability (using the same criteria and same individual records) was relatively high, with kappa values ranging between 0.56 and 0.77 [29]. It is likely that intra-observer variability would be even higher when not the same individual records are used. Thus, intra-observer variability is likely to have played a role in heterogeneity between studies.

About a fifth are reported to remain seizure-free after treatment withdrawal (**Figure 5**), which is substantially less than the overall estimate of two thirds for all types of epilepsy [30,31]. Estimates between studies, however, varied widely. A potential cause of heterogeneity is age at withdrawal and therewith duration of seizure-freedom, as these variables are predictors of seizure recurrence in the general epilepsy population [30] and JME has shown to subside with age [32]. Age at AED withdrawal was rarely reported, but the three studies reporting a good

prognosis included mostly people over 40 years of age [7,21,33], while the two studies reporting that all subjects had seizure recurrence included mainly people in their twenties [22,34]. It is possible that the actual proportion of seizure-freedom after AED withdrawal is higher for older subjects. Insufficient information about individuals who attempted AED withdrawal was available to allow identification of potential prognostic factors. Future studies are needed to evaluate who is most likely to remain seizure-free after treatment withdrawal. Our meta-analyses revealed 6 significant risk factors for refractoriness, but could not provide evidence for the other 4 clinical variables to be significantly associated (**Table 1**). It is likely that these variables are inter-related. For example, a history of CAE relates to having absence seizures, and to an earlier age at epilepsy onset [6], and most people with JME who have absence seizures had three seizure types [35].

Due to the cross-sectional nature of the studies, cause and effect cannot be established. We cannot rule out that psychiatric comorbidities are due to AED side-effects or to having prolonged refractory seizures, rather than being the cause of it. It is also possible that people with psychiatric comorbidities are less adherent to treatment rather than being non-responsive to AEDs.

It remains uncertain whether the risk factors for refractory JME represent a lack of response to treatment or a higher disease burden. People with early disease onset, multiple seizure types and psychiatric comorbidities may have more severe brain disease, which makes it more difficult to control all seizure types. Conversely, someone with only occasional seizures can be well controlled even when the medication is only mildly effective. It has also been suggested that people with CAE progressing into JME represent a distinct clinical entity, with a different inheritance pattern and seizure outcome [6]. They rarely become completely free of all seizures. Most described individuals, however, do become free of myoclonic seizures and GTCS, with only absences persisting [6]. This suggests the possibility that different

seizure types respond differently to treatment. A genetic study comparing drug-responsive in JME with those that are refractory could unravel a distinct genetic basis of treatment response, a higher genetic overlap with CAE, or a higher polygenic burden of JME associated risk alleles.

. Further studies using individual data are required to assess which variables are independent predictors of refractory JME, to allow for an individualized prediction of seizure outcome to be used to guide treatment.

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## FIGURE LEGENDS

Figure 1: Flowchart of search strategy and study selection.

Figure 2: Meta-analysis of the prevalence of refractory JME. The proportion of subjects that were refractory is displayed on the x-axis. A total of 43 studies describing seizure outcome in 3311 individuals with JME were included. RE: random-effects model.

Figure 3: Meta-analyses of the prevalence of refractory JME stratified by definition of seizure-freedom. N: number of studies; $I^2$: heterogeneity.

Figure 4: Meta-regression of refractory JME by publication year. The proportion of refractory subjects per study is plotted by publication year. Each study is represented by a circle whose size is proportional to the sample size. A meta-regression trend line with 95% confidence interval (dotted lines) is plotted as a solid line.

Figure 5: Meta-analysis of seizure-recurrence after AED withdrawal. The proportion of well-controlled subjects who experienced recurrence of seizures after AED withdrawal are displayed on the x-axis. A total of 11 studies describing 246 subjects were included. RE: random-effects model.

Table 1: Risk factors for refractory JME, assessed with random-effects meta-analysis. Significant associations, defined as a meta-analysis P-value <0.05, are highlighted in bold. GTCS: generalised tonic-clonic seizures.