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CLINICAL TRIAL ARTICLE

Rapid versus slow withdrawal of antiepileptic monotherapy in two-year seizure-free adults patients with epilepsy (RASLOW) study: A pragmatic multicentre, prospective, randomized, controlled study

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Abstract

Purpose To establish whether a slow or a rapid withdrawal of antiepileptic monotherapy influences relapse rate in seizure-free adults with epilepsy and calculates compliance and differences in the severity of relapses, based on the occurrence of status epilepticus, seizure-related injuries, and death.

Methods This is a multicentre, prospective, randomized, open label, non-inferiority trial in people aged 16 + years who were seizure-free for more than 2 years. Patients were randomized to slow withdrawal (160 days) or rapid withdrawal (60 days) and were followed for 12 months. The primary outcome was the probability of a first seizure relapse within the 12-months follow-up. The secondary outcomes included the cumulative probability of relapse at 3, 6, 9, and 12 months. A non-inferiority analysis was performed with non-inferiority margin of − 0.15 for the difference between the probabilities of seizure recurrence in slow versus rapid withdrawal.

Results The sample comprised 48 patients, 25 randomized to slow withdrawal and 23 to rapid withdrawal. Median follow-up was 11.9 months. In the intention-to-treat population, 3 patients in the slow-withdrawal group and 1 in the rapid withdrawal group experienced seizure relapses. The corresponding probabilities of seizure recurrence were 0.12 for slow withdrawal and 0.04 for rapid withdrawal, giving a difference of 0.08 (95% CI − 0.12; 0.27), which is entirely above the non-inferiority margin. No patients developed status epilepticus and seizure-related injuries or died. Risks were similar in the Per-Protocol population.

Conclusions Seizure-relapse rate after drug discontinuation is lower than in other reports, without complications and unrelated to the duration of tapering.

Keywords Seizure freedom · Drug withdrawal · Tapering · Seizure relapse · Antiseizure medication

Introduction

Population studies of people with newly diagnosed epilepsy followed for several decades showed that up to 80% enter prolonged periods of seizure remission and up to 50% continue to be seizure-free after treatment discontinuation [1, 2]. Antiseizure medication (ASM) withdrawal can be an option for patients who have been seizure-free for some years. A careful evaluation of risks and benefits should be undertaken before the decision to stop or continue treatment. Benefits of discontinuation include disappearance of drug-related side effects, particularly on neuropsychological performance and reduction of costs [3–5]. On the contrary, a relapse of seizures may have short-term consequences (seizure-related injuries and even death [6, 7]) as well as more widespread and long-term effects on social life.

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The guidelines on treatment discontinuation by the Italian League Against Epilepsy [8] identify some conditions that may increase the relapse rate, like adult age, presence or worsening of EEG abnormalities, specific etiologies and epileptic syndromes, female sex, and partial-onset seizures. With regard to tapering rate, few data are available to determine whether a ''rapid'' withdrawal is associated with a higher risk of relapse compared with a ''slow'' withdrawal. A survey among UK and Eire clinicians [9] revealed a substantial lack of consensus in tapering rates. Some prospective studies have been conducted only in children, with variable timelines [10–12]. A single study [12] documented an independent association between rapid discontinuation of ASM treatment and a higher risk of relapse. A Cochrane review of randomized controlled studies on rapid versus slow withdrawal of ASM [13] defined rapid tapering when the ASM was discontinued within 3 months and slow tapering when discontinuation took more than 3 months. This review identified a single study comparing a rapid withdrawal schedule (6 weeks) to slow withdrawal (9 months) in children who had been seizure free during 2–4 years [14]. That study failed to identify significant differences in terms of relapse between the groups. Thus, the Italian Guidelines [8] recommend a ''slow'' treatment discontinuation, without specifying a time schedule. Moreover, little is known about patients' preferences and adherence to different withdrawal schedules and on the severity of relapses after ASM discontinuation. On this background, the main objective of the present study was to establish whether a slow (within 160 days) or a rapid (within 60 days) withdrawal schedule of antiepileptic monotherapy influence relapse rate in adult patients with epilepsy, who have been seizure free for at least 2 years. Secondary objectives were to establish the compliance rates with these two schedules and the differences in terms of severity of relapses, based on the occurrence of status epilepticus, seizure-related injuries, and death.

Material and methods

The RApid versus SLOW withdrawal (RASLOW) study of antiepileptic monotherapy in seizure-free adult patients with epilepsy is a multicenter, prospective, randomized open-label, non-inferiority trial performed between October 9, 2017, and January 31, 2021. The protocol of the study has been published elsewhere [15]. In brief, inclusion criteria were diagnosis of focal or generalized epilepsy (according to ILAE 1989 criteria [16]), age at epilepsy onset of 16 years or older, seizure freedom for at least 2 years, treatment with one of the ASMs available for monotherapy in Italy (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate zonisamide), and adherence to the protocol and visit schedules. Exclusion criteria were inability to understand the aims or modalities of the study, ongoing pregnancy, and plans to become pregnant during withdrawal period, history of seizure relapse after discontinuation of treatment, history of psychogenic non-epileptic seizures, and history of status epilepticus. The primary endpoint was the probability of a first seizure relapse within the 12-month follow-up. Secondary endpoints were the cumulative probability of relapse at 3, 6, 9, and 12 months, compliance with the assigned withdrawal schedule and the severity of relapses, in terms of seizure-related injuries, status epilepticus (SE) during or after withdrawal period, and mortality.

Included subjects were randomized to ASM discontinuation following one of the two following schedules:

1. Rapid withdrawal: reduction by about 20% of initial dosage every 15 days until complete discontinuation (total withdrawal time: 60 days).
2. Slow withdrawal: reduction by about 20% of initial dosage every 40 days, until complete discontinuation (total withdrawal time: 160 days).

A 1:1 central randomization was stratified for type of epilepsy (focal versus generalized). Randomization was carried out using scratch cards in which randomization arm was obscured and not visible from the outside.

Enrolled patients were followed for 12 months after randomization. During follow-up, patients underwent 11 visits with a predetermined schedule: every 15 days from 1st to 60th day, every 30 days from 61st to 180th day, and every 3 months until the end of the study. Patients experiencing a seizure relapse were instructed to call the local investigators within 24 h after an ictal event. Seizure relapse was confirmed by local investigators. If the study staff was confident about the epileptic nature of the event, the patient was instructed to restart ASMs and to come for the final study visit within 72 h.

All subjects randomized and starting withdrawal schedule were included in the intention-to-treat analysis and those satisfying the protocol requirements were included in the per-protocol analysis. Descriptive statistics were performed separately in the two arms. Differences between arms were assessed by chi-square or the Fisher exact test for categorical variables and the Wilcoxon-Mann–Whitney test for continuous variables.

For the primary endpoint (seizure relapse within 12 months), a non-inferiority analysis was performed using the following system of hypotheses:

$H0: p2\text{-}p1 \geq 0.15$ (null hypothesis – inferiority).
$H1: p2\text{-}p1 < 0.15$ (alternative hypothesis – non-inferiority)

where p1 was the probability of relapse in subjects randomized to slow withdrawal, p2 the probability of relapse in those randomized to rapid withdrawal, and 0.15 was the non-inferiority margin.

In equivalent terms, the above system of hypotheses could be expressed as:

H0: p1-p2 ≤ *-0.15* (null hypothesis – inferiority)
H1: p1-p2 > *-0.15* (alternative hypothesis – non-inferiority)

The null hypothesis of inferiority is accepted if the 95% confidence interval of the difference (*p1-p2*) includes values equal to or lower than − 0.15. The alternative hypothesis of non-inferiority is rejected (declaring non-inferiority) if the 95% confidence interval of the difference (*p1-p2*) includes only values higher than − 0.15.

The system of hypotheses described above was tested using the Farrington-Manning test [17].

The cumulative probabilities of seizure recurrence were calculated separately in the two treatment arms using the Kaplan–Meier method. Differences between the cumulative probabilities of recurrence in slow versus rapid withdrawal were calculated at 3, 6, 9, and 12 months and 95% confidence intervals for the proportion difference were calculated using the normal approximation. Confidence intervals were then compared to the non-inferiority margin. All analyses were performed using the SAS statistical package (version 9.4, SAS Institute, Cary, NC, USA).

Sample size calculation

The expected relapse rate in the two groups was estimated as 35%. The sample size was calculated at 159 patients/group with 80% power and an α error of 0.05, assuming a non-inferiority margin of 15%. Allowing for a 10% dropout rate, a total of 350 participants were required.

This clinical study was designed, implemented, and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. All screened patients signed an informed consent form. The protocol was registered with the EudraCT number 2015–00,482,730 and in Clinicaltrial.gov with identifier NCT05236166.

Results

Subjects were enrolled by 8 Italian epilepsy centers (Arezzo, Bari, Como, Novara, Perugia, Reggio Calabria [coordinating unit], Roma, Varese). The study started on October 2017. Patients' admission was stopped on February 2020, when 48 patients had been recruited.

Intention-to-treat population

The intention-to-treat population comprised 48 patients, 25 randomized to slow withdrawal and 23 to rapid withdrawal. The baseline characteristics of the sample are illustrated in Table 1. The sample included 10 women and 38 men aged 20–83 years. Twenty-nine patients (60.4%) had focal to bilateral tonic–clonic seizures. At disease onset, seizure frequency was less than 2/month in 35 cases (72.9%). Focal epilepsy of unknown etiology was diagnosed in 28 cases (58.3%). The median seizure-free period at study entry was 5.4 years (interquartile range, IQR 3.3–9.3). Levetiracetam was the commonest drug (16 patients) followed by oxcarbazepine (10 patients) and topiramate (9 patients). All baseline variables were equally distributed in the two treatment arms. Median follow-up was 11.9 months (IQR 8.9–12.0).

Primary outcome

Three patients in the slow-withdrawal group and one in the rapid withdrawal group experienced seizure relapses. The corresponding probabilities of seizure recurrence were 0.12 for slow withdrawal and 0.04 for rapid withdrawal, giving a difference of 0.08. The 95% confidence interval for the difference between slow and rapid arm was (− 0.12; 0.27), which is entirely above the non-inferiority margin (− 0.15) and the Farrington-Manning test is significant ($p = 0.0108$); therefore the non-inferiority for rapid withdrawal vs. slow withdrawal can be declared.

Using the Kaplan–Meier method, the cumulative probabilities of relapse at 1, 3, 6, 9, and 12 months in the rapid withdrawal group were 0.0%, 4.7%, 4.7%, and 4.7%, respectively. The corresponding values for the slow withdrawal group were 0.0%, 8.9%, 13.5%, and 13.5% (Fig. 1; Table 2). The difference between cumulative probabilities, with the corresponding 95% confidence intervals for the difference, is shown in Table 2. At each of the evaluated time points, the confidence interval for the difference was above the non-inferiority margin of − 0.15. This confirms that rapid withdrawal can be declared non-inferior to slow withdrawal.

Secondary outcomes

All randomized patients were fully compliant with the assigned treatment schedule. Moreover, no enrolled subjects developed SE, no injury was reported following a seizure relapse, and no death occurred.

Table 1 Baseline characteristics of the sample by treatment arm: Intention-to-Treat population

	Slow withdrawal		Rapid withdrawal		*p* value
	n	%	n	%	
Sex					0.8822
Women	5	20.0	5	21.7	
Men	20	80.0	18	78.3	
Seizure types					0.4398
Focal simple	6	24.0	6	26.1	
Focal secondarily generalized	14	56.0	15	65.2	
Generalized tonic–clonic	4	16.0	1	4.4	
Other generalized	1	4.0	0	0.0	
Unknown	0	0.0	1	4.4	
Seizure frequency at onset					0.1738
< 2/month	15	60.0	20	87.0	
3–5	6	24.0	2	8.7	
6–10	2	8.0	1	4.3	
> 10	2	8.0	0	0.0	
Epilepsy syndrome					0.2485
Focal cryptogenic	15	60.0	13	56.5	
Focal idiopathic	1	4.0	2	8.7	
Focal symptomatic	6	24.0	6	26.1	
Generalized idiopathic	3	12.0	0	0.0	
Undetermined	0	0.0	2	8.7	
Ongoing ASM					0.8422
Carbamazepine	3	12.0	2	8.7	
Levetiracetam	8	32.0	8	34.8	
Lamotrigine	1	4.0	0	0.0	
Oxcarbazepine	5	20.0	5	21.7	
Phenobarbital	1	4.0	0	0.0	
Topiramate	4	16.0	5	21.7	
Valproate	2	8.0	3	13.0	
Zonisamide	1	4.0	0	0.0	
Standard EEG					0.5887
Aspecific	4	18.2	2	9.5	
Epileptic	3	13.6	1	4.8	
Slow	4	18.2	5	23.8	
Normal	11	50.0	13	61.9	
Missing	3		2		
	Median	q1-q3	Median	q1-q3	
Age	43.1	26.6–58.9	48.4	26.5–61.6	0.6083
Age at diagnosis	38.1	17.1–51.0	35.1	19.9–57.2	0.6227
Disease duration at diagnosis	1.0	0.1–2.6	0.8	0.0–6.8	0.9340
Years of remission on treatment	5.4	3.6–7.8	5.3	3.2–9.8	0.9509

Per-protocol population

Excluded from the per-protocol analysis were four patients assigned to slow withdrawal (one protocol violation, one lost to follow-up and 2 withdrawals for other reasons) and four patients assigned to rapid withdrawal (three for withdrawal of consent and one lost to follow-up). Per-protocol population included 40 patients, 21 assigned to slow withdrawal and 19 to rapid withdrawal. No differences were detected between the two treatment groups with reference to the main demographic and clinical baseline characteristics (Table 3). Median follow-up was 11.9 months (IQR 9.0–12.0).

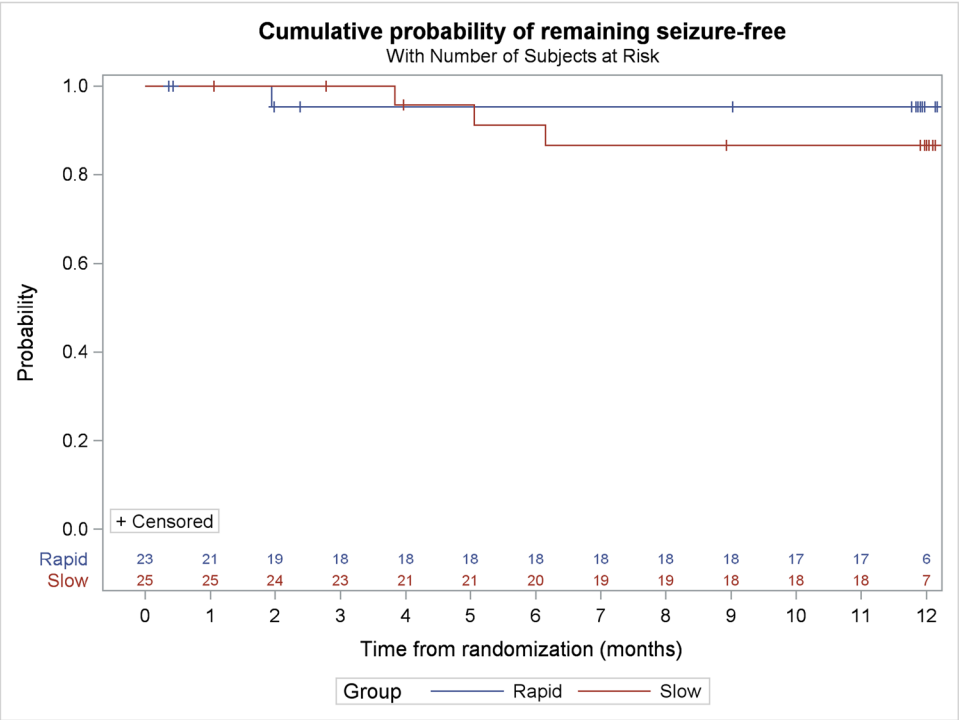

Fig. 1 Cumulative probability of remaining seizure-free in the two treatment arms: Intention-to-Treat population

Table 2 Proportion of relapses by treatment arm with difference in the intention-to-treat population

Month	p1	p2	Difference	95% Confidence limits	
1	0.00000	0.000000			
3	0.00000	0.047619			
6	0.08903	0.047619	0.041408	-0.10755	0.19036
9	0.13458	0.047619	0.086957	-0.08158	0.25549
12	0.13458	0.047619	0.086957	-0.08158	0.25549

Primary outcome

Three patients in the slow-withdrawal group and one in the rapid withdrawal group experienced seizure relapses. The corresponding probabilities of seizure recurrence were 0.14 for slow withdrawal and 0.05 for rapid withdrawal, giving a difference of 0.09. The 95% confidence interval for the difference between slow and rapid arm was (−0.13; 0.31), which is entirely above the non-inferiority margin (−0.15) and the Farrington-Manning test is significant ($p = 0.0165$); therefore the non-inferiority for rapid withdrawal vs. slow withdrawal can be declared.

Using the Kaplan–Meier method, the cumulative probabilities of relapse at 1, 3, 6, 9, and 12 months in the rapid withdrawal group were 0.0%, 5.3%, 5.3%, and 5.3%, respectively. The corresponding values for the slow withdrawal group were 0.0%, 9.5%, 14.3%, and 14.3% (Fig. 2; Table 4). The difference between cumulative probabilities, with the corresponding 95% confidence intervals for the difference, is shown in Table 4. At each of the evaluated time points, the confidence interval for the difference was above the non-inferiority margin of −0.15. This confirms that rapid withdrawal can be declared non-inferior to slow withdrawal.

Safety analysis

Excluding seizure relapses occurred during follow-up and a total of six adverse events were reported, two of them in patients assigned to slow withdrawal (1 patient experienced flu-like symptoms and one transient and mild "stiffness" of the right arm) and four in patients assigned to rapid withdrawal (generalized anxiety in two patients, dizziness in one; psychogenic non-epileptic event in one). All adverse events were reported as unrelated to the assigned treatment schedule. No serious adverse event was reported.

Discussion

During recruitment, only 48 patients could be enrolled. In the intention-to-treat population, 13.5% of patients in the slow-withdrawal group and 4.7% in the rapid withdrawal group experienced seizure relapses, giving a 7.7% difference. The corresponding proportions in the per-protocol population were 14.3% and 5.3%, giving a 9.0% difference. Both differences were below the 15% margin selected to

Table 3 Baseline characteristics of the sample by treatment arm: per-protocol population

	Slow withdrawal		Rapid withdrawal		*p* value
	n	%	n	%	
Sex					0.8742
Women	4	19.1	4	21.1	
Men	17	80.9	15	78.9	
Seizure types					0.6753
Focal simple	6	28.6	5	26.3	
Focal secondarily generalized	12	57.1	12	63.1	
Generalized tonic–clonic	2	9.5	1	5.3	
Other generalized	1	4.8	0	0.0	
Unknown	0	0.0	1	5.3	
Seizure frequency at onset					0.1086
< 2/month	12	57.1	17	89.5	
3–5	5	23.8	2	10.5	
6–10	2	9.5	0	0.0	
> 10	2	9.5	0	0.0	
Epilepsy syndrome					0.3225
Focal unknown etiology	12	57.1	9	47.4	
Focal idiopathic	1	4.8	2	10.5	
Focal symptomatic	6	28.6	6	31.6	
Generalized idiopathic	2	9.5	0	0.0	
Undetermined	2	0.0	2	10.5	
Ongoing treatment					0.8580
Carbamazepine	2	9.5	2	10.5	
Levetiracetam	8	38.1	6	31.6	
Lamotrigine	1	4.8	0	0.0	
Oxcarbazepine	5	23.8	5	26.3	
Phenobarbital	0	0.0	0	0.0	
Topiramate	2	9.5	3	15.8	
Valproate	2	9.5	3	15.8	
Zonisamide	1	4.8	0	0.0	
Standard EEG					0.9353
Aspecific	3	15.8	2	11.8	
Epileptic	2	10.5	1	5.9	
Slow	4	21.1	4	23.5	
Normal	10	52.6	10	58.8	
Missing	2		2		
	Median	q1-q3	Median	q1-q3	
Age	46.6	26.6–59.2	48.4	25.6–61.6	0.9143
Age at diagnosis	41.2	18.1–51.0	35.1	17.9–57.2	1.0000
Disease duration at diagnosis	0.99	0.1–3.5	0.5	0.0–11.5	0.6539
Years of remission on treatment	5.6	3.8–7.8	6.3	3.5–9.8	0.5728

declare non-inferiority. All patients were fully compliant with the assigned schedule and none developed severe relapses (SE) or injuries or died during follow-up.

Our relapse rates are lower than in published reports. In a critical review of 28 studies on ASM discontinuation, accounting for 4571 patients (2758 children, 1020 adults and a combined group of 793), most with at least 2 years of seizure remission, the proportion of patients with relapses ranged from 12 to 66% [4]. Using life-table analysis, the cumulative probability of remaining seizure-free in adults was 39–74% at 1 year. In a meta-analysis of 25 studies in all ages (only one in adults), the total proportion of patients who relapsed ranged from 0.12 to 0.67 [3]. The cumulative risk of relapse at 1 year was 0.25 (95% CI 0.21–0.30). Our mean seizure-free period before withdrawal was longer (5–6 years). For this reason, we

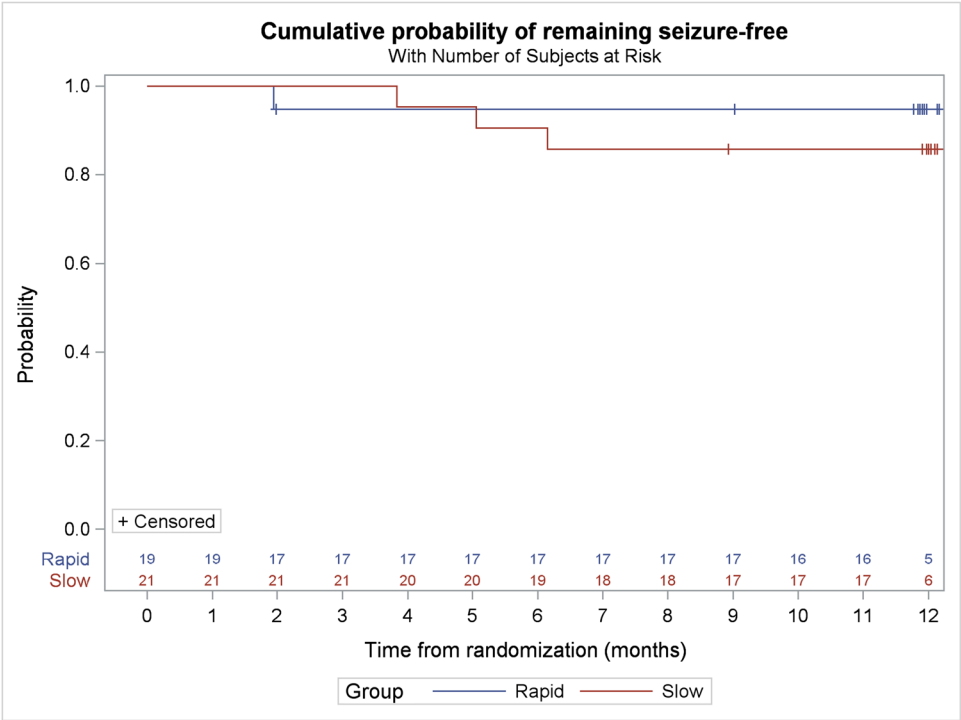

Fig. 2 Cumulative probability of remaining seizure-free in the two treatment arms: Per-Protocol population

Table 4 Proportion of relapses by treatment arm with difference in the Per-Protocol population

Month	p1	p2	Difference	95% Confidence limits	
1	0.00000	0.000000			
3	0.00000	0.052632			
6	0.09524	0.052632	0.042607	−0.11816	0.20337
9	0.14286	0.052632	0.090226	−0.09000	0.27045
12	0.14286	0.052632	0.090226	−0.09000	0.27045

cannot exclude that our eligible patients could be at lower risk of relapse after treatment discontinuation.

The meta-analysis of studies comparing slow to rapid tapering of ASM [13] included only one trial in 149 children [14] and found that patients relapsing in the rapid taper group (six weeks, 81 participants) and in the slow taper group (9 months, 68 participants) were 40 and 44, respectively, at the end of 1-year follow-up (OR 0.53, 95% CI 0.27–1.03). Our findings are in line with that study.

Our data might reflect the type of drugs used before withdrawal. As ASMs are symptomatic drugs and there were no patient in the per-protocol population who were taking barbiturates or benzodiazepines (the compounds most likely associated with drug withdrawal seizures), we can confirm that seizure relapse is not associated with the duration of the tapering period.

The study has strengths and limitations. The major strength is the robustness of randomization. Compared to observational studies, a randomized trial is the best design to compare two treatment strategies. However, several limitations must be also acknowledged. The major weakness is the small sample size, which leads to imprecise estimates. Of course, a wider sample could be helpful to confirm our findings. Enrolled patients, except for the predominance of men, are a fairly representative sample of Italian adults with focal or generalized epilepsies in long-term remission [18] and participating centers had a national distribution. In addition, this is a study done in adults. Our findings cannot be applied to children and adolescents, the population most deeply investigated in previous reports. Then, we do not know to what extent rapid withdrawal compares to slow withdrawal in people who are seizure-free for periods of time different from ours. Last, we cannot predict the outcome of the two treatment strategies after longer follow-up periods.

In conclusion, our study suggests that seizure-relapse after drug discontinuation in seizure-free patients with epilepsy is unrelated to the duration of tapering. Patients with long periods of remission have a fairly low relapse rate regardless of the duration of tapering. Further studies are awaited to confirm our findings in children and adolescents and in patients with shorter periods of remission before drug withdrawal.

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Declarations

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Regione Calabria, SezioneArea SUD (No. 28/2017).

Conflict of interest The authors declare no competing interests.

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