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RESEARCH ARTICLE

Reappraisal of the Medical Research Council Antiepileptic Drug Withdrawal Study: Contamination-adjusted and dose-response re-analysis

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Abstract

Objective: The 1991 Medical Research Council (MRC) Study compared seizure relapse for seizure-free patients randomized to withdraw vs continue of antiseizure medications (ASMs). We re-analyzed this trial to account for crossover between arms using contamination-adjusted intention to treat (CA ITT) methods, to explore dose-response curves, and to validate predictions against external data. ITT assesses the effect of being randomized to withdraw, as-treated analysis assesses the confounded effect of withdrawing, but CA ITT assesses the unconfounded effect of actually withdrawing.

Methods: CA ITT involves two stages. First, we used randomized arm to predict whether patients withdrew their ASM (logistic) or total daily ASM dose (linear). Second, we used those values to predict seizure occurrence (logistic).

Results: The trial randomized 503 patients to withdraw and 501 patients to continue ASMs. We found that 316 of 376 patients (88%) who were randomized to withdraw decreased their dose at every pre-seizure visit, compared with 35 of 424 (8%) who were randomized to continue ($p < .01$). Adjusted odds ratios of a 2-year seizure for those who withdrew vs those who did not was 1.3 (95% confidence interval [CI] 0.9–1.9) in the as-treated analysis, 2.5 (95% CI 1.9–3.4) comparing those randomized to withdraw vs continue for ITT, and 3.1 (95% CI 2.1–4.5) for

CA ITT. Probabilities (withdrawal vs continue) were 28% vs 24% (as-treated), 40% vs 22% (ITT), and 43% vs 21% (CA ITT). Differences between ITT and CA ITT were greater when varying the predictor (reaching zero ASMs) or outcome (1-year seizures). As-treated dose-response curves demonstrated little to no effects, but larger effects in CA ITT analysis. MRC data overpredicted risk in Lossius data, with moderate discrimination (areas under the curve ~0.70).

Significance: CA ITT results (the effect of actually withdrawing ASMs on seizures) were slightly greater than ITT effects (the effect of recommend withdrawing ASMs on seizures). How these findings affect clinical practice must be individualized.

KEYWORDS

antiseizure medication, clinical trials, drug withdrawal, epilepsy, risk prediction

1 | INTRODUCTION

Epilepsy affects 50 million people worldwide.[1] Although antiseizure medications (ASMs) render two-thirds of patients seizure-free,[2] medication-related adverse effects reduce quality of life.[3–6] ASM withdrawal has been shown to improve key patient outcomes such as mood[7] and cognition,[8–10] and after a period of remission up to 70% will remain seizure-free after discontinuing ASM treatment.[11] Thus guidelines have suggested that after a sufficient seizure-free duration, seizure risk may eventually fall low enough to justify discontinuation.[12]

Decisions require that clinicians, people with epilepsy, and caregivers understand the effect of withdrawal on seizure relapse, as well as the risk if treatment is continued. Yet, the most recent guidelines endorse considerable uncertainty about the effect of withdrawal.[13] Lossius et al.[14] provides the only available double-blinded randomized-controlled trial (RCT) in adults but may have been underpowered to find a significant effect ($N = 149$), enrolled an unusually low-risk population, and had a narrow geographic region of enrollment. The Medical Research Council (MRC) Drug Withdrawal Study Group study[15] is the only other available RCT estimating the effect of withdrawal on seizure relapse in adults. It was much larger ($N = 1013$) and diverse (40 centers in the UK).

Despite its strengths, MRC's original intention to treat (ITT) analysis still could have underestimated the effect of ASM withdrawal on seizure relapse. ITT evaluates the influence of randomizing patients to a certain treatment, but may not reflect the influence of actually adhering to a given course of treatment if patients do not adhere perfectly to their assigned treatment,[16,17] whereas, as-treated analysis does estimate the effect of actually receiving a given treatment, but introduces self-selection bias.

Key points

- We re-analyzed the Medical Research Council Antiepileptic Drug Withdrawal study using contamination-adjusted intention to treat (CA ITT) methods.
- CA ITT analyses generally estimated larger effects of withdrawing on seizures compared with ITT analyses.
- We display dose-response curves for time to first seizure among this withdrawing population.
- Treatment may be slightly more effective than previously appreciated, although decisions must be individualized.

A newer technique called contamination-adjusted ITT (CA ITT) mitigates these limitations. Like as-treat analysis, CA ITT estimates the effect of "actually withdrawing versus continuing." But, CA ITT does so while also accounting for the randomized arm (like ITT), which "unconfounds" the as-treated results.[18] CA ITT increases the ITT effect according to the degree of crossover between arms.[19]

We executed CA ITT re-analyses of the MRC trial, including dose-response analyses, which have not been previously performed, and validated predictions against the data of Lossius et al.

2 | METHODS

2.1 | Study design and data set

The MRC study included adults and children with at least two unprovoked seizures, taking at least one ASM,

without progressive neurological impairment, who had been seizure-free for at least 2 years.[15] It was not blinded, and randomized patients to withdraw (decrementing every ~4 weeks over at least 6 months until off), vs continue existing doses. Randomization spanned 1984–1988, with up to seven study visits (median 5.0 years of follow-up, interquartile range 4.0–5.9). In those randomized to withdraw vs continue, 33% vs 12% had a seizure by 1 year and 41% vs 22% had a seizure by 2 years.

2.2 | Procedures involving human subjects

This study was deemed exempt by the University of Michigan Institutional Review Board.

2.3 | Variables and statistical analysis

Baseline variables included age at randomization, sex, epilepsy characteristics (seizures impairing awareness, myoclonic/tonic-clonic [which we collapse here into "motor"; note purely "tonic" seizures was not an available classification], prior status epilepticus, nocturnal seizures, years between first and most recent seizure, years of seizure freedom at the time of randomization), prior ASM withdrawal attempts, ASMs (names, doses), prior electroencephalography (EEG) studies (as in the original trial, we considered EEG results before or up to 90 days after randomization), and epilepsy risk factors (birth trauma [not further defined in the original trial], developmental delay [not further defined in the original trial], primary family history of epilepsy, head injury with post-traumatic amnesia >24 h, intracranial surgery, meningitis, neonatal seizures, neurological deficit on exam, psychiatric conditions, and special schooling). All models below were performed unadjusted, and then adjusted for these variables.

2.3.1 | ITT analysis: "The effect of being randomized to withdraw"

The predictor in each ITT model was the randomized arm. We reproduced the original trial's Kaplan-Meier curves including a Cox proportional hazards model where the randomized arm predicted time to first seizure. Because arms diverged quickly initially and then plateaued, and Shoenfeld residuals interacted significantly with time (nonproportional hazards, $p < .01$), we also restricted follow-up to the first year during which hazards were proportional ($p = .24$).

After the above Cox model, our study's models were all logistic regressions. The primary outcome was 2-year seizure occurrence. We performed sensitivity analyses modifying the outcome to be either 1-year seizure occurrence or 2-year tonic-clonic seizure occurrence. Because patients up to age 15 years were all allowed to withdraw at 1 year if they wished, we performed another sensitivity analysis excluding patients 15-years-old or younger.

2.3.2 | As-treated analysis: "The confounded effect of withdrawal"

The primary dichotomous predictor was whether the total dose of ASMs decreased at every visit in the first year prior to seizure occurrence or the patient reached and stayed off ASMs. We calculated the total dose of ASMs at every visit by summing the "defined daily dose" of each ASM at each visit. The World Health Organization specifies a defined daily dose for each medication as its average therapeutic dose (Table S1). For example, one defined daily dose is considered 1500 mg per day of valproate, 1000 mg per day for carbamazepine, and 300 mg per day for phenytoin. Outcomes were the same as in the ITT models.

Because any dichotomous definition distills complex longitudinal information, we performed sensitivity analyses:

1. Changed the timespan to define "withdrew" as the first 2 years.
2. Changed the definition of "withdrew" to be reaching and remaining at zero ASMs.
3. Changed the definition of "withdrew" to be decreasing below the baseline dose at any point.

To further understand the "dose-response" curve, we performed discrete time logistic models.[20,21] Each month after randomization represented a row; we entered either the total defined daily dose or the number of ASMs as the main predictor, adjusted for all covariates as in the previous models, and censored patients at their first seizure, if applicable. Discrete time logistic regressions are somewhat similar to Cox models, but do not require the proportional hazards assumption, and allow more flexible functional forms between treatment and time. We allowed a treatment*time interaction and allowed up to a cubic effect of time. We displayed survival curves obtained by taking the cumulative product akin to a Kaplan-Meier curve and performed 1000 bootstrap replications to obtain confidence intervals at each 1-year timepoint.

2.3.3 | CA ITT analysis: "The unconfounded effect of withdrawal"

Figure S1 illustrates CA ITT assumptions.[22–24] Conceptually, we wish to choose a variable (here, randomized arm) that externally manipulates treatment received without having any other influence on the outcome, and shares no confounders with the outcome.[25] The first assumption (randomization influences treatment) is testable from the data. The second and third assumptions are not empirically testable from the data. They are reasonable though because the "coin flip" of randomization should affect the outcome only by virtue of influencing treatment received, and randomization should share no confounders with other variables.

For every "as-treated" model, we performed a corresponding CA ITT analysis, as detailed in the Methods S1. Briefly, CA ITT involves two stages[18,24]:

- Stage 1, randomized arm predicts treatment received: The output is the predicted value of whether the patient withdrew within each randomized arm. This step "unconfounds" the treatment variable by virtue of using the randomized arm to predict treatment received.
- Stage 2, predicted treatment received predicts the outcome: This uses the "unconfounded" treatment from Stage 1 to predict the outcome. Conceptually, because the predicted probability of withdrawing is slightly more than 0 for those randomized to continue and is slightly less than 1 for those randomized to withdraw, the "influence of a 1-unit step in randomized arm on outcome" corresponds to a "less than 1-unit step in predicted probability to withdraw on the outcome." Hence the CA ITT effect may be larger than the ITT effect, increased proportional to the amount that actual withdrawal differs from whether patients were randomized to withdraw. For the simplest dichotomous case, the CA ITT effect is equivalent to: the ITT effect) / (the proportion in the group randomized to withdraw who actually withdrew minus the proportion in the group randomized to continue who actually withdrew.

2.3.4 | External validation

As detailed in the Methods S1, we compared MRC-based predictions with data from Lossius et al. 2008.[14] Lossius et al. analyzed the effect of ASM withdrawal in 149 patients with epilepsy in Norway who were seizure-free for at least 2 years, age 18–67, and taking ASM monotherapy. We included only the 390 MRC patients that may have been eligible for the Lossius study. We calculated 1-year predicted seizure probabilities for each patient in the Lossius study (given that their double-blinded period lasted 1 year), using a model developed based on MRC data. Note that Lossius had very little crossover (randomized to withdraw: 71/72 [99%] withdrew; randomized to continue: 2/77 [3%] withdrew); hence we expected ITT and CA ITT validations to be similar. For both approaches, we obtained the areas under the curve from a logistic regression on 1-year seizure outcomes to quantify discrimination and plotted observed vs predicted risk calibration.

2.4 | Data availability statement

Requests to share the code and data would be considered upon reasonable request.

3 | RESULTS

There were 503 patients randomized to withdraw and 510 patients randomized to continue. Covariates were similar between groups (Table 1).

For the 800 of 1013 patients (79%) for whom we could calculate whether they withdrew, 331 of 376 (88%) who were randomized to withdraw decreased their dose at every considered visit, compared with 35 of 424 (8%) who were randomized to continue ($p < .01$). For whether patients reached a dose of zero, these numbers were 228 of 376 (61%) vs 21 of 424 (5%) ($p < .01$). For whether any dose reduction occurred, these numbers were 342 of 376 (91%) vs 84 of 424 (20%) ($p < .01$).

Mean defined daily doses appeared similar at baseline; then arms diverged (Figure 1) However, on average, the total dose for the continuation arm decreased slightly over time and the withdrawal arm's mean defined dose remained above zero throughout (i.e., "crossover" compared to randomized arm).

The hazard ratio (HR) of being randomized to withdraw on time to first seizure (ITT effect) was 1.7 (95% confidence interval [CI] 1.4–2.1). In the first year when the proportional hazards assumption was not violated, the HR was 3.2 (95% CI 2.3–4.3) (Figure S2).

We then compared ITT, as-treated, and CA ITT treatment effects (Table 2: adjusted; Table S2: unadjusted). For our primary model, the adjusted odds ratio [OR] of a consistently decreasing dose on having at least one 2-year seizure was 1.3 (95% CI 0.9–1.9) for as-treated, 2.5 (95% CI 1.9–3.4) for ITT, and 3.1 (95% CI 2.1–4.5) for CA ITT analysis. This corresponded to absolute predicted probabilities (withdrawal vs continue) of 28% vs 24% (as-treated), 40% vs 22% (ITT), and 43% vs 21% (CA ITT) (Figure 2). Similar patterns emerged throughout sensitivity models; as-treated ORs were the lowest and CA ITT

TABLE 1 Population description at baseline (prior to randomization)

	No. (%) or median (IQR)	
	Withdraw	**Continue**
N	503	510
Demographics		
Age at randomization, years	27 (17–40)	27 (17–43)
Female sex	256 (51%)	260 (51%)
Seizure characteristics at randomization		
Impairing awareness	164 (33%)	163 (32%)
Motor	436 (87%)	440 (86%)
Prior status epilepticus	35 (7%)	30 (6%)
Nocturnal	61 (12%)	79 (15%)
Prior withdrawal attempt		
0	445 (88%)	450 (88%)
1	54 (11%)	57 (11%)
2	3 (1%)	3 (1%)
4	1 (<1%)	0 (0%)
Tonic-clonic, number	5 (2–12)	4 (2–10)
Years of seizures	5 (1–12)	4 (1–12)
Years since last seizure	3 (2–6)	4 (2–6)
Antiseizure medication at randomization		
Number		
1	418 (83%)	424 (83%)
2	80 (16%)	81 (16%)
3	5 (1%)	5 (1%)
Defined daily dose[a]	0.6 (0.4–1.0)	0.6 (0.4–1.0)
Name[b]		
Phenytoin	173 (34%)	168 (33%)
Carbamazepine	171 (34%)	171 (34%)
Valproate	152 (30%)	160 (32%)
Phenobarbital	92 (18%)	99 (20%)
Primidone	29 (6%)	22 (4%)
Ethosuximide	15 (3%)	7 (1%)
EEG abnormalities, up to 3 months after randomization[c]		
Focal spikes	31 (6%)	36 (7%)
Focal paroxysmal activity	112 (22%)	134 (27%)
Generalized spikes	59 (12%)	59 (12%)
Generalized paroxysmal activity	158 (31%)	158 (31%)
Additional epilepsy risk factors		
Birth trauma	34 (7%)	33 (6%)
Developmental delay	78 (16%)	75 (15%)
Family history (primary) of epilepsy	73 (15%)	79 (16%)
Head injury	18 (4%)	12 (2%)
Intracranial surgery	9 (2%)	8 (2%)
Meningitis	13 (3%)	21 (4%)
Neonatal seizures	55 (11%)	42 (8%)
Neurological deficit	17 (3%)	15 (3%)
Psychiatric condition	51 (10%)	55 (11%)
Special school	81 (16%)	84 (17%)

Abbreviations: %, percent; EEG, electroencephalogram; IQR, interquartile range.

[a]Defined daily dose: The World Health Organization lists a defined daily dose, or the number of milligrams per day suggested to be an average dose for each medication. This variable sums the defined daily dose for each antiseizure medication. https://www.whocc.no/atc_ddd_index/

[b]Other medication names: Sulthiame (Withdraw 4 vs Continue 6), clonazepam (3 vs 6), clobazam (2 vs 0), vigabatrin (1 vs 1), prominal (1 vs 2), beclamide (1 vs 3), nitrazepam (1 vs 1). Note that column totals may add up to more than the number of patients, given that each patient can be on more than one medication.

[c]Determination of spikes was unavailable for 80 (16%) in the withdrawal group and 65 (13%) in the continue group. Determination of paroxysmal activity was unavailable for 38 (7%) and 24 (5%), respectively. Missingness was greater for spikes because this was based on only a single set of EEG fields, whereas paroxysmal activity was listed in two sets of EEG fields spanning two possible EEG studies.

ORs were the highest for each model. The relative effect of withdrawal was increased in sensitivity models changing the predictor (reaching a dose of zero) or outcome (1-year seizure).

Figure 3 displays dose-response curves. Across the range of studied defined daily doses (top), unadjusted as-treated curves (left) appeared in the reverse order of what might be expected (greater dose was associated with greater seizure probability), adjusted curves were all nearly identical (middle), but CA ITT curves clearly separated each dose in the expected direction. A similar pattern appeared when studying number of ASMs, although the category "at least two ASMs" had wide CIs overlapping the other CA ITT curves.

Baseline characteristics of data elements of patients who would have met inclusion criteria for both the MRC and Lossius studies are shown in Table S3. In the MRC data set, 1-year seizure relapse occurred in 84 of 388 patients (22%) (randomized to withdraw: 59/199 [30%]; randomized to continue: 25/189 [13%]). In the Lossius data set, 1-year seizure relapse occurred in 17 of 149 (11%) [randomized to withdraw: 11/72 (15%); randomized to continue: 6/77 (8%)]. Areas under the curve were 0.71 for ITT and 0.70 for CA ITT methods. Figure 4 displays that both methods had similar calibration and overpredicted risk in Lossius data.

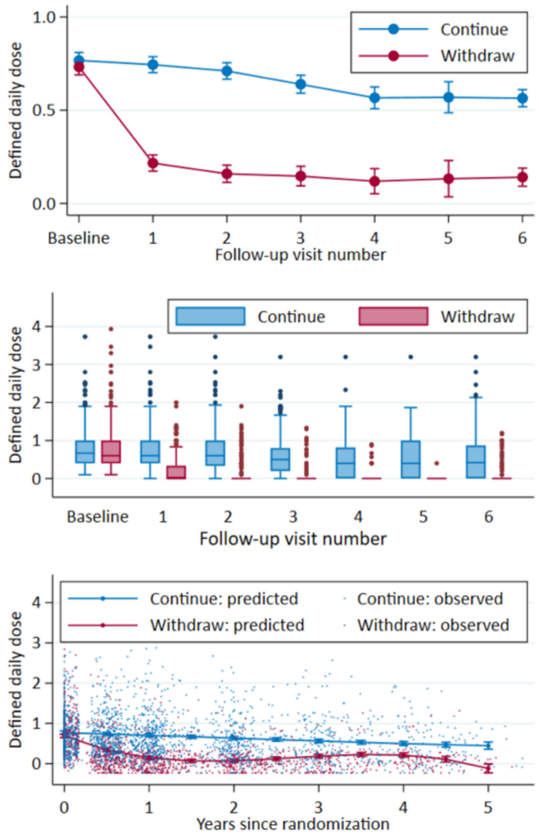

FIGURE 1 Defined daily dose by randomized arm over time. Top: Linear mixed model using each study visit, randomized arm, and their interaction as predictors. Middle: Boxplots by study visit and randomized arm. Bottom: Linear mixed model using time, time^2, time^3, randomized arm, all time interactions with randomized arm, with predictions displayed every 6 months and superimposed observed data. Note the bottom plot has some added jitter between datapoints for visualization (observed points are all at least 0). The top and bottom plots display 95% confidence intervals surrounding means at each timepoint. Only data before the first seizure occurrence for each patient are shown for all plots. *Interpretation*: Doses were similar at baseline between arms; then the withdrawal group decreased their dose more than the continuation group, although the continuation group slightly decreased their dose over time and the withdrawal group still had a mean dose above zero throughout

4 | DISCUSSION

4.1 | General discussion

We performed a re-analysis of the 1991 MRC Antiepileptic Drug Withdrawal Trial. We applied CA ITT methods to answer the question: "What would be the unconfounded risk of seizure recurrence if everyone in the trial withdrew versus continued ASMs?" This was in contrast to the question answered by the typical ITT approach ("What was the risk of seizure recurrence in patients encouraged to withdraw vs continue?") or an as-treated approach ("What was the confounded risk of seizure recurrence in patients who happened to withdraw vs continue?"). Throughout our estimates, CA ITT effects were larger than ITT effects. For example, the CA ITT OR of a 2-year seizure for decreasing the dose of medication at each visit was 3.1 vs 2.5 for the ITT effect. This would correspond to a number needed to harm of 4.5 for the CA ITT approach (43% vs 21%) compared with a number needed to harm of 5.6 for the ITT approach (40% vs 22%). The difference was even larger when considering the effect of reaching complete withdrawal, or when considering a 1-year seizure. Furthermore, we provide novel dose-response curves across a range of total daily doses regarding time to first seizure.

An accurate understanding of treatment effects is critical to decision-making, and our work responds to recent guidelines calling for more rigorous data estimating the effect of withdrawal on seizure risk.[13] Overestimating the benefit of treatment risks overtreatment, which would be harmful given that ASM-related adverse effects predict worsened quality of life.[3–6,26–28] Underestimating the benefit of treatment likewise poses a risk of other harms.[29] Having more than one convulsion in the prior year increases risk for sudden unexpected death in epilepsy (SUDEP) 27-fold, and being on an ASM decreases risk for SUDEP 2- to –3-fold.[30] In addition, seizure frequency worsens quality of life.[4]

As with any complex health care decision, what to do with this information must be individualized. Although clinicians may wish for a single answer in terms of "what is the risk increase due to withdrawal," our tables emphasize that this question has different answers depending on the exact population, predictor, outcome, and model type. The CA ITT approach is most useful to address the effect of unconfounded effect of withdrawing, although the ITT approach remains useful to address the effect of whether the physician recommends that a patient withdraw, which inevitably will not be perfectly followed.[31] Despite a nearly doubled OR comparing CA ITT vs ITT effects in some analyses, whether this absolute magnitude of difference is sufficient to change recommendations must be considered on a case-by-case basis incorporating patient preference. Current data do not inform any single known relapse risk below or above which withdrawal is known to be beneficial vs harmful. Data exist suggesting that withdrawal may correlate with psychosocial benefits[32] or improved quality of life,[28] although Lossius et al.[14] found no difference in quality of life between arms such that no strong conclusion can yet be drawn about which patients benefit from withdrawal.[13] For some patients and clinicians, a small increase in seizure risk may be sufficient to dissuade

TABLE 2 Adjusted[a] effect sizes using intention to treat (ITT), as-treated, and CA ITT (contamination-adjusted ITT)

X = Predictor Y = Outcome		As-treated	ITT	CA ITT
X: Decreasing dose Y: 2-year seizure	*N*	750	975	966
	Odds ratio	1.3 (0.9–1.9)	2.5 (1.9–3.4)	3.1 (2.1–4.5)
	P(Y), withdraw	28% (24%–33%)	40% (36%–44%)	43% (37%–48%)
	P(Y), continue	24% (20%–28%)	22% (19%–26%)	21% (17%–25%)
X: Reached zero Y: 2-year seizure	*N*	750	975	966
	Odds ratios	0.7 (0.4–1.0)	2.5 (1.9–3.4)	4.5 (2.9–9.1)
	P(Y), withdraw	21% (16%–26%)	40% (36%–44%)	52% (45%–61%)
	P(Y), continue	28% (24%–32%)	22% (19%–26%)	22% (18%–25%)
X: Any decrease Y: 2-year seizure	*N*	750	975	966
	Odds ratio	1.1 (0.8–1.5)	2.5 (1.9–3.4)	3.5 (2.2–5.3)
	P(Y), withdraw	27% (23%–31%)	40% (36%–44%)	42% (36%–47%)
	P(Y), continue	25% (20%–29%)	22% (19%–26%)	19% (14%–23%)
X: Decreasing dose Y: 2-year tonic-clonic seizure	*N*	750	951	942
	Odds ratio	1.6 (1.1–2.3)	2.6 (1.9–3.6)	3.3 (2.0–5.1)
	P(Y), withdraw	23% (19%–27%)	33% (29%–37%)	36% (30%–41%)
	P(Y), continue	17% (13%–20%)	17% (14%–20%)	16% (12%–19%)
X: Decreasing dose Y: 1-year seizure	*N*	758	984	975
	Odds ratio	1.4 (0.9–2.1)	3.8 (2.6–5.4)	4.9 (3.0–7.8)
	P(Y), withdraw	18% (14%–22%)	32% (28%–36%)	35% (30%–41%)
	P(Y), continue	14% (11%–17%)	12% (9%–15%)	11% (8%–14%)
Excluding age ≤15 (remaining *N* = 816) X: Decreasing dose Y: 2-year seizure	*N*	597	787	779
	Odds ratio	1.3 (0.9–2.0)	2.7 (2.0–3.8)	3.6 (2.2–6.1)
	P(Y), withdraw	29% (24%–34%)	43% (39%–48%)	47% (41%–53%)
	P(Y), continue	25% (20%–29%)	24% (20%–28%)	22% (17%–26%)

[a]All adjusted models included the following: developmental delay, special schooling, neurological deficit, birth trauma, intracranial surgery, head injury, meningitis, psychiatric disorder, neonatal seizures, febrile seizures, family history of epilepsy, nocturnal seizures, simple/complex with/without tonic-clonic seizures, myoclonic seizures, simple or complex absence seizures, history of status epilepticus, number of antiseizure medications at baseline, lifetime number of tonic-clonic seizures, prior withdrawal attempts, sex, years of seizure-freedom before randomization, years between first and last seizure before randomization, age at first seizure, age at randomization, focal and/or generalized paroxysmal finding on EEG up to 3 months after randomization, driver's license.

them from attempting withdrawal. For many others, a small change may not be enough to change decisions, particularly if the patient more strongly wishes to avoid medication or if their past seizures were not disabling.

There were clear differences between as-treated vs CA ITT results, particularly in dose-response curves. As-treated analyses tended to find a less- harmful effect of withdrawal compared with ITT or CA ITT effects

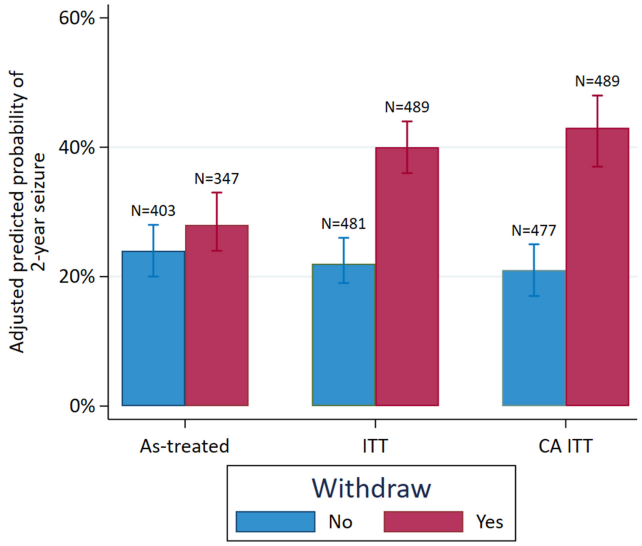

FIGURE 2 Predicted probabilities of having at least one 2-year seizure in a logistic regression including the predictor "decreasing dose," randomized arm, and their interaction (the first row of Table 2, fully adjusted model). *Interpretation*: Withdrawal demonstrated a slightly greater risk difference when using the contamination-adjusted intention to treat (CA ITT) approach compared with the ITT approach. As-treated analysis demonstrated similar adjusted predicted risk in patients who withdrew vs continued, suggesting residual confounding

(sometimes even "beneficial"), even after adjusting for a wide array of variables shown to predict seizures.[33] This emphasizes the importance of our approach, leveraging randomization to overcome such confounding. It also emphasizes that confounders exist beyond those captured here, such that future non-randomized observational studies may consider measuring baseline and post-randomization variables, which are not typically measured such as sleep, alcohol, substance use habits, and side effects.

Our finding that the MRC overpredicted Lossius data also underscores the need for additional variables in future studies particularly aimed at flagging "low-risk" individuals. Two validation studies[34,35] of the current individualized post-withdrawal seizure risk calculator[36] found moderate external performance including some overprediction, whereas another recent study found poor external performance.[37] The calculator relies heavily on MRC data.[37] Future studies should capture the covariates measured in the Lossius data, which were not measured in MRC data (e.g., progressive neurologic disease especially dementia, juvenile myoclonic epilepsy, and other "serious disease which may influence health status"), which all may better identify truly low-risk individuals who may be withdrawal candidates.

4.2 | MRC data set limitations

Our work shares the limitations of the original MRC data set.

First, the trial was unblinded. Patients might relatively overreport seizures in the withdrawal arm given the knowledge that they were decreasing their doses ("subtraction anxiety") and thus overestimate withdrawal effects.[38] That could have been another reason that MRC data overpredicted risk in the Lossius et al. data set, which was double-blinded and therefore was not subject to this bias. Though, prior unblinded external validation work also found that models heavily based on MRC data tended to overpredict risk.[34,35] Given MRC overpredicted risk even in unblinded external data, lack of blinding in MRC may not be the only explanation. Lack of blinding could also lead the withdrawal group to enact compensatory lifestyle changes to reduce seizures,; thus these data do not inform the degree to which ASMs vs consequent lifestyle changes could influence seizures.

Second, given that the MRC study was conducted in the 1980s to 1990s, it lacks magnetic resonance imaging (MRI) data and newer-generation ASMs. However, newer-generation ASMs have not been shown to be more effective than older generation ASMs,[2] and these older-generation ASMs remain in widespread use today.[39,40] Still, future studies including these more current practice elements would be beneficial.

Third, typically any one trial tests only a single withdrawal protocol, and time-varying effects of treatment could be different with different withdrawal protocols. Although no literature to date informs the optimal withdrawal regimen for adults,[13] MRC's particular withdrawal protocol was somewhat prolonged (intended over at least 6 months). If anything, faster withdrawal could predict an even higher initial relapse effect.

Fourth, even with the trial's large sample size, the CI particularly around the survival curve for "at least two ASMs" was quite wide given that most patients started on monotherapy and then many patients tapered off their additional ASMs. Our defined daily dose "dose-response" curve also does not distinguish whether patients took ASMs with different mechanisms of action.

4.3 | CA ITT approach limitations

First, CA ITT relies upon several untestable assumptions, namely, that the randomized arm does not independently influence seizures, and that the randomized arm and seizures have no shared causes (confounders). Still, these

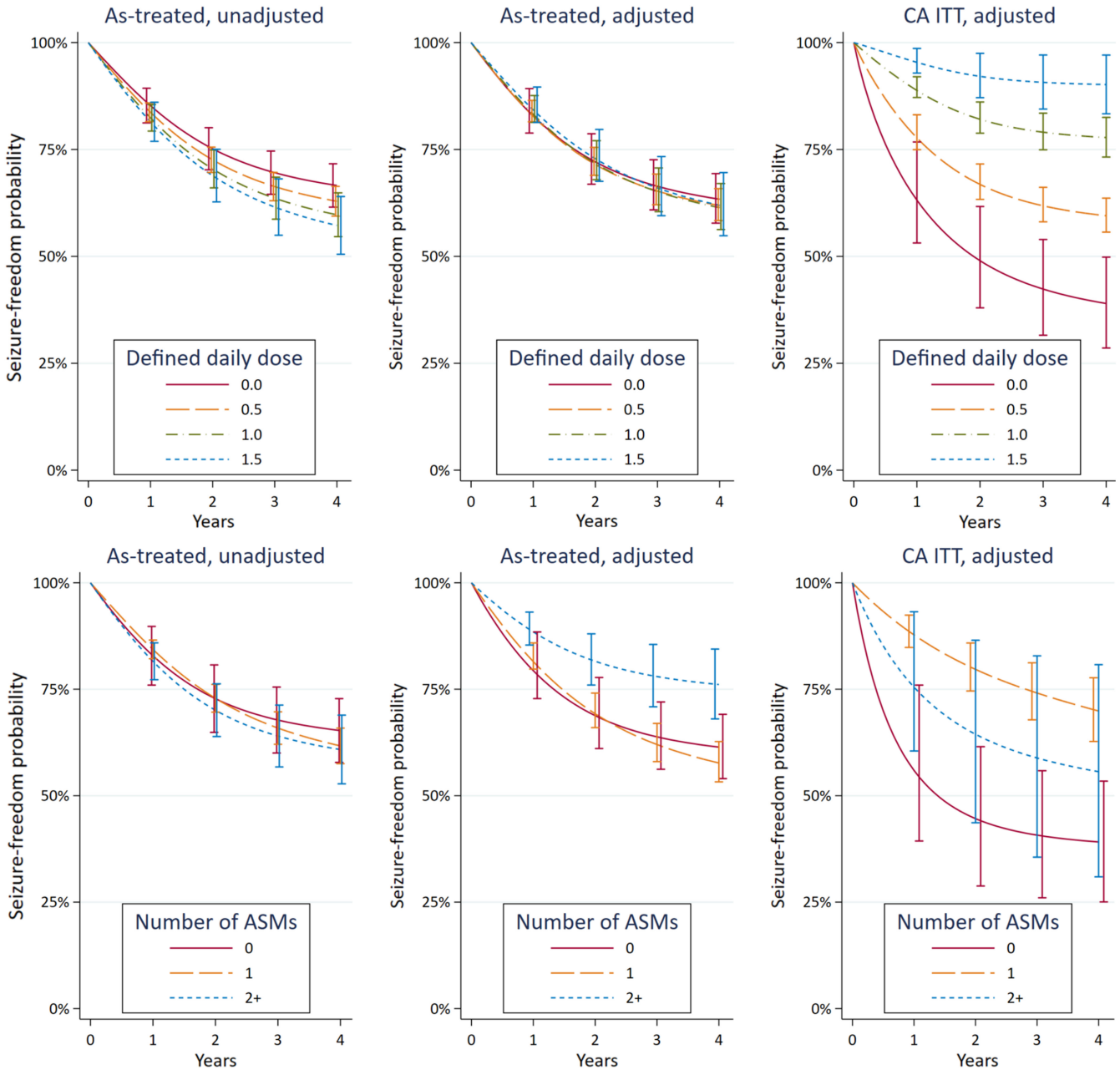

FIGURE 3 Dose-response curves. These curves were produced by discrete time logistic regressions, allowing the dose (top) and number of antiseizure medications (ASMs; bottom) to update at each study visit, censored upon occurrence of the first seizure. Adjusted curves are adjusted for the same covariates as in Table 2. *Interpretation*: As-treated approaches appeared to suffer from residual confounding, whereas the CA approach clearly distinguished curves. Note though that for number of ASMs, the "at least two ASM" group had wide confidence intervals due to a smaller number of such time points

assumptions are reasonable, given that the randomized arm is a coin flip.

Second, CA ITT results have a particular target of inference.[18,23] CA ITT effects pertain to the theoretical population of patients who would comply with their randomized assignment. An assumption of CA ITT thus is that the effect of treatment would have been the same among compliers and noncompliers, although we have no reason to believe this would be untrue.

Third, in this context, there is no one single gold standard definition of whether a patient "withdrew." Selection bias could occur if both seizure risk and whether a patient withdrew influence selection. Clearly seizure risk influences selection—we had insufficient data to compute whether patients withdrew for patients with early seizures prior to any follow-up visit. However, whether a patient withdrew was unlikely to influence selection, given that 99% of our sample had

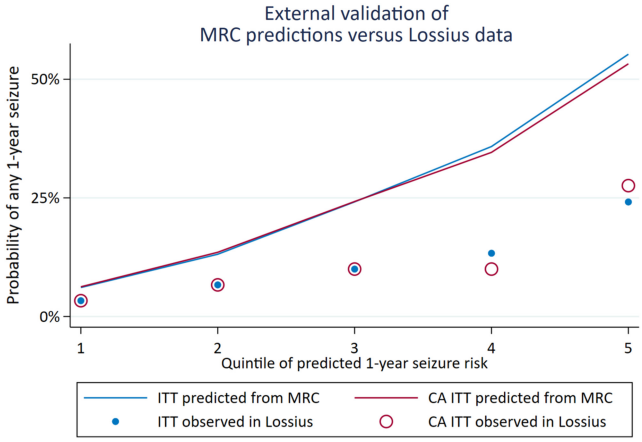

FIGURE 4 Calibration of predicted probabilities from MRC tested against observed probabilities of having at least one seizure in the 1-year following randomization from Lossius et al. "Predicted" lines refer to probabilities that each model based on MRC data would predict for patients in Lossius data. "Observed" dots refer to probabilities actually observed in Lossius data. *Interpretation*: Both methods based on MRC data tended to overpredict risk in Lossius et al. data (Lossius had lower risk than would have been predicted by MRC-based models). Calibration appeared similar between contamination adjusted and conventional intention to treat methods. Abbreviations: CA ITT, contamination adjusted intention to treat; ITT, intention to treat; MRC: Medical Research Council.

a visit within 2 years by which to calculate follow-up doses. Dichotomous "withdrawal" definitions also collapse complex longitudinal information. Thus we created numerous dichotomous and longitudinal sensitivity definitions.

Finally, CA ITT results provide population-averaged treatment effects rather than individualized risk predictions.

5 | CONCLUSIONS

We re-analyzed data from the landmark MRC drug withdrawal study according to randomized arm while still accounting for treatment received. We found greater effects of ASM withdrawal on seizure relapse using this CA ITT approach compared with the original ITT approach, although absolute risk differences were small. We also display dose-response curves using CA ITT methods. Whether the increase in effects that we show here are sufficient to dissuade a patient who might have otherwise considered withdrawal is not a simple question, and choices must be individualized to an individual patient's risk tolerance regarding none vs partial vs full withdrawal. The need remains for an updated multicentered randomized double-blinded sufficiently powered trial including a broader range of time-varying confounders to better understand the influence of ASM withdrawal on seizures.

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None.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

S.W.T. conceived of and designed the study, executed the statistical analysis, and wrote the manuscript. All others contributed important intellectual content to and edited the manuscript. All coauthors have been substantially involved in the study and the preparation of the manuscript. There are no undisclosed groups or persons who have had a primary role in the study and/or in manuscript preparation. All coauthors have seen and approved the submitted version of the paper and accept responsibility for its content.

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