

The safety of antiepileptic drug withdrawal in patients with non-epileptic seizures

M Oto, C Espie, A Pelosi, M Selkirk, R Duncan



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See end of article for authors' affiliations

Correspondence to:
Dr M Oto, Southern
General Hospital, Institute
of Neurological Sciences,
1345 Govan Road,
Glasgow G51 4TF, UK;
meritxelloto@hotmail.com

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Background: To determine whether withdrawal of anticonvulsant drugs (AED) can be carried out safely in patients with non-epileptic seizures (NES).

Methods: Prospective evaluation of safety and outcome in 78 patients with NES who satisfied a standardised set of criteria for excluding the diagnosis of coexisting or underlying epilepsy.

Findings: The patients were taking from one to three AED. Sixty four patients were withdrawn as outpatients, 14 as inpatients. Five patients stopped their drugs abruptly, and two had AED restarted and had to be withdrawn again. Otherwise all patients adhered to withdrawal schedules. A new type of attack in addition to NES was seen in three patients (complex partial seizures in all three cases). NES frequency declined in the group as a whole over the period of the study (follow up 6–12 months) in all individuals except for eight patients in whom there was a transient increase. Fourteen patients reported new physical symptoms after withdrawal; however, no serious adverse events were reported.

Conclusions: With appropriate diagnostic investigation and surveillance during follow up withdrawal of AED can be achieved safely in patients with NES.

Non-epileptic seizures (NES, pseudoseizures) can be defined as events that resemble or may be mistaken for epileptic seizures, but which are not associated with abnormal EEG discharges and which have a presumed or known psychological cause. The diagnosis and management of NES represents a significant clinical problem. Patients with NES may present to a variety of doctors (for example, physicians, accident and emergency specialists), with attacks that are mistaken for and treated as epileptic seizures or status epilepticus.^{1–3}

Most patients with NES do not have epilepsy.^{3–7} Nonetheless up to 80% are exposed to antiepileptic drugs (AED),⁸ and even when the diagnosis of NES is confirmed and no evidence of epilepsy has been found a substantial proportion of patients (20–44%) remain on single or multiple AEDs.⁹ This may also apply to other medically unexplained symptoms, where some patients continue to be prescribed medication despite there being no evidence of a physical problem.¹⁰

There are various good reasons why patients with NES in whom there is no evidence of epilepsy should not be on AED. Teratogenicity is important in a population with a majority of women of childbearing age.¹¹ The cost implications of giving unnecessary treatment¹² are also important, as are potential medicolegal consequences. There is evidence that drugs may actually exacerbate NES¹³ and that continuation of AED after diagnosis is associated with a poor outcome.^{7 14} When NES present to non-specialists, the fact that the patient is on AED may lead doctors to accept a diagnosis of epilepsy, encouraging inappropriate treatment with potentially life threatening drugs.¹⁵

Why, then, may patients who do not have epilepsy remain on AED? There is little published research but some factors may be important. One factor may be lack of confidence in excluding possible underlying epilepsy, with consequent perception that AED withdrawal is associated with significant risk of serious adverse outcomes such as status epilepticus. Even when this is not the case, drug withdrawal does entail a non-medical explanation for the attacks, leading to a potential collision with patient expectations.¹⁶

In order to determine whether it can be safe to withdraw AED in patients who have NES but have no evidence of epilepsy, we have studied outcomes in a series of patients with video-EEG proven NES, who satisfied a standardised set of criteria for excluding concomitant epilepsy and who were withdrawn from AED.

METHODS

The NES clinic is part of the West of Scotland regional epilepsy service. As part of normal clinical practice, all patients had an extensive clinical assessment by semistructured interview, including detailed description of events by patient and eyewitnesses. All had video electroencephalographic (EEG) recording of events, either as an outpatient^{17 18} or as an inpatient. Recorded events were carefully compared with eyewitness accounts (and in some cases shown to eyewitnesses) to make sure that they represented the patient's typical event, and that no other type of event was occurring. Once the diagnosis of NES was confirmed, a concomitant diagnosis of epilepsy was regarded as excluded if the following criteria were satisfied:

- all current types of event described by patient and eyewitnesses recorded and identified as NES;
- no descriptions of past events raising suspicion of epilepsy rather than NES;
- no history of events during childhood*;
- no interictal epileptiform abnormalities on EEG.

Patients were seen at the clinic where the diagnoses were communicated in a non-judgemental and supportive manner, backed by written information for patients and relatives.

Abbreviations: AED, antiepileptic drugs; NES, non-epileptic seizures

* NES may occur in childhood; however, in the context of an adult clinic it is difficult to ascertain in retrospect the clinical semiology of childhood events. We therefore regarded childhood events as a risk factor for underlying epilepsy.

Table 1 Characteristics of the study population compared with the whole clinic population with "NES only" in the same period

	Study population (n = 78)	Whole clinic population (n = 184)
Female	57 (73%)	138 (74%)
Male	21 (27%)	46 (25%)
Learning disability	9 (11.5%)	11 (6%)
Age at referral (years) (mean (SD))	39.62 (14.35)	38.09 (14.17)
Age of first event (years) (mean (SD))	32.42 (15.35)	31.49 (14.49)

*Confirmed diagnosis of non-epileptic seizures only.
NES, non-epileptic seizures.

Patients with a diagnosis of NES and who satisfied the above criteria for the exclusion of concomitant epilepsy were entered into a standardised AED withdrawal programme (see the appendix). Where the patient was on multiple AED, drugs were tapered and withdrawn sequentially.

Data were entered prospectively into an Access database on a dedicated PC and were regularly checked for completeness and accuracy. For this descriptive study the information has been taken from this database and for the purpose of analysis the data were transferred to SPSS. Follow up information was collected at six and 12 months from the completion of the AED withdrawal.

As this was an observational study no ethical approval was required.

Patient sample

Of the total cohort of 235 consecutive patients, 184 had a video-EEG confirmed diagnosis of NES and satisfied criteria for "no epilepsy". The remainder were either awaiting video-EEG (25/235, 10.6%) at the end of the study, or had coexisting epilepsy (26/235, 11.1%).

Of the 184 with confirmed NES alone, 99 (53.8%) were taking AED. The remaining 38 (20.6%) had never been on AED or their drugs had been withdrawn before clinic attendance (47/184, 25.5%).

Of the 99 eligible patients, 78 were included in this study. The remainder (21/99, 21%) were excluded for the following reasons: patient refusal to withdraw AED (2/99, 2%); AED withdrawal not yet complete by time of data analysis (7/99, 7%); lost to follow up (12/99, 12%). Table 1 shows the general characteristics of the study population and those of the patients who were seen at the clinic but were not included in the study.

At presentation there was a high prevalence of medically unexplained symptoms other than NES (56/78, 72%) and psychological symptoms, commonly depression (44/78, 56%). Social morbidity was also high as reflected by dependence on benefits (53/78, 68%).

Prescription of AED was by a neurologist or general physician in 38 of the 78 patients (49%) and unknown in 20 (26%). At the time of referral patients were taking a median of two AED (range 1 to 3, mean 1.4); 28 (36%) were on more than one AED and 20 (28%) reported side effects.

When questioned about the impact of AED on their attacks, four patients (5%) reported an increase in attack frequency after starting AED, while six (8%) reported a sustained improvement and 27 (35%) reported a temporary improvement. The rest (36/78, 46%) reported no change.

Antiepileptic drug withdrawal

In the majority of patients (64 of 78, 82%) tapering and withdrawal was managed in the outpatient setting, by giving clear oral and written instructions to the patients and their general practitioner (GP), supervised by regular review at the clinic. Of these patients, 57/64 (89%) followed the titration protocol as planned. Five patients (7.8%) stopped their drugs completely as soon as the diagnosis was given, and in two patients (3%) the treatment was stopped suddenly by their GP.

Fourteen patients (14/78, 18%) were admitted for drug withdrawal, because of patient or carer anxiety, or because the patient had failed to complete previous attempts of withdrawal as an outpatient.

Two patients were restarted on AED after withdrawal, in one case by the GP and in the other as a result of attendance at an accident and emergency department (A&E). In both cases the AED was withdrawn again successfully.

RESULTS

To assess outcome after AED withdrawal we studied the following end points: evidence of emergent epilepsy, AED restarted, frequency of NES, reported new symptoms, and morbidity.

Follow up data were available in all patients at six months after completion of withdrawal and in 71 of 78 (91%) at 12 months; the remaining seven (9%) were lost to follow up.

Evidence of coexisting epilepsy after drug withdrawal

Three patients (3.8%) presented with a new type of attack as well as their existing NES, identified in all three cases as complex partial seizures. One patient had a risk factor in the form of a resected glioma, although seizures did not occur until one year after withdrawal. In the other two patients, there were no factors that might have indicated a pre-existing epilepsy. The follow up arrangements quickly identified the new attacks, and the epileptic seizures were controlled with

Table 2 Changes in frequency of non-epileptic seizures at six and 12 months following withdrawal of antiepileptic drugs

Time after start of withdrawal	Mean attacks per month	SD	Median	Range	n
At referral	22.23	30.78	15	0.5 to 180	78
At 6 months	13.01	38.46	2	0 to 300	78
At 12 months	9.01	32.51	0	0 to 250	71

AED monotherapy and at lower doses in all cases. All three patients accepted the dual diagnosis. Two remain free of NES at the time of writing, and the third had a substantial reduction.

None of the five patients who unilaterally stopped their AED suddenly reported any adverse effect (none was taking barbiturates or benzodiazepines).

Antiepileptic drugs restarted

Two patients were restarted on AED, in one case by the GP because of persistence of events and in the other as a result of attendance at an A&E department. In both cases drug treatment was withdrawn again successfully. In one further patient the GP had continued to issue repeat prescriptions of AED, a situation that was easily rectified.

Frequency of NES after drug withdrawal

There was a significant and sustained reduction in attacks over time, whether attack frequency data were analysed by changes between groups, within individual subjects, or by total number of patients who were attack-free (table 2).

A Wilcoxon signed rank test was used to compare data between the diminishing sample size groups. The analysis showed that there was a significant difference in attack frequency between referral and the six month follow up ($p < 0.001$). At 12 months the remaining 71 patients had also significantly fewer attacks than at referral ($p < 0.001$) or at the six month follow up ($p < 0.001$).

At 12 months after AED withdrawal, 35 of 71 patients (49%) were free of attacks for more than two months. Only eight patients (10%) reported an initial increase in frequency of NES; in all cases but one they had resolved by six months.

Morbidity and mortality after AED withdrawal

No serious adverse events, including admissions to intensive care (ITU) or death, were reported.

Our definition of pseudostatus was a prolonged NES thought to be epileptic and treated by AED. Twenty three patients (29%) had episodes of pseudostatus before withdrawal, but only four had episodes afterwards (all had previous episodes). Ten patients (13%) continued to report minor injury (bruises and grazes) after withdrawal.

New medical and psychological symptoms

Fourteen patients (18%) reported new symptoms, while three (3.8%) reported an exacerbation of previous symptoms, and nine (11.5%) had investigations for new complaints. In two patients the new complaint (chest pain and fatigue) represented the main source of disability and health care utilisation at follow up. Ten patients (13%) were started on new drugs, in most cases (6/10) an antidepressant drug.

Five patients (6.4%) reported new psychological symptoms: low mood (three patients), irritability, and anxiety. None required psychiatric intervention. One patient with a past psychiatric history self harmed transiently after AED withdrawal.

DISCUSSION

To our knowledge this study is the largest observational study of the outcome of AED withdrawal in this complex population. Although the study population represents a selected sample, the general characteristics of the group were comparable with the rest of our clinic patients and with those described in most reports on NES,¹⁹⁻²¹ although the mean age of onset of events of our group was at the upper end of the range of most studies. Our data give an indication of the possible outcome and potential risks of withdrawing AED in patients with NES selected in a similar way.

In our view, two factors are critical to patient safety: the confidence with which a possible underlying epilepsy is excluded, and the quality of monitoring of the patients during and after AED withdrawal.

The best indicator of the accuracy of criteria for excluding epilepsy is whether or not epileptic seizures occur on withdrawal of AED. Interestingly, relapse occurred soon after withdrawal in the two patients in whom it occurred unexpectedly, indicating that these patients had a controlled epilepsy rather than an epilepsy in remission. In the third patient, who had a history of resected frontal low grade glioma, complex partial seizures occurred just over a year after AED withdrawal. This suggests that either a pre-existing epilepsy was in remission or that a new epilepsy had arisen (not inconceivable given the past history), and suggests the need to monitor patients over an extended period. Our study ended in January 2003 and no more patients have since had epileptic seizures. This is compatible with the results of studies of relapse rate in patients with epilepsy following AED withdrawal, which show that the majority of relapses occur within six months after withdrawal.²²

Our criteria for excluding epilepsy are straightforward, and are applied with care, particularly in the matter of being sure that descriptions of all events are as accurate as they can be, and that they are carefully compared with the events that have been recorded. Nonetheless, when a patient has controlled epilepsy and has not had an epileptic seizure for some years, it may be unrealistic to expect accurate descriptions of early events in all cases.¹⁹ This may particularly be the case if the original events were complex partial seizures that were promptly controlled, and when the present NES are much more frightening and dramatic in the eyes of relatives.

Despite the absence of recurrent major seizures in our series, it is clear that close supervision of the withdrawal process is an important safety measure, not only to ensure that the occurrence of epileptic seizures is rapidly detected and communicated to the NES team, but also to ensure that patients (and doctors) comply with withdrawal schedules. There is evidence that good information for patients and GPs is important to ensure that AED withdrawal is successfully completed.¹⁴ It is possible that our care in giving clear instructions to patients and their GPs contributed to the low rates of non-compliance with withdrawal advice.

Overtreatment of epileptic seizures is common in patients who also have NES.²⁴ For the small number of our patients in whom epileptic seizures appeared after AED withdrawal we were able to titrate AED treatment sensibly, resulting in monotherapy and lower doses.

The level of reporting of new physical or psychological complaints following AED withdrawal was low in our patients, particularly considering the high rates of reported psychopathology and physical symptoms at presentation. In those who reported new medically unexplained symptoms, it was unclear whether this was associated with the removal of the diagnosis of epilepsy, with withdrawal itself, or with the reduction in NES frequency that took place at the same time. Medically unexplained symptoms are common in patients with NES⁹ and it is perhaps unsurprising that the removal of one psychogenic symptom might sometimes provoke the appearance of another.

Overall our patients had a generally good outcome with a significant reduction in frequency of NES after drug withdrawal and only a minority of patients reporting an increase. Similar rates of reduction of attack frequency have been reported in other follow up studies using different methods for diagnosis and management,^{7,9} which suggests that the reduction is probably a result of multiple factors, of which

AED is one. It would require a randomised controlled trial of drug withdrawal to establish the extent to which there is a causal relation between AED withdrawal and a good outcome of NES and we are in the process of carrying out such a trial.

The MRC AED withdrawal study indicates that a patient who has had tonic-clonic convulsions but has been seizure-free on a single AED for two years has a 60% risk of seizures in the first year after drug withdrawal.²² While the number of patients in our study is relatively small, our data suggest a much lesser risk in appropriately selected and monitored patients with NES, yet patients often remain on AED. We cited some potential adverse consequences of AED in the introduction; it may be worth adding that of the 34 of our patients who were women of childbearing age nine had had pregnancies while on AED.

Using our diagnostic criteria and monitoring programme, AED were withdrawn safely in all our study patients. We conclude that in appropriately selected patients with NES, and where suitable expertise and monitoring are available, AED withdrawal can be safe. Patients who are thought to have NES should therefore be referred to appropriate centres.

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Authors' affiliations

M Oto, M Selkirk, R Duncan, West of Scotland Regional Epilepsy Service, Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK

C Espie, Department of Psychological Medicine, University of Glasgow
A Pelosi, Department of Psychiatry, Hairmyres Hospital, East Kilbride, Lanarkshire, UK

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APPENDIX

DRUG WITHDRAWAL PROTOCOL

- Withdrawal programme agreed and discussed with patient
- Patients and primary care physicians given written withdrawal programme
- Patients, relatives, and primary care physicians instructed to report any new event type to the clinic
- Contact phone number supplied
- Clinical follow up at three monthly intervals
- Psychology treatment programme of two to six visits during study period

DRUG WITHDRAWAL SCHEDULES

Phenytoin

100 mg/week until dose is 100 mg/day, then 25 mg/week

Carbamazepine

200 mg/week until dose is 1000 mg/day, then 100 mg/week

Sodium valproate

500 mg/week until dose is 500 mg, then 200 mg/week

Vigabatrin

500 mg every 2 weeks until dose is 500 mg, then 500 mg alternated days for 2 weeks

Lamotrigine

100 mg/week until dose is 300 mg, 50 mg/week till dose is 50 mg, then 25 mg/week

Gabapentin

800 mg/week until dose is 1200 mg, then 400 mg/week

Topiramate

100 mg/week until dose is 200 mg, 50 mg/week till dose is 50 mg, then 25 mg/week

Levetiracetam

500 mg/week until dose is 1000 mg, then 250 mg/week

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