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Special Communication

# Management of seizures in patients with multiple sclerosis; an Iranian consensus

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ABSTRACT

*Purpose:* Cooccurrence of a seizure in a patient with multiple sclerosis (MS) may complicate the management process. Questions, which may complicate the management process of a patient with MS and seizure, include "how should we approach to the patient", "how should we treat the patient", "how should we modify the patient's MS treatment strategy", etc.
*Methods:* We searched the electronic database PubMed on March 30, 2018 for articles in English that included the following search terms: "epilepsy" AND "multiple sclerosis" or "seizure" AND "multiple sclerosis" since 2013, to obtain the best recent relevant scientific evidence on the topic. A working group of 6 epilepsy and 5 MS experts took part in two consensus workshops in Tehran, Iran, in 2018. The final consensus manuscript was prepared and approved by all participants.
*Results:* The search with words "seizure" and "multiple sclerosis" yielded 121 entries; 10 were relevant to the topic. The search with words "epilepsy" and "multiple sclerosis" yielded 400 entries; 7 were relevant to the topic. We reviewed these 17 articles and also some other references, derived from these articles or relevant to the topic, for the purpose of our review.
*Conclusion:* Cooccurrence of a seizure in a patient with MS may complicate the management process. In this review, we tried to provide answers to the frequently asked questions, considering the best available scientific evidence and expert opinion.



## 1. Introduction

Multiple sclerosis (MS) is a chronic disabling disease of the central nervous system (CNS). Comorbid neurological disorders such as epilepsy are more common in patients with MS compared with that in the general population [1]. In a systematic review [1], the authors observed that the incidence of seizures was 2.28%, while the prevalence was 3.09% in patients with MS. In a study of 920 patients with MS from Iran [2], 3.15% of the patients experienced one or more seizures. This rate is consistently similar in many developed and developing countries [1–5]. This is while the incidence of epilepsy in the general population is about 47 cases per 100,000 people, and its prevalence is almost 7 cases per 1000 people [6].

Cooccurrence of a seizure in a patient with MS may complicate the management process and bring about anxiety, both for the patient and for the treating physician. Questions, which may complicate the

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management process of a patient with MS and seizure, include "how should we approach to the patient", "how should we treat the patient", "how should we modify the patient's MS treatment strategy", etc.

The objective of our endeavor was to reach to a consensus between experts on epilepsy and multiple sclerosis in Iran on how to manage seizure(s) in patients with MS, considering the best available scientific evidence and also the expert opinion.

## 2. Methods

We searched the electronic database PubMed on March 30, 2018 for articles in English that included the following search terms: "epilepsy" AND "multiple sclerosis" or "seizure" AND "multiple sclerosis" since 2013, to obtain the best recent relevant scientific evidence on the topic. We limited the search to the title and abstract. The first two authors (AAA and MAS) selected the relevant articles after reviewing their titles, abstracts, and full texts (consecutively) (Fig. 1). The first two authors (AAA and MAS) prepared the primary draft of the manuscript. A working group of 6 epilepsy and 5 MS experts took part in two consensus workshops in Tehran, Iran, in 2018. In a Delphi method, the experts answered the following questions, which were provided by the first two authors (AAA and MAS) after reviewing the literature, in two rounds. After the first round, the first author provided a summary of the experts' comments and concerns. In the second round, the experts revised their earlier answers in light of the replies from other members of the panel. The final consensus manuscript was prepared and approved by all the participants.

We tried to provide answers to the following questions considering the best available scientific evidence and also the expert opinion:

1. How should we approach to a patient with MS who has experienced his/her first seizure?
2. Should occurrence of a single seizure trigger start of an antiepileptic medication in a patient with MS?
3. Should occurrences of more than one seizure trigger start of an antiepileptic medication in a patient with MS?
4. Which antiepileptic drugs (AEDs) are better options in patients with MS?
5. How long should the patients continue taking their AEDs, if they started to do so?
6. Is there a correlation between MS treatments and occurrence of epileptic seizures?
7. Should occurrence of any seizure trigger performing a brain MRI in a patient with MS?
8. Should occurrence of any seizure trigger start of immunomodulatory therapy in a patient with MS?
9. Should we consider a seizure as a relapse in a patient with MS?
10. If a patient with MS develops a seizure that is compatible with a relapse, should we escalate the MS therapeutic regimen?
11. How should we manage status epilepticus in a patient with MS?

## 3. Results

The search with words "seizure" and "multiple sclerosis" yielded 121 entries; 10 were relevant to the topic. The search with words "epilepsy" and "multiple sclerosis" yielded 400 entries; 7 were relevant to the topic (excluding the duplicates) (Fig. 1). We reviewed these 17 articles and also some other references, derived from these articles or relevant to the topic, for the purpose of our review.

### *3.1. How should we approach to a patient with MS who has experienced his/her first seizure?*

Any person, who experiences a seizure for the first time, should be investigated by an expert. The first step is to confirm that the attack has an epileptic nature and is not a nonepileptic event (e.g., paroxysmal nonepileptic demyelinating symptoms, psychogenic nonepileptic seizures, or other paroxysmal disorders such as syncope). It is of utmost importance to differentiate whether the seizure has happened as a manifestation of an epilepsy syndrome [e.g., temporal lobe epilepsy (TLE) associated with mesial temporal sclerosis (MTS) or juvenile myoclonic epilepsy (JME)] or MS has caused the seizure (either as a presenting manifestation or in the course of the disease). The most important and valuable piece of information is a detailed clinical history. A complete physical examination including a through neurological examination is mandatory. If the diagnosis of an epilepsy syndrome cannot be established by history and physical examination, one should obtain further testing and diagnostic information. Electroencephalography (EEG) is a valuable ancillary test, particularly for classification of epilepsy syndromes. One valuable option is to obtain long-term video-EEG monitoring, when a definite diagnosis cannot be reached by history, physical examination, and a routine EEG [7]. In all patients with known MS who present with a seizure, a brain magnetic resonance imaging (MRI) study, with and without contrast, with epilepsy protocol and also MS protocol should be considered. It is important to perform an epilepsy protocol brain MRI for the first postseizure imaging study to investigate all possible etiologies [e.g., MTS] appropriately [8]. It is also important to add MS protocol MRI to investigate the cause of the seizure thoroughly. Other studies

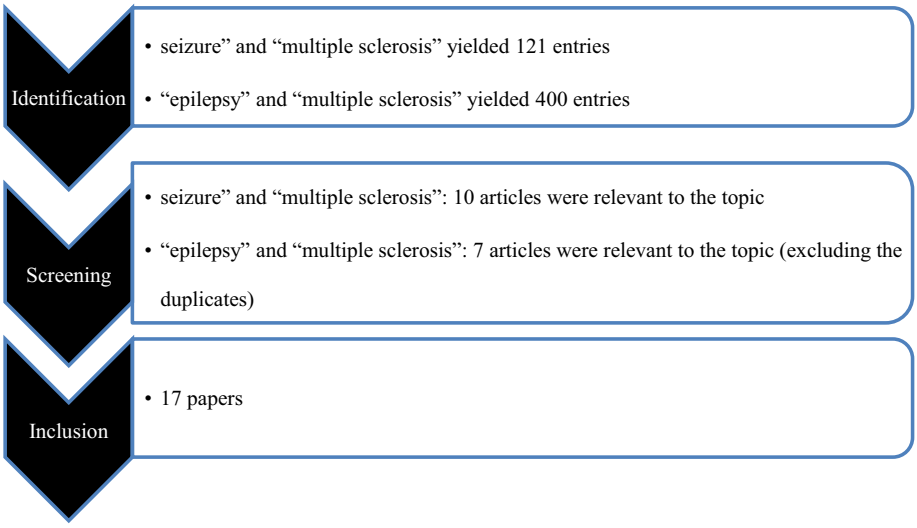


**Fig. 1.** The search and inclusion process.

may be performed to determine the cause of a new seizure. These may include electrolyte and liver function tests, toxicology screen, chemistry panel, and electrocardiography (ECG) if a patient is seen acutely after a seizure with no obvious cause. Lumbar puncture is performed only if an infection or malignancy is suspected [8].

### 3.2. Should occurrence of a single seizure trigger start of an antiepileptic medication in a patient with MS?

The new practical clinical definition of epilepsy proposed by the International League Against Epilepsy (ILAE) considers epilepsy to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome [9]. Epilepsy may be due to genetic causes (inherited trait to have seizures), brain tumors, infections (meningitis or encephalitis), brain trauma, stroke, developmental anomalies (e.g., cortical dysplasia), malformations (tuberous sclerosis, neurofibromatosis), vascular malformations (arteriovenous malformations), and other causes. Once an epilepsy syndrome [e.g., JME or TLE] has been diagnosed based on the clinical and other diagnostic information, an AED appropriate for that syndrome may be prescribed. After all, MS does not protect anyone against specific epilepsy syndromes (acquired or genetic), and a patient with MS may have comorbid epilepsy (e.g., JME, TLE, posttraumatic epilepsy, etc.) [8].

If a clear electroclinical epilepsy syndrome could not be diagnosed, the seizure might be attributed to MS itself. In one study, of 102 patients with MS and epileptic seizures, in 67 patients (66%), epileptic seizures could not be explained by any cause other than MS [10]. Seizures can occur at any stage during the course of MS; however, they are more common during the early stages of the disease [2]. The increased risk of seizures in patients with MS may be due to the effects of inflammation or glial reactions around the demyelinating lesions, or the direct effects of the demyelinating lesions [1,3,5]. Multiple sclerosis is not only a white matter disease, but may also affect gray matter in the cerebral cortex [3,11]. Increased number of both juxtacortical and cortical lesions in patients with MS and comorbid epilepsy has been reported [12,13].

In one recent study of the assessment of risk of epilepsy after a single seizure in patients with MS [14], the authors observed that the 10-year risk of epilepsy was 51.4% (95%CI: 44.0–58.9) for patients with MS and 41.3% (95%CI: 33.5–49.1) for controls. The risk was 46.1% (95% CI: 35.3–56.9) for patients with relapsing remitting MS (RRMS) and 60.7% (95% CI: 46.6–74.8) for patients with secondary progressive MS (SPMS). For patients with MS who experienced status epilepticus (SE), the 10-year risk of epilepsy was 85.9% (95%CI: 67.9–100) [13]. The recent ILAE clinical definition of epilepsy allows diagnosis of epilepsy after a single unprovoked seizure if the 10-year recurrence risk exceeds 60% [8]. Therefore, if a patient with RRMS experiences a seizure that could not be explained by any cause other than MS, starting a long-term AED regimen is not justified. These patients have a similar risk as controls of developing epilepsy after a single seizure [14]. However, a 46% risk over 10 years also needs to be considered in terms of impact on driving license and other social and vocational variables; some patients may choose to take an AED in this instance. This is a discussion that should be held with the patient, explaining the fact that they have RRMS and it does not alter the odds, and that most people will choose not to take treatment. In addition, if the seizure is considered to be a relapse of MS in a patient with RRMS (see question 9), one may want to prescribe an AED (e.g., lacosamide or levetiracetam; see Section 3.4) until the acute phase is over, often for 4–6 weeks (the authors' opinion). A provoked seizure associated with MS relapse is generally transient, often occurs as a single episode with good prognosis, and prolonged AED treatment is not recommended due to adverse effects of many AEDs [15,16]. If a patient with SPMS experiences a seizure that could not be explained by any cause other than MS, advantages and disadvantages of starting an AED should be discussed with the patient. Patients with SPMS could run a greater risk of subsequent epilepsy [14,17], but the risk does not significantly exceed the threshold specified by the ILAE [9,14]; however, the authors are in favor of starting an appropriate AED (long-term) for these patients. Patients with MS who experience SE, that could not be explained by any cause other than MS, have a high risk of subsequent epilepsy [14], that justifies the start of an appropriate AED (long-term). However, well-designed clinical trials are needed to provide more evidence for the above strategy (specifically, for the duration of therapy).

### 3.3. Should occurrences of more than one seizure (more than 24 h apart) trigger start of an antiepileptic medication in a patient with MS?

The evidence is lacking, but we suggest initiating AED treatment following the second seizure in patients with MS because of the risks associated with recurring seizures (e.g., injuries, SE, mortality, etc.) [18,19].

### 3.4. Which antiepileptic drugs (AEDs) are better options in patients with MS?

All patients with MS, who experience epileptic seizures that could not be explained by any cause other than MS, have focal epilepsy [3]; in other words, focal brain pathology in MS is the main cause of the comorbid epilepsy [3]. In two studies [20,21], it was observed that gray matter lesions in temporal lobes may underlie susceptibility to seizures in patients with MS. To answer to the question above, we should answer to a central question: "What is the evidence that the treatment for seizures in MS should be different from that in the treatment for other focal onset seizures?" The answer is that there is really a lack of high quality and robust evidence, but we can extrapolate from some evidence as follows.

Most patients with MS and epilepsy responded well to AED monotherapy in one study [3]. Some authors suggested that in provoked seizures associated with MS relapses prolonged AED treatment was not advised due to adverse effects of AEDs [22,23]. In one small study of AED utilization (often for neuropathic pain and paroxysmal symptoms), in a cohort of patients with MS [15], carbamazepine was prescribed in 36 patients, with adverse effects reported in 20 (56%) patients. Gabapentin was prescribed in 94 patients, with adverse effects reported in 16 (17%). Lamotrigine was prescribed in 22 patients, with adverse effects reported in 4 (18%) patients [15]. Therefore, adverse effect profile of AEDs is a significant determining factor in selection of an appropriate AED to treat seizure(s) in a patient with MS.

Drug interactions have been reported between AEDs, especially enzyme-inducing AEDs, and some medications used in MS. Carbamazepine, phenobarbital, primidone, and phenytoin may decrease plasma levels of cyclophosphamide, cyclosporine, dexamethasone, methotrexate, methylprednisolone, and prednisolone. Oxcarbazepine may decrease cyclosporine plasma levels. Methotrexate may decrease valproic acid plasma levels. No significant interactions have been reported between AEDs and disease-modifying drugs in MS [8,22].

In this context and considering all the above information, the choice of AEDs should be based upon the availability and tolerability of the medication. Patients with MS commonly have other neurological symptoms (e.g., neuropathic pain and paroxysmal demyelinating symptoms), and many AEDs have drug–disease interactions (e.g., gabapentin is also helpful for neuropathic pain and carbamazepine is helpful for paroxysmal demyelinating symptoms). In addition, consideration of possible adverse effects of AEDs in the context of the patient's symptoms (e.g., cerebellar symptoms, cognitive dysfunction, psychiatric problems, etc.) should guide the choice of the AEDs [24]. We favor three AEDs for use in patients with MS: lamotrigine, levetiracetam, and lacosamide. Lamotrigine is widely available and inexpensive, has a favorable adverse effect profile,

and no significant drug interactions with MS medications, but its slow titration schedule may hamper its use [8]. Levetiracetam has no drug interactions with MS medications, has oral and intravenous formulations available (for use in emergency situations and rapid titration), and has a reasonable adverse drug profile. However, in patients with suicidal ideation, depression, and behavioral problems (e.g., aggressive behavior), it is not an optimal option (considering the fact that depression is common in patients with MS) [8,25]. In addition, it is more expensive than lamotrigine. Lacosamide has no drug interactions with MS medications, has oral and intravenous formulations available (for use in emergency situations and rapid titration), and has a reasonable adverse drug profile [8]. However, it is not widely available worldwide and is much more expensive than both levetiracetam and lamotrigine. Gabapentin is widely available and less expensive than levetiracetam and lacosamide, has a favorable adverse effect profile, and no significant drug interactions with MS medications, but is less efficacious than other agents [23]. In a comparison study, lamotrigine had the same efficacy as carbamazepine with regard to seizure control for focal seizures, and both drugs were superior to oxcarbazepine, which had similar efficacy as topiramate. Gabapentin had the least efficacy compared with the others. With respect to adverse effects and tolerability, lamotrigine was better than gabapentin; gabapentin was better than oxcarbazepine, and oxcarbazepine was better than carbamazepine and topiramate. With regard to time to treatment failure (considering both efficacy and tolerability), lamotrigine was the best; oxcarbazepine and carbamazepine were next, and they were better than either topiramate or gabapentin for focal epilepsies [23]. In conclusion, selection of an AED should be based on the patient's profile (e.g., age, sex, medical and psychiatric comorbidities, comedications, etc.), adverse effects of the treatment, cost, and shared decision making with the patient and the caregivers.

### *3.5. How long should the patients continue taking their AEDs, if they started to do so?*

There is no good quality data to answer to this question properly. While some authors suggested that provoked seizures associated with MS relapses were transient or occurred as single episodes with good prognosis, and prolonged AED treatment was not advised [3,15], other authors have demonstrated poor epilepsy prognosis in patients with MS who had chronic epilepsy and SE [22]. As for SE, many patients with MS and epilepsy develop recurrent seizures after their first epileptic seizure [22,24,26]. One possible explanation for this controversy is that the authors who reported a good prognosis did not follow the strategy that we have described above for initiation of AEDs; they might have started AEDs even in patients with RRMS and a single seizure. Considering the fact that evidence does not exist to support any recommendations, we suggest if in a patient with MS the treating physician decided to start an AED (e.g., lacosamide, lamotrigine, or levetiracetam; based on the above recommendations), they should consider long-term therapy (at least 2 years) with the drug. However, if the seizure is considered to be a relapse of MS in a patient with RRMS, one may want to prescribe an AED (e.g., lacosamide or levetiracetam) until the acute phase is over in order to minimize the risk of further seizures or SE, often for 4–6 weeks (the authors' opinion).

### *3.6. Is there a correlation between MS treatments and occurrence of epileptic seizures?*

Although, increased seizure occurrence with many treatment options for patients with MS has been reported, in a large study of 5041 patients with MS [10], the authors found no correlation between MS treatments, in particular interferon-b, and occurrence of epileptic seizures. This is consistent with the literature, despite some reports of lowering of seizure threshold by some MS treatments [10,26]. Baclofen and aminopyridines have been associated with significantly increased rate of seizures in patients with MS [26]. Dalfampridine extended release is contraindicated in patients with history of seizure(s) [27]. Frequent and severe seizures (e.g., SE) have been reported in patients with natalizumab-associated progressive multifocal leukoencephalopathy (PML) and one group recommended preventative AED treatment in these patients [28]. Fingolimod has shown to have neuroprotective and antiinflammatory effects, possibly decreasing seizures, in an animal study [29].

### *3.7. Should occurrence of any seizure trigger performing a brain MRI in a patient with MS?*

A seizure in a patient with MS could be due to one of the following reasons: an acute symptomatic seizure associated with a new MS plaque; a seizure associated with an old plaque, which has a high risk of seizure recurrence; and a seizure due to a comorbid epilepsy syndrome, among other reasons [1,2,10]. In all patients with MS, who have their first seizure, brain MRI studies with epilepsy protocol and also with MS protocol are indicated. Recurrence of the seizure (i.e., the second seizure) should trigger performing an MS protocol brain MRI in all patients to investigate the reason (e.g., a new plaque). Recurrence of more seizures may necessitate performing an MS protocol brain MRI if the seizure could not be reliably attributed to an epilepsy syndrome (e.g., a typical focal seizure with impaired awareness in TLE with known MTS).

### *3.8. Should occurrence of any seizure trigger start of immunomodulatory therapy in a patient with MRI compatible with MS?*

When a seizure occurs in a patient without any other clinical event in previous time and brain MRI demonstrate multiple hyperintense lesions compatible with MS, three different scenarios could be contemplated:

a. Based on the clinical history, semiology, EEG, and brain MRI, the seizure could be confidently attributed to an epilepsy syndrome (e.g., JME, TLE, etc.); there is no need to start immunomodulatory therapy in this situation (authors' opinion). However, this patient should be considered as radiologically isolated syndrome (RIS), and the patient should be followed and managed according to RIS management protocols.
b. Based on the clinical history, semiology, EEG, and brain MRI, the seizure could be confidently attributed to an MS plaque; seizure could be considered as an exacerbation or first manifestation of a demyelinating event and immunomodulatory therapy is recommended in this situation, but there is no need for methylprednisolone pulse therapy for a single seizure (see question 11) (authors' opinion).
c. Based on the clinical history, semiology, EEG, and brain MRI, the seizure could not be confidently attributed to either an epilepsy syndrome or an MS plaque; since cooccurrence of epilepsy syndromes and MS is not common (the prevalence of epilepsy in patients with MS is about 4 times that of the general population; therefore, one might reasonably expect that only about one fourth of the association to be cooccurrence and the rest to be a linked pathology), we suggest to consider seizure as a manifestation of MS and advise to start immunomodulatory therapy in this situation (authors' opinion). However, we have to mention that we held a robust discussion on this issue and reached to this opinion by consensus; others may hold a different opinion; for example, one of the reviewers of this paper suggested that a patient presenting with a single seizure who has MRI findings suggestive of demyelination plaque should be investigated and followed up further to see whether they meet the diagnostic criteria for MS over time.

### *3.9. Should we consider a seizure as a relapse in a patient with MS?*

A seizure is as a paroxysmal event and should be treated as so. In patients with MS, seizures may be due to the effects of inflammation or

glial reactions around the demyelinating lesions, or the direct effects of the demyelinating lesions [1,3,5]. In addition, MS is not only a white matter disease, but may also affect gray matter in the cerebral cortex [3,11–13]. If based on the clinical history, semiology, and EEG, the seizure could be confidently attributed to a new MS plaque (a new T2 lesion or a gadolinium enhancing lesion) on a recent MRI (or the seizure could not be explained by any causes other than this plaque), this would be considered as a relapse of MS (authors' opinion).

### *3.10. If a patient with MS develops a seizure that is compatible with a relapse, should we escalate the MS therapeutic regimen?*

Most available data on this issue provide recommendations on typical attacks of MS, and the number of patients with seizures was not enough to draw a firm conclusion. However, considering the existing protocols [30,31], we suggest if there is only one new T2 lesion on a recent brain MRI, there is no need to escalate the MS therapeutic regimen, and if there are two or more new lesions, we advise to escalate the MS therapeutic regimen.

### *3.11. How should we manage status epilepticus in a patient with MS?*

Status epilepticus or serial seizures in a patient with MS could be due to any of the following reasons (among other etiologies in a general population): SE associated with comorbid epilepsy; SE associated with MS relapse; and SE associated with autoimmune epilepsy [16,22,24]. In any patient with SE or serial seizures, AED treatment should be initiated immediately, similar to the condition attributed to other causes. If no response is obtained soon (after the first and the second line of therapies for SE or serial seizures; the authors' opinion), antiinflammatory drugs should be initiated [16,22,24]. We propose starting steroid (methylprednisolone pulse therapy) and escalation of the MS treatment strategy in these patients. In patients with MS and SE, long-term AED therapy should be considered, as the risk of seizure recurrence is high [14]. In all patients a comprehensive investigation including a brain MRI, AED drug levels (if already taking some), and other tests, as clinically indicated, should be performed.

## 4. Conclusion

Cooccurrence of a seizure in a patient with MS may complicate the management process. In this review, we tried to provide answers to the frequently asked questions considering the best available scientific evidence and also the expert opinion.

## Conflicts of interest

Ali A. Asadi-Pooya, M.D., consultant: Cerebral Therapeutics, LLC, and UCB Pharma; Honorarium: Hospital Physician Board Review Manual, Cobel Daruo; Royalty: Oxford University Press (Book publication); MAS: has received educational, research grants, lecture honorarium, travel supports to attend scientific meetings from Biogen-Idec, Merck-Serono, Bayer-Schering-Novartis, Cinnagen, Osveh, Zistdaru, Zahravi, Nano-Alvand, and Genzyme.

SMB: has received lecture honorarium, travel supports to attend scientific meetings from Biogen-Idec, Merck-Serono, Novartis, Cinnagen, Osveh, Zistdaru, Zahravi, Nano-Alvand, and Genzyme. Others report no conflicts of interest.

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