Antiseizure Medication Withdrawal in Seizure-Free Patients: What is New for the Pediatrician?

ARPITA GUPTA, KUNAL KUMAR

From Department of Pediatrics, Maulana Azad Medical College & Associated Lok Nayak Hospital, New Delhi.
Correspondence to: Dr Kunal Kumar, Department of Pediatrics, Maulana Azad Medical College, Associated Lok Nayak Hospital, Jawahar Lal Nehru Marg, New Delhi 110 002.
kumarkunal1993@gmail.com

The American Academy of Neurology (AAN) has recently updated its practise advisory on antiseizure medication withdrawal. The recommendations have been formulated for pediatric as well as adult epilepsy, with emphasis on the risk factors for seizure relapse, occurrence of status epilepticus or death on drug withdrawal, and effect on quality of life in both age groups. We herein list the important aspects of the updated recommendations in pediatric epilepsy for the benefit of the general pediatricians. The full update is available at the AAN website.

Keywords: *American Academy of Neurology, Epilepsy, International League Against Epilepsy, Italian League Against Epilepsy.*

After a patient with epilepsy has initiated an anti-seizure medication (ASM) and achieved a sustained period of seizure freedom, the decision regarding continuation of therapy indeterminately, can be perplexing. Stopping ASMs is routinely practiced in patients who have epilepsy in remission. However, in literature there are no established guidelines that can lead to the constant application of a universally accepted withdrawal protocol in adults as well as children.

With obvious reason of drug associated side effects (behavioral, cognitive and chronic side effects) and the possibility of achieving 65-85 % of remission with ASM therapy, it is prudent to consider for ASM withdrawal. However, as the risk of relapse is around 23.7%, the decision of ASM withdrawal becomes controversial even in individuals with well controlled epilepsy [1,2]. The Akershus study done to assess effect of ASM withdrawal on cognitive function, seizure relapse and health related quality of life in adults, showed significant improvement in neuropsychological performance at 12 months of stopping ASM with relative risk of seizure relapse of 2.46, compared to those continuing the therapy [3].

The physician contemplating ASM withdrawal is faced with two important considerations i.e., time of withdrawal and mode of withdrawal. American Academy of Neurology (AAN), in 1996, recommended two to five years of seizure-free period before stopping ASMs [4]; however, the minimum period of seizure freedom has been indicated to be two years according to the recent literature [5]. There is no consensus on the mode of withdrawal, and the drug tapering can range from slow (spread over up to 2 years) to rapid withdrawal (within 3 to 6 months). Slow tapering has also been defined as drug withdrawn over more than three months, and rapid tapering as, drug withdrawn within three months [6]. A recent Cochrane review [6] did not find a reliable agreement on the optimal rate of drug tapering based on the results of two randomized control trials done in pediatric population.

Another important point of contemplation in drug withdrawal is monotherapy versus polytherapy. Studies have revealed a higher relapse rate in patients receiving polytherapy as compared to those receiving mono-therapy after stopping ASMs [7]. However, the interplay with other factors in patients with polytherapy e.g., higher age at seizure onset and longer duration of epilepsy before treatment, may contribute to recurrence. Therefore, a practical approach would be slow and steady withdrawal in patients receiving polytherapy.

In order to decide suitability for ASMs withdrawal, it is necessary to consider factors related to patients' profile, epilepsy characteristics and specific pharma-cological treatments, which may predict the chances for seizure recurrence after stopping ASMs [7-10] **(Table I)**.

Majority of the published guidelines lack a universal protocol on ASM withdrawal after a period of seizure remission. It has been mentioned in various guidelines that neuroimaging and electroencephalogram play an important role in identifying the seizure etiology and aid in prognostication for future relapse. Access to these

Table I Prognostic Factors Associated With Risk of Seizure Reccurrence

Increased risk	*No increased risk*
Patient-related factors (neuropsychiatric conditions) [8-10]	–
Abnormal neurological examination Global developmental delay Intellectual disability History of neonatal seizures Late childhood/adolescent onset of seizure	
Factors related to epilepsy [5,8,10]	
Symptomatic generalized and partial epilepsies Juvenile myoclonic epilepsies Juvenile absence epilepsies Presence of status epilepticus Epileptiform EEG pattern before or after drug withdrawal EEG changes: Focal slow abnormalities or paroxysmal abnormalities	Symptomatic, cryptogenic or idiopathic epilepsy, Benign childhood epilepsy with centrotemporal spikes, Benign infantile seizures etc.
Factors related to therapy [7,10]	
Polytherapy needed for seizure control	–

modalities may modify the clinician's decision regarding the ASM withdrawal, even in a well-controlled epilepsy.

American Academy of Neurology (AAN) has recently updated its recommendations on ASM withdrawal [11]. The recommendations are listed separately for children and adults (≥18 years), and focal seizures are distinguished from generalized seizures. The outcome measures considered in formulation of recommendations in patients who withdrew ASM after 12 months or more of seizure remission vs those who did not, included *i*) seizure relapse among those with electroclinical syndromes, epilepsy surgeries; *ii*) Risk factors for seizure recurrence in terms of Odds Ratio; *iii*) Quality of life data; *iv*) Occurrence of status epilepticus; and *v*) Mortality.

We, herein, list the major recommendations on ASM withdrawal and discuss some of the important changes of the revised AAN practice advisory [11] along with the recommendations from Italian League against Epilepsy (LICE), 2013 [5] (**Table II**).

AAN, 2021 RECOMMENDATIONS

The recommendations applicable to pediatric population are discussed here.

Risk of Seizure Recurrence

The new practice advisory states that there is no significant difference in seizure recurrence rate in children who taper ASMs at 2 years vs 4 years (Level B); however, there is insufficient evidence to comment on risk of seizure recurrence in children who taper ASMs at 18 vs 24 months. Moreover, different electroclinical syndrome have different set of characteristics (specific age of onset, semiology, EEG changes) that would influence seizure relapse rate. Thus, natural course of a specific electroclinical syndrome must be known to the pediatrician as it may influence the seizure reoccurrence rate in individual syndromes (Level A). Insufficient evidence was found to support or refute that a variety of risk factors (age, sex, type of seizure, intellectual disability, perinatal insult etc.) may predict the possibility of recurrence. Abnormal EEG before ASM withdrawal and EEG with interictal epileptiform discharges is associated with likely increased rate of seizure recurrence. There is insufficient evidence to suggest the type of EEG required (sleep deprived), or length of EEG needed to predict seizure recurrence risk.

Risk of Status Epilepticus

The advisory states that ASM withdrawal possibly may not increase the risk of status epilepticus in adults; however, there is insufficient data on children. Though the evidence is low, recurrent seizures may put children at risk of status epilepticus and death, and this aspect of ASM withdrawal should always be discussed with the patient's family. (Level B**)**

Effect on Quality of Life

There is scarcity of data on quality of life (QOL) in children with ASM usage, and therefore, it is suggested that the other contributors to QOL should be taken into consideration while making a decision regarding ASM withdrawal in children. (Level B)

Speed of Medication Withdrawal

According to the new practice advisory, children who are seizure free for at least 18-24 months, withdrawal of ASMs at

Table II Summary of Recommendation for Antiseizure Medication (ASM) Withdrawal in Pediatric Patients

Italian league Against Epilepsy, 2013 [5]	*American Academy of Neurology, 2021 [11]*
Duration of seizure free period	
At least 2 years of seizure freedom (Level B).	2 years of seizure freedom (Level B).
Risk factors for seizure recurrence in epilepsy type	
Benign epilepsy with centrotemporal spikes and most idiopathic generalized epilepsies are associated with favorable prognosis.	
The presence of partial seizures should not be considered per se a risk factor for relapse, in absence of other relevant seizure predictors (abnormal EEG and/or documented etiology) (Level B).	
Female sex, family history of epilepsy, history of febrile seizures, disease length/severity, and number and type of drugs taken should not influence the decision to stop treatment (level C)	
Prolonged duration of active disease before and during treatment and high seizure frequency per say should not stop ASM withdrawal (Level C).	-
Electro-clinical syndrome	
Specific epileptiform EEG should preclude the decision of ASM withdrawal (Level B).	Clinicians must know about the natural history of the specific electroclinical syndrome when counselling about ASM withdrawal (Level A).
Abnormal EEG at ASM withdrawal	
A patient with abnormal EEG (with or without epileptiform activity) at the time of ASM withdrawal should be informed of an increased risk of relapse but should not be encouraged to withhold treatment if abnormal EEG is the only negative prognostic predictor (Level B).	In children seizure-free for at least 18–24 mo, an EEG should be ordered before attempting ASM withdrawal (Level B). Interictal epileptiform activity on EEG possibly increases the risk of seizure recurrence in children (low confidence). There is insufficient evidence to suggest the type and length of EEG required to predict the seizure recurrence risk.
Documented seizure etiology including mental retardation and perinatal insult	
A patient with a documented seizure etiology should be informed of an increased risk of relapse but should not be encouraged to withhold treatment if this is the only negative prognostic predictor. (Level B).	Insufficient evidence to refute or support.
Risk of status epilepticus/SUDEP after ASM withdrawal	
No recommendation	Clinicians should counsel that recurrent seizures may put children at risk for status epilepticus and death; although, existing data do not suggest an increased risk of status epilepticus or death after ASM withdrawal (Level B).
Rate of ASM withdrawal	
Slow discontinuation of AEDs should be encouraged and the duration of the tapering period should be tailored to the patient's needs and preferences (Level B).	ASM withdrawal should be offered, at a rate no faster than 25% every 10–14 d (Level B). There is a small risk to treatment non-responsiveness if seizure reoccurs during or after ASM withdrawal (Level B).
Follow up after ASM withdrawal	
A patient discontinuing treatment for seizure freedom should be followed for no less than 2 y (Level B).	No recommendation

SUDEP: sudden unexpected death in epilepsy.

a rate of 25% every 10 days to 2 weeks is not significantly different in increasing the risk of seizure recurrence than withdrawal at a rate of 25% every 2 months. Therefore, ASM may be withdrawn rapidly at the rate of 25% every 10-14 days (Level B).

These new guidelines lacks specific recommen-dations on commonly seen pediatric epileptic conditions (meningitis, neurocysticercosis, post trauma epilepsy etc.) in developing countries like India.

CONCLUSION

The decision to withdraw ASM in seizure-free patients is a difficult aspect of pediatric epilepsy management as parental anxiety and presence of other risk factors make it more challenging. The new AAN practice advisory is likely to aid in making a decision regarding the ASM withdrawal in seizure-free patients. High-quality studies are required to further investigate the unexplored parameters and address the following questions: *i*) should different seizure free period be considered for ASM withdrawal? *ii*) should epilepsy syndrome with specific character and seizure morphology preclude or favor ASM withdrawal? *iii*) should any of specific EEG or MRI brain findings and genetic testing add to the prognosis for seizure recurrence?

Funding: None; *Competing interests*: None stated.

REFRENCES

1. Shorvon SD, Goodridge DMG. Longitudinal cohort studies of the prognosis of epilepsy: Contribution of the national general practice study of epilepsy and other studies. Brain. 2013;136:3497-510.
2. Incecik F, Herguner OM, Altunbasak S, et al. Risk of recurrence after discontinuation of antiepileptic drug therapy in children with epilepsy. J Pediatr Neurosci. 2014;9:100-4.
3. Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: A randomized, double-blind study (Akershus Study). Epilepsia. 2008;49:455-63.
4. Practice parameter: A Guideline for Discontinuing Antiepileptic Drugs in Seizure-Free Patients-Summary Statement. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 1996;47:600-2.
5. Beghi E, Giussani G, Grosso S, et al. Withdrawal of Antiepileptic Drugs: Guidelines of the Italian League Against Epilepsy. Epilepsia. 2013;54:2-12.
6. Ayuga Loro F, Gisbert Tijeras E, Brigo F. Rapid versus slow withdrawal of antiepileptic drugs. Cochrane Database Syst Rev. 2020;1:CD005003.
7. Wang Y, Xia L, Li R, et al. Comparison of long-term outcomes of monotherapy and polytherapy in seizure-free patients with epilepsy following antiseizure medication withdrawal. Front Neurol. 2021;12:669703.
8. Ramos-Lizana J, Aguirre-Rodríguez J, Aguilera-López P, Cassinello-García E. Recurrence risk after withdrawal of antiepileptic drugs in children with epilepsy: A prospective study. Eur J Paediatr Neurol. 2010;14:116-24.
9. Olmez A, Arslan U, Turanli G, Aysun S. Risk of recurrence after drug withdrawal in childhood epilepsy. Seizure. 2009;18:251-6.
10. Vurucu S, Saldir M, Unay B, Akin R. Determination of risk factors associated with seizure relapse after antiepileptic drug withdrawal. Cent Eur J Med. 2010;5:251-56.
11. Gloss D, Pargeon K, Pack A, et al. AAN Guideline Sub committee. Antiseizure Medication Withdrawal in Seizure-Free Patients: Practice Advisory Update Summary: Report of the AAN Guideline Subcommittee. Neurology. 2021;97:1072-81.