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EDITORIAL

How can we overcome neuropsychological adverse effects of antiepileptic drugs?

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Antiepileptic pharmacotherapy can very well have positive effects on cognition and behavior via control of seizures and interictal epileptic discharges, and/or via improvements of mood and psychiatric comorbidity. However, more frequent and less appreciated are adverse effects of antiepileptic drugs (AEDs), causing new cognitive or behavioral problems or aggravating preexistent neuropsychological impairments [1,2].

As it stands, the risk of side effects increases with a higher drug load, i.e. with higher doses and serum levels, and with each additional drug in polytherapy [3–6]. Another proposed risk factor is the speed of uptitration [7]. While the aforementioned effects are more nonspecific, the neuropsychological side effect profiles can vary among the different antiepileptic agents (Table 1), in terms of qualitative (i.e. the profile and number of affected domains) and quantitative (i.e. the magnitude of affection) disparities.

The cognitive domain of attention and executive functions is most frequently affected by AEDs [8] (Table 1). Drug-induced deteriorations of language, memory, and further higher brain functions can manifest as well, but in this regard it is important to consider that these impairments most often cooccur with or are mediated by the affection of the executive functions (e.g. a seemingly verbal comprehension deficit as the consequence of a reduced working memory capacity). In addition, they may be secondarily caused by deficits of upstream basic functions such as attention (e.g. concentration deficits can compromise memory encoding).

Adverse cognitive and behavioral side effects of AEDs are mostly reversible and may resolve after complete withdrawal or even after dose reduction. Important exceptions are the potentially lifelong consequences of in utero exposition to AEDs or of antiepileptic pharmacotherapy for the cognitive development in children with epilepsy [9].

The relevance of adverse neuropsychological effects of AEDs for patients is high since cognitive and psychiatric side effects represent the least tolerated class of side effects [10]. Moreover, neuropsychological side effects may negatively affect daily functioning and are known to reduce quality of life and the long-term retention of AEDs [11]. Therefore, the central and clinically highly relevant question is how to overcome such neuropsychological adverse effects of AEDs.

First of all, the earlier stated risk factors are fortunately under direct control of the treating neurologist who can minimize the risk of adverse neuropsychological side effects (1) by slow titration rates (when feasible), (2) by choosing lower but still efficacious target doses, (3) by considering pharmacokinetics (e.g. selecting controlled-release AEDs to prevent high serum peak levels), (4) by restricting polytherapy to few compatible AEDs with consideration of pharmacodynamic interactions, and (5) by selecting and combining AEDs according to their cognitive and behavioral profile (Table 1).

The strategies to address and overcome adverse neuropsychological side effects of AEDs are summarized in Table 2.

Despite these attempts and also in the light of possible idiosyncratic drug effects, the occurrence of neuropsychological side effects can never be ruled out and thus they need to be addressed in daily clinical practice. First, we would recommend to increase the awareness by informing the patient and his/her relatives about the potential cognitive side effects of a newly prescribed AED. This may increase the acceptance of actually occurring side effects and may lead to earlier follow-up visits that give the opportunity to alleviate the side effects by the outlined countermeasures.

Furthermore, we would recommend a routine cognitive monitoring along with relevant changes of an individual antiepileptic treatment. A valid evaluation of treatment effects requires at least two assessments, a baseline before modification of the medication and a follow-up under stable conditions after the final target dose has been attained. Meanwhile, some subjective self-rating scales have been devised that explicitly assess side effects including cognitive and behavioral impairments [8]. Although there is evidence that a systematic screening with one of those scales can guide treatment decisions to achieve a clear reduction of adverse AED effects [12], it is important to underscore that subjective measures cannot substitute for an objective neuropsychological assessment [8]. Sometimes, patients are not even aware of significant cognitive side effects, either because of preexistent neuropsychological impairments, reduced everyday cognitive demands or as consequence of cognitive side effects themselves (anosognostic effects or indolence) or not recognizing changes due to slow titration. Finally, a very robust finding is that subjective cognitive complaints rather reflect actual mood problems than

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Table 1. Hierarchy of AEDs according to their known effects on cognition (assessed via objective tests) and behavior.

	Attention and executive functions	Memory	Language	Behavior and mood[a]
Lamotrigine	0/↑	0	0	(↓)/↑
Lacosamide	0			0
Levetiracetam	0/↑	0/(↑)		↓/(↑)
Oxcarbazepine	(↓)/(↑)	0		(↑)
Rufinamide	0			
Eslicarbazepine acetate	(↓)	0		
Vigabatrin	0	0	0	↓
Perampanel	0	0		↓
Stiripentol				↓
Pregabalin	0	(↓)	0	↓/↑
Valproic acid	↓	0/(↓)	0	↑
Tiagabine	0	0/(↓)	0	↓
Ethosuximide	(↓)			↓
Felbamate	(↓)			↓
Gabapentin	0/(↓)	0/(↓)	0	(↓)/↑
Clobazam	↓	0		(↓)/↑
Carbamazepine	↓	↓	(↓)	↑
Zonisamide	(↓)	(↓)	(↓)	↓
Phenobarbital/ primidone	↓	(↓)		↓
Phenytoin	↓	↓		↓/(↑)
Topiramate	↓	↓	↓	↓/(↑)

↓: negative effect; ↑: positive effect; (): possible effect; 0: no effect; blank: no sufficient evidence; AED: antiepileptic drug.
[a]For details see [1].
No sufficient information on neuropsychological side effects was available for brivaracetam, retigabine, and sultiame.

objective test performance. Therefore, a brief cognitive screening comprising both objective and subjective measures would be ideal. The employed objective neuropsychological measures should be chosen according to their sensitivity to AED effects, and they should be time-economic and suitable for reassessment. An overview of available and suitable measures, further methodological considerations, and potential pitfalls with regard to a cognitive monitoring of individual antiepileptic pharmacotherapies has been outlined in another publication [8].

Another suggested approach would be to counteract neuropsychological side effects of an efficacious antiepileptic treatment with cognition-enhancing pharmacological agents, i.e. nootropics. However, in the light of the earlier stated negative cognitive effect of an increasing total drug load and potential adverse drug interactions, this rather seems to be an option of last resort, also with regard to economic considerations.

Another idea of last resort could be to address specific cognitive side effects of an efficacious antiepileptic treatment with means of cognitive training. To our knowledge, this has not been done previously.

Finally, the development and introduction of new AEDs with novel mechanisms of actions (e.g. cannabidiol and galanin) that may have neutral or even positive effects on cognition and behavior would be highly appreciated.

Expert opinion

The medical treatment of epilepsy strives for early seizure control and a concomitant improvement of quality of life. Both efficacy and tolerability determine the success of an individual antiepileptic pharmacotherapy. The risk of neuropsychological side effects largely depends on treatment decisions.

In this regard, keeping the drug load as low as clinically reasonable seems to be one decisive factor. This also implies restricting the number of concurrent AEDs, since each

Table 2. Strategies to address and overcome adverse neuropsychological side effects of antiepileptic drugs (AEDs).

Strategy	Expert opinion
Treatment decisions	
• Selecting AEDs with superior neuropsychological side effect profiles	The neuropsychological side effect profiles can vary among the different antiepileptic agents. Choosing AEDs according to their cognitive and behavioral risk (and benefit) profile is one major factor to overcome neuropsychological side effects.
○ Also considering positive effects on mood and behavior	
• Restricting polytherapy to few compatible AEDs	Keeping the total drug load low is another decisive factor. With each additional drug in polytherapy, objective cognitive performance may decrease, especially with regard to attention and executive functions.
○ Avoiding adverse interactions	
• Striving for low efficacious target doses and blood serum levels	Again, keeping the drug load low is an important factor. However, not all AEDs exert a dose-dependent impact on cognition and behavior. Individual susceptibilities may lead to side effects even with low doses.
• Employing careful titration rates when clinically feasible	Subjective complaints may become less likely, because this approach may lead to a poorer recognition of actual side effects. There is no evidence that slower uptitration will prevent any objective neuropsychological side effect.
• Considering pharmacokinetics	Controlled-release variants of an antiepileptic agent may prevent high serum peak levels and associated cognitive side effects.
• Individual balancing of the degree of seizure control and AED-related side effects	Especially necessary if complete seizure control cannot be achieved with acceptable side effects. The aim of this balancing is a constellation that provides the highest possible quality of life for the individual patient.
• Prescribing cognition-enhancing pharmacological agents (nootropics) to counteract side effects	An option of last resort in case of an efficacious antiepileptic treatment with unacceptable side effects, not compatible with keeping the total drug load low.
Non-pharmacological strategies	
• Informing the patient and his/her relatives about potential side effects of a newly prescribed AED	A higher awareness of cognitive side effects may increase the acceptance of actually occurring side effects and may lead to earlier follow-up visits that give the opportunity for countermeasures.
• Detection and monitoring of neuropsychological AED effects	A systematic screening before and after relevant treatment changes is highly recommended for the reliable detection of neuropsychological side effects. This information can guide treatment decisions to achieve a reduction of adverse AED effects.
○ Employing valid objective and subjective measures	
• Cognitive training to address specific cognitive side effects	An option of last resort in case of an efficacious antiepileptic treatment with unacceptable side effects. No evidence available.

additional drug in polytherapy does matter [4,6]. If seizures cannot be fully controlled, two important questions arise: (1) how many AEDs are needed to achieve a significant clinical improvement and (2) whether the same degree of seizure control can be achieved with less AEDs and side effects [13].

A further major factor is the choice of drugs with low risks for cognition and behavior. From a neuropsychological perspective, lamotrigine, levetiracetam, and lacosamide appear to have preferable cognitive profiles whereas topiramate, phenytoin, phenobarbital, and presumably also zonisamide would represent the last choice with regard to objective cognitive side effects (Table 1). However, beyond the suggested hierarchy presented in Table 1, an explicit ranking according to the objective cognitive risks of the AEDs (in-between) is not available. A meta-analytic approach to disclose such a hierarchy is complicated by heterogeneous study designs and the use of a large variety of different neuropsychological outcome measures among the many cognitive AED-studies. Therefore, new studies based on direct head-to-head comparisons of various AEDs with the same valid objective assessment tools would be highly appreciated. Meanwhile and in addition to Table 1, a preliminary ranking of established AEDs according to the incidence of intolerable cognitive side effects can be taken from the analysis of the large Columbia Antiepileptic Drug Database comprising almost 3000 patients [14]. However, the data are based on medical records, not on objective cognitive assessments.

Another conceivable selection criterion for AEDs could be their neuroprotective potential that might have a positive effect on cognitive performance in the long run. However, evidence is sparse and some AEDs with demonstrated neuroprotective properties can induce inacceptable cognitive side effects.

It is important to emphasize that neuropsychological side effects of specific AEDs may vary across patients due to individual susceptibilities (idiosyncratic effects) and/or reserve capacities (resilience factors). So an AED with a preferable cognitive profile according to available studies (that are mostly based on group analyses) may exert a significant negative effect on a minority of patients. The opposite pattern is also possible, i.e. an unaffected cognitive status under AEDs with a high risk of cognitive side effects.

Therefore, even if specific AEDs or drug combinations have known negative side effects, there are always patients who tolerate the chosen treatment. Thus, before one refrains from using potentially very efficacious AEDs with high risks of neuropsychological side effects, the treatment should be monitored instead by repeated application of neuropsychological screening tools [15].

Ideally, a routine valid and time-economic neuropsychological monitoring along with all relevant treatment changes would be desirable [8].

The selection of AEDs would be highly facilitated if valid biomarkers (such as genetic testing or pharmaco-fMRI) would be discovered that reliably predict the individual efficacy and (cognitive) tolerability, but this is all still up in the air.

Finally, if complete seizure control cannot be achieved with acceptable side effects, an individual balancing of the degree of seizure control and AED-related side effects becomes necessary striving for a constellation that provides the highest possible quality of life [10].

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