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Commentary

Playing soft, with tough players: Controlling adverse drug effects while tuning antiepileptic drugs, epilepsy & the person

Accumulated evidence over the past decades clearly indicates that successful treatment of epilepsy is based on antiepileptic drugs (AEDs). To be considered successful, it has to be an optimally weighted treatment when the efficacy, safety/tolerability and costs of one or more AEDs are calculated individually for each person with epilepsy. Dozens of AEDs were introduced with various positive neuropsychiatric effects and documented effectiveness in epilepsy[1,2], but also with various adverse effects related to cognition, emotions, behaviour and somatic functions[2-4]. Epilepsy poses a substantial economic burden for health systems, individuals and their families, with AEDs being one of the major sources of expenditure[5], including their adverse effects[6].

In the study by Joshi *et al*[7] in this issue, adverse effects, AEDs load, seizure frequency and biochemical alterations were found to be associated with the total number of AEDs prescribed. This study, although limited due to its cross-sectional design, showed us that various adverse effects were associated with number of AEDs rather than frequency of epileptic seizures. It also showed that polytherapy with a combination of three or more AEDs was probably associated with higher adverse effects and lower seizure control compared to both monotherapy and combination of two AEDs. However, no marked relationship of biochemical parameters with different AED regimens was observed. Taken together, the results of this study closely resemble data from randomized controlled trials primarily showing that adults taking AEDs mostly report more than one AED-related adverse effect, with even 83 per cent of people with epilepsy treated with polytherapy reporting two or more adverse effects[3,8,9]. In addition, the results agreed with a recent study that documented a considerable adverse effect of a higher drug load on cognition[4]. However, one previous cross-sectional study showed that adverse effects did not differ between monotherapy and polytherapy and did not correlate with AED load, what was considered to be a result of physicians' intervention in individualizing treatment regimens[10].

Here, I would like to reflect upon the ways in which Joshi *et al*[7] could extend the study in future projects. First, the outcomes of the association of adverse effects and AEDs are shaped throughout the individualized treatment regimen, which should be studied in a follow up approach considering a network of the various factors. Thus, it would be important to evaluate various individual characteristics (*e.g.*, behavioural, cognitive or social), which might be differently linked to adverse effects in monotherapy and polytherapy. The authors studied age, gender and biochemical parameters and the results were more or less the same to the previously reported ones. Second, an important aspect to include is how specific neurocognitive performances in an individual are linked to adverse effects of a particular AED. Different positive and negative cognitive and behavioural effects for AEDs were documented over the past two decades[11], and studying prospectively cognitive functions in relations to adverse effects on individual levels would be important. Third, it was found that individual AEDs independently predicted some specific adverse effects, but not overall high adverse effect burden[3]. Thus, it would be interesting to study how two or more AEDs predict adverse effects in an individual, as well as their interactions in the case of polytherapy. Fourth, studying the severity of epilepsy beyond a simple measure of seizure frequency as linked to individual adverse effects is another necessary consideration. Recent data showed that the excitability levels in neural tissue mattered most when quantifying the outcomes of AEDs[12]. Finally, in the constellation of these various factors, it would be relevant to the study to which extent monotherapy and polytherapy influence the everyday living, whereas adverse effects could negatively affect the quality of life in epilepsy[13,14].

The second relevant point is that Joshi *et al*[7] also evaluated the prescribed daily dose (PDD) and defined daily dose (DDD) for each AED included in the treatment regimen as an indicator for the AED load. It was reported that AED load did not have any correlation with the occurrence of adverse effects, although it was observed that the greater the number of prescribed AEDs, the higher the occurrence of adverse effects. This is an important finding for determining whether specific AED therapy is rational and it deserves an analysis of possible factors for these associations reported. There are some conflicting data on AED load and adverse effects; some authors have shown that AED toxicity may be related to total drug load rather than to the number of AEDs administered[6,15], for example, Canevini *et al*[10] provided evidence that adverse events did not differ between monotherapy and polytherapy and did not correlate with AED load.

Although these are hypothetical (*i.e.*, research) considerations, but on the other hand, taking a clinical approach might lead us to further extend the research on adverse effects in a patient-centred way to optimize health outcomes in active epilepsy[16]. Dealing with a person suffering from epilepsy in a routine clinical practice is as fine as tuning a violin to play perfectly. The person her/himself, epilepsy and ADEs form a complex neuropsychopharmacological triangle. Epilepsy is 'a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition'[17], while AEDs act by reducing the excitability levels in neural tissue to reduce seizure severity and frequency[3,4], each of these having a specific pharmacological profile[2]. Thus, we have the person, epilepsy, and the AEDs that might influence each other and each self to various degrees creating a unique predisposition (*i.e.*, variance) at an individual level to develop specific adverse effects. Weighting these aspects with a person with epilepsy or his/her caregivers would be of significant relevance for successful treatment, which should be effective, safe and least-expensive.

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