The impact of anti-seizure medications on psychiatric disorders among children with epilepsy: Both a challenge and an opportunity?

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Abstract

Psychiatric disorders are common co-existing conditions in children with epilepsy and can precede or follow epilepsy onset. Therefore, when selecting anti-seizure medications (ASMs) for children with epilepsy, in addition to seizure control, careful consideration of behavioral and psychotropic effects (BPEs) is critical, as they can have a negative impact on ASM adherence and quality of life. The goal in supporting children with epilepsy is an individualized approach to maximize seizure control and minimize negative BPEs. A previous history of a psychiatric disorder is the most significant risk factor for negative BPEs. Therefore, systematic screening for psychiatric symptoms can guide ASM selection and prompt intervention as needed. Besides familiarity with different ASM profiles, awareness of risk factors for negative BPEs including rapid dose titrations and weaning schedules, polypharmacy, high ASM doses, and drug interactions are important. In children with co-existing psychiatric disorders, ASMs with mood stabilizing, behavior regulating or anxiolytic properties may be preferred choices. Overall, a comprehensive and coordinated approach, with family psychoeducation and a mutual understanding of clinical aspects between the disciplines of neurology and psychiatry will enable better outcomes in children with epilepsy. Further pediatric “real-world” studies will expand knowledge of BPEs and potential risk factors. For some children, timely epilepsy surgery or precision therapies targeting a pathological defect may reduce the ASM burden in a child’s life and subsequent BPEs. The ability to predict an individual child’s susceptibility to negative BPEs with valid biomarkers may become available in the near future with advances in pharmacogenomics and technology.

Key Words: seizure, epilepsy, co-morbidity, adverse effect, drug

Résumé

Les troubles psychiatriques sont des états commun coexistants chez les enfants souffrant d’épilepsie et ils peuvent précéder ou suivre le début de l’épilepsie. Par conséquent, lorsqu’on choisit des médicaments anticonvulsivants (MAC) pour des enfants souffrant d’épilepsie, outre le contrôle des convulsions, il faut prendre sérieusement en considération les effets comportementaux et psychotropes (ECP) car ils peuvent avoir un effet négatif sur l’adhésion aux MAC et à la qualité de vie. Soutenir les enfants souffrant d’épilepsie a pour but une approche individualisée afin de maximiser le contrôle des convulsions et de minimiser les ECP négatifs. Des antécédents d’un trouble psychiatrique constituent le facteur de risque le plus significatif des ECP négatifs. Donc le dépistage systématique des symptômes psychiatriques peut guider la sélection des MAC et provoquer une intervention au besoin. Autre que la familiarité avec différents profils de MAC, la connaissance...
Introduction

Epilepsy is one of the most common pediatric neurological conditions, with a lifetime prevalence ranging from 3.5 to 10.7 per 1000 persons in developed countries (1). Anti-seizure medications (ASMs) are the mainstay of therapy. When selecting ASMs, seizure control is at the forefront of considerations; however, drug attributes including pharmacokinetics and tolerability are equally important. Adverse effects (AEs) are critical for discontinuing ASMs and ensuing suboptimal seizure control, with increased injuries, hospitalizations and mortality. AEs also negatively affect quality of life (QOL), sometimes more detrimental than seizures themselves (2). Overall, newer ASMs have better tolerability and fewer drug interactions, but not necessarily better efficacy or without significant AEs (3).

Attention to potential behavioral and psychotropic effects (BPEs) of ASMs is critical, as co-existing psychiatric disorders are common, preceding or following epilepsy onset (4, 5). In children with epilepsy (CWE), psychiatric disorders are 4.8 times higher than the general population, and 2.5 times higher than children with other chronic conditions (6). Intellectual disabilities and autism spectrum disorders commonly accompany pediatric epilepsy and often are associated with behavioral difficulties that may be further exacerbated by ASMs.

Effects of ASMs

Epilepsy and psychiatric disorders are on a biological spectrum and the treatment of some symptoms affects others. ASMs cause BPEs via direct mechanisms, including alteration of ion channels and neurotransmitters. Indirect mechanisms include improved seizure control with potential improvements in alertness and cognition, or conversely forced normalization characterized by the emergence of
psychiatric disturbances following the establishment of seizure control or reduction in the epileptic activity in a patient with previous uncontrolled epilepsy (7).

Drug pharmacokinetics, often overlooked, contribute to BPEs. For example, cytochrome P450 enzyme inducers, like CBZ, may increase metabolism of psychotropic drugs, possibly worsening mood, while inhibitors, like VPA may decrease P450 metabolism, possibly resulting in toxicity. Vigilance is required for patients who discontinue mood-stabilizing ASMs that alleviated co-existent mood disorders, as they might present with a worsening of mood disorder or acute psychosis. BPEs of ASMs are summarized in Table 1.

### Negative BPEs

Negative BPEs of ASMs include behavioral disturbances, depression, anxiety, attentional problems and hyperactivity, which can simulate primary psychiatric conditions.

#### Behavior

Behavioral issues, including excessive aggression, anger and irritability, are common in CWE, especially with neurodevelopmental disorders (7). Behavioral AEs are common with GABAergic ASMs, such as BZPs and barbiturates (8). There is variability among other ASMs, with rates of 10-30% with BRV, CLB, LEV, PER, and TPM, (9-11) but significantly lower with CBZ, ESL, LCM, LTG, OXC, RUF and VPA (11-13).
LEV is associated with BPEs, including agitation, hostility, and irritability and should be used cautiously in patients with a history of psychopathology (11, 14, 15). LEV-BPEs occurred in 13% percent of patients in a phase III trial (14). However, the rate of 30% reported in a pediatric systematic review seems more relatable to clinical practice (16). In children that achieve seizure control but experience negative BPEs with LEV, switching to BRV, with a similar mechanism of action, can ameliorate BPEs (17). A recent randomized control trial demonstrated improvement of negative LEV-BPEs with pyridoxine supplementation, although results are inconsistent in clinical practice (18).

CLB has high rates of BPEs compared to placebo or ASMs like CBZ and PHT (19). In one study, 11% of children on CLB developed aggression, self-injurious behavior, insomnia and hyperactivity, which reversed with weaning CLB. These CLB-BPEs may be even higher in everyday practice, especially in children with autism or an intellectual disability (20).

Among newer ASMs, BRV, potentially more favorable than LEV, is associated with BPEs in 5 to 10% of CWE (21). PER has a unique profile, as patients can develop suicidal and homicidal ideation, for which a boxed warning exists (22-24). PER-BPEs occur more frequently in children than adults (23). Doses of 8 mg per day or lower can prevent or reverse negative PER-BPEs (25). Counterintuitively, mood-stabilizing ASMs, like LTG, may induce BPEs in patients with cognitive impairment, possibly by forced normalization (26). VPA can worsen behavior at high doses or if co-existing hyperactivity exists (27, 28).

**Attention-deficit/hyperactivity disorder (ADHD)**

ADHD co-exists in 30% of CWE, (29, 30) with a bi-directional relationship (31). Children with polypharmacy, neurodevelopmental disorders and frequent seizures have a higher propensity for ADHD (30). Many families of CWE have trepidation that starting ADHD treatments will exacerbate seizures, but can be reassured that stimulants such as methylphenidate, do not worsen seizure control, and may improve cognition and QOL (32). CWE and ADHD may benefit from atomoxetine and amphetamines, although safety and efficacy data are limited to small studies (30, 33). ASMs have variable impacts on ADHD symptoms, and further data are needed. TPM and ZNS may worsen attention (13). In one report, VPA improved EEG inter-ictal abnormalities and ADHD ratings (34). However, VPA can worsen attention in childhood absence epilepsy and its use in pregnancy is associated with inattentiveness and hyperactivity in offspring (30).

**Depression and Anxiety**

Overall, depression is underreported in children and likely in CWE (35). Recognition of depression is challenging for neurologists, as children present with diverse symptoms, including agitation, alterations in sleep and appetite, irritability, anger, academic decline, regression, lethargy, and other somatic symptoms (35, 36). Furthermore, ASMs, such as BRV, CLB, ESM, FBM, LEV, PER, TPM, VGB, and ZNS can negatively impact mood (7). TPM has mixed effects, it worsens mood in 10 to 20% of patients, especially at higher doses or with polypharmacy, but can be effective for treating major depression with prominent anger and aggression (37). There is a very low risk for depression with CBZ, ESL, GBP, LAC, LTG, OXC, PHT, RFM, and VPA (7).

Anxiety, also prevalent in CWE, (7) can be aggravated or result from withdrawal of certain ASMs, such as the GABA-ergic drugs, including BZ, GBP, PB, VGB, and VPA (38). Psychosis can be caused by PER, PHT, TPM, VGB, VPA, and ZNS (39). Forced normalization or the abrupt wean of mood stabilizing ASMs can also result in psychosis (7).

**Suicidal Ideation**

In 2008, the FDA issued a warning that patients on ASMs had a 1.8 times increased risk of suicidality based on a meta-analysis of 199 placebo-controlled trials of 11 ASMs for three different indications, including epilepsy. However, there were several methodological weaknesses, (40, 41) and supporting evidence is lacking (42). Nevertheless, the study brought widespread awareness of BPEs of ASMs. It is plausible that negative BPEs exacerbate co-existing mood symptoms in people with epilepsy, leading to suicidal ideation. Furthermore, interpretation of study results require context that individuals with epilepsy have a higher inherent risk of suicidality. The Rochester Epidemiology Project demonstrated the hazard ratio of self-injurious behavior and/or suicidal ideation to be 1.56 times higher among CWE than age-matched control patients (43). Therefore, screening for suicidality in neurology clinics is of utmost importance. When suicidality is identified in CWE, prompt assessments by psychiatrists are needed. Hence, close collaboration between neurologists and psychiatrists is essential.

**Positive Psychotropic Effects of ASMs**

The availability of ASMs with positive BPEs provide a valuable clinical advantage. ASMs with mood stabilizing (CBZ, LTG, OXC and VPA) or anxiolytic (GBP, PGB) properties are potentially preferred in children with current or previous psychiatric disorders (13). ASMs are used off-label for most psychiatric symptoms in children. Some
ASMs have Health Canada approval for adult psychiatric indications, including CBZ and VPA for bipolar disorder and BZPs for anxiety disorder (44).

LTG has evidence of benefit for symptoms of aggression, impulsivity and bipolar disorder, with acute and prophylactic antidepressant properties (45-47). However, in patients with frequent seizures, it may not be optimal, as it requires a very slow titration schedule to reduce the incidence of rash, resulting in delayed seizure control. Many CWE have cognitive impairment, so it is beneficial that OXC, a mood stabilizer also has cognitive benefits with attention tasks and manual writing speed (48, 49). Notably, LEV can improve alertness and communication (50). TPM, associated with cognitive AEs, may be effective in patients with obesity and/or binge-eating disorder, due to appetite suppressant properties (51). Many neurologists favor LCM due to its tolerability and drug interaction profile, and it may lead to improvements in mood, anxiety and QOL (52, 53). RFM has no known increased risk of negative BPEs, (54, 55) which is clinically relevant, as it often utilized in children with intractable epilepsies and neurodevelopmental disorders, such as Lennox-Gastaut Syndrome.

It is advantageous to know that some ASMs may be beneficial for anxiety and related disorders. Adult studies show that LTG may be beneficial in post-traumatic stress disorder and VPA in panic disorder (56). GBP and PGB, although less efficacious for seizure control, may be effective in social anxiety disorder and PGB may be effective in generalized anxiety disorder (13).

Clinical Risk Factors

A personal or family history of psychiatric disorders is the most significant predictor of BPEs, possibly related to genetic predisposition (11, 15). Patients with a pre-existing psychiatric history are more than twice as likely to experience negative BPEs with newer ASMs (15). Notably, a pediatric study demonstrated that baseline hyperactivity is a risk factor for negative BPEs, irrespective of the ASM tried (27). Children with chronic epilepsy have significantly higher symptoms of depression compared to new-onset epilepsy (57). Seizure characteristics, including etiology, localization and type are not consistent risk factors among various studies (11, 15). Age is a potential risk factor; with younger children experiencing more behavioral effects and adolescents more mood related BPEs (27). Children are more susceptible to negative PER-associated BPEs than adults (23).

Higher doses or serum concentrations of ASM are a risk-factor, with ASMs, like GBP, PER, TPM, VPA, and ZNS exhibiting a dose dependent effect on BPEs (26). Many neurologists devise slow ASM titration and even slower weaning schedules, especially for tolence-building ASMs, such as BZs, to minimize negative BPEs (13). Children with intellectual impairment are particularly vulnerable to rapid changes in ASMs. Cross-sensitivity among ASMs can predict skin rash, and potentially BPEs (58, 59). The risk of negative BPEs with LEV or ZNS is higher if similar BPEs occurred with any other ASM (60). The risk of negative BPEs overall is higher if adverse BPEs occurred with LTG (61). Polypharmacy should be used prudently, especially with ASMs with pharmacokinetic interactions or with similar BPE profiles, such as CLB and LEV (62). The addition of LTG to LEV is shown to be protective against negative LEV-associated BPEs, which is intuitive, as LTG has mood-stabilizing properties (63). Although not routinely screened for, folate deficiency, associated with polypharmacy or ASMs like CBZ, PHB and PHT, increases susceptibility for mood disorders (64).

Current issues and future directions

Difficulty determining true incidence of BPEs

The true incidence of BPEs of ASMs is unclear due to differences in methodology, BPE definitions, reporting mechanisms and patient populations between studies. The underestimation of BPEs in clinical trials occur due to restraints of a controlled trial, including seizure characteristics (etiopathology, comorbidities, and concomitant ASMs), that are more flexible in a real-world setting, thereby including more children susceptible for BPEs (17). Moreover, most ASMs have initial approval in adults, requiring extrapolation of data on efficacy and BPEs for a spectrum of chronological ages. Post-trial studies demonstrate higher rates of negative BPEs with ASMs, including CLB, LEV, and PER (especially significant due to higher risk of harm to self or others) (17, 20, 25). Particularly for newer ASMs, more pediatric real-world data are required for a more comprehensive understanding of BPEs.

Screening and education

Undiagnosed psychiatric disorders can be confused with BPEs, leading to changes to ASMs and jeopardizing seizure control. It also may not be intuitive for patients to report mood, or behavioral changes, or be cognizant that psychiatric symptoms are BPEs. Parsing out BPEs and psychiatric comorbidities is challenging. For accurate identification of BPEs and prompt interventions, the use of standardized validated screening tools is essential before ASM initiation, for baseline psychological functioning, and at various time points of follow-up. Unfortunately, this is not standard...
practice in many clinics. Family psychoeducation, encompassing psychiatric co-morbidities and BPEs, may help improve mental health and QOL in CWE, but is often overlooked, due to time constraints in a busy neurology clinic or lack of awareness and resources (65).

**Mutual understanding between Neurology and Psychiatry**

Neurologists and psychiatrists may not be proficient with relevant clinical aspects of each other’s specialties. Many neurologists are better skilled at tracking seizure frequency than psychiatric symptoms. Moreover, clinical screening instruments are inadequate for making a formal psychiatric diagnosis, which requires specialist evaluations. Some patients require psychotropic drugs or cognitive behavioral therapy to manage symptoms, which is beyond the scope of most neurologists. Similarly, psychiatrists may not be familiar with BPEs or the efficacy of new ASMs for different seizure types (66). Both disciplines may prescribe ASMs off-label, before all pharmacological properties of an ASM are fully known (67) and may be unfamiliar with drug interactions between ASMs and psychotropic drugs (68). Close collaboration between specialties is required to co-manage CWE; albeit it can be challenging with limitations of time, providers, and separate clinical spaces. This holds true for other specialists prescribing ASMs for conditions including migraine, movement disorders, sleep and chronic pain. Clinical pharmacists, when available, provide valuable advice on interactions between ASMs and psychotropic drugs.

**Biomarkers**

There is a need for predictive biomarkers for individualized treatment plans in epilepsy, an area that is still in early stages. The link between HLA typing and CBZ-induced rash is well established (69). Recently, PER-BPEs are shown to be more likely in patients with the HLA-DQB1*06:01, DRB1*08:03, and B*54:01 alleles in a Korean population study (70). LEV-BPEs are more likely in patients carrying genetic variants associated with decreased dopaminergic activity, including the rs1800497 polymorphism (71). Further studies of the impact of pharmacogenomics on BPE of ASMs are required for integration of these tools into every day clinical use.

Recent advances in fMRI methodology, enable better understanding of the impacts of ASMs on specific cognitive/behavioral networks; referred to as Pharmacoc-fMRI (72). Pharmacoc-fMRI has provided insights on aberrant language defects with TPM, and may provide surrogate biomarkers in predicting ASM BPEs.

**Reduced ASM load**

Select children benefit from epilepsy surgery or neuro-modulation modalities, such as deep brain stimulation. However, delays in referrals or access to specialized epilepsy care exist (73). Early epilepsy surgery often results in better outcomes, with reduced ASM load and BPEs. Advances in genetic testing have led to novel therapies targeting the pathophysiological defect at the molecular level, such as mTOR inhibitors in tuberous sclerosis complex (74), or gene therapies for Dravet syndrome, (75) with potential for reduction of ASM load. However, many precision therapies show efficacy in vitro, but not in vivo. Furthermore, there are inconsistencies with access and utilization of genetic testing amongst different centers.

**Conclusion**

In supporting CWE, seizure control with minimal BPEs is an important aim. The stakes are high with ASM selection, as negative BPEs lead to increased morbidity, mortality and worsened QOL, therefore necessitating a comprehensive therapeutic approach. The knowledge that ASMs can worsen or improve psychopathology provides clinicians both a challenge and an opportunity. Careful consideration of ASM profiles, baseline and evolving psychiatric symptoms and avoidance of unnecessary drug interactions and polypharmacy inform effective treatment strategies. Advances in pharmacogenomics, molecular biology and technology will potentially improve prediction of a child’s susceptibility to BPEs and personalized therapies.

**Conflict of Interest**

This work received no funding. The author has no conflicts of interest to declare.

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