Review Article

Mechanisms Underlying Aggressive Behavior Induced by Antiepileptic Drugs: Focus on Topiramate, Levetiracetam, and Perampanel

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Antiepileptic drugs (AEDs) are effective against seizures, but their use is often limited by adverse effects, among them psychiatric and behavioral ones including aggressive behavior (AB). Knowledge of the incidence, risk factors, and the underlying mechanisms of AB induced by AEDs may help to facilitate management and reduce the risk of such side effects. The exact incidence of AB as an adverse effect of AEDs is difficult to estimate, but frequencies up to 16% have been reported. Primarily, levetiracetam (LEV), perampanel (PER), and topiramate (TPM), which have diverse mechanisms of action, have been associated with AB. Currently, there is no evidence for a specific pharmacological mechanism solely explaining the increased incidence of AB with LEV, PER, and TPM. Serotonin (5-HT) and GABA, and particularly glutamate (via the AMPA receptor), seem to play key roles. Other mechanisms involve hormones, epigenetics, and “alternative psychosis” and related phenomena. Increased individual susceptibility due to an underlying neurological and/or a mental health disorder may further explain why people with epilepsy are at an increased risk of AB when using AEDs. Remarkably, AB may occur with a delay of weeks or months after start of treatment. Information to patients, relatives, and caregivers, as well as sufficient clinical follow-up, is crucial, and there is a need for further research to understand the complex relationship between AED mechanisms of action and the induction/worsening of AB.

1. Introduction

With a prevalence of about 0.6–0.7% in developed countries, epilepsy is the fourth most common neurologic disease after migraine, Alzheimer’s disease, and stroke [1, 2]. Most patients receive treatment with antiepileptic drugs (AEDs), and up to 70% of them become seizure-free [3]. However, AEDs are potent agents that can induce numerous adverse reactions and drug-drug interactions. Psychiatric and behavioral adverse reactions (PBAR) are common. They include depression, anxiety, psychosis, and aggressive behavior (AB) [4]. In everyday practice, the numerous clinical expressions of AED-induced PBAR may be difficult to distinguish from endogenous clinical manifestations in the individual patient.

Levetiracetam (LEV), perampanel (PER), and topiramate (TPM) are currently identified as AEDs with the strongest evidence for AB. However, benzodiazepines, brivaracetam (BRV), phenobarbital, tiagabine, vigabatrin, and zonisamide are also associated with a higher occurrence of AB compared to other AEDs [4]. The risk is increased in patients with a previous history of psychiatric disorders [4–6]. This kind of adverse effect can become a significant clinical problem since
these AEDs often are used in difficult-to-treat epilepsy. When improved seizure control is achieved with these drugs, the occurrence of intolerable PBAR necessitating discontinuation of the effective drug is highly unfortunate.

It is unclear which pharmacological mechanisms evoke AB. Eventually, multiple mechanisms of action (MOAs) have been identified for most AEDs. Despite this, AEDs are usually classified according to their proposed “main” or “principal” MOA, although such categorization is of limited clinical value. This is illustrated by the observation that AEDs with different principal MOAs can have identical therapeutic effects, while AEDs with a similar principal MOA can have divergent therapeutic effects. Likewise, AEDs with different principal MOAs can induce identical adverse effects, while AEDs with an identical principal MOA may have different safety profiles.

LEV, PER, and TPM have divergent pharmacological profiles with several different MOAs. Yet, they can all induce AB. While LEV and PER have been assigned a principal MOA, TPM has been actively marketed as a “multiple-MOA” AED.

These three main culprit drugs will be used as models to discuss established knowledge as well as various hypotheses about AB as an adverse effect of AEDs. Three main questions will be addressed:

(1) Which MOAs can induce AB?
(2) Do these AEDs (LEV, PER, and TPM) have a common MOA that is responsible for this particular adverse effect?
(3) Could AB be an indirect effect, i.e., the consequence of the clinical efficacy of these AEDs?

This review is based on searches in various online repositories (PubMed, ResearchGate, Google Scholar, and EMBASE) using “antiepileptic drugs”, “levetiracetam”, “perampanel” and “topiramate”, combined with terms such as “behavior”, “psychiatric side effects”, “aggression”, “agitation”, “irritability”, and “adverse effects”. The searches included publications until February 2018.

2. Aggressive Behavior: Epidemiology, Etiology, and Treatment

It is well-documented that the prevalence of psychiatric conditions is higher in people with epilepsy than in the general population. It is estimated that as much as 30% of newly diagnosed and 50% of treatment-resistant patients have a psychiatric disorder, mainly depression, anxiety, and psychosis [7]. It may therefore be assumed that AB is common in people with epilepsy. However, the actual prevalence is not known [8].

Aggression is a social behavior that is aimed at eliciting discomfort, pain, or physical damage, to oneself, to another person, or to things or at defending oneself against a threat. AB can be defensive, instrumental (planned with the intention of achieving a goal), or impulsive (in anger and after provocation) [4].

AB can occur as a symptom of various medical conditions such as brain damage, encephalitis, drug use, dementia, intoxication, psychosis, affective disorders, and personality disorders as well as in relational, behavioral, developmental, and adaptational disorders [9]. This implies that AB occurs not only as a permanent personality trait but also as a temporary behavior change. It is estimated that up to 60% of people with intellectual disability exhibit signs of AB [10].

The heterogeneity of AB suggests a complex etiology [11]. Indeed, AB has been associated with genetic, epigenetic, neurobiological, and psychosocial factors [12]. Several cortical and subcortical brain networks are involved, predominantly those mainly modulated by the monoamines serotonin (5-HT), dopamine (DA), and norepinephrine (NE), but also glutamate and gamma-aminobutyric acid (GABA) play an important role. Dysregulation of several proteins in these networks contribute to AB. These include 5-HT1A and 5-HT2A receptors, 5-HT transporters, DA D1 and D2 receptors, DA transporters, a1 and a2 adrenoceptors, monoamineoxidase (MAO) A, GABA A and GABA B receptors, GABA transaminase, glutamatergic N-methyl-D-aspartate (NMDA), and a-amino-3-hydroxy-5-methyl-4-isoxazoloproopionic acid (AMPA) receptors, as well as voltage-regulated sodium and calcium channels [13, 14].

Other neuroactive substances may also interact with these networks, e.g., steroid hormones, vasopressin, histamine, substance P, nitrogen monoxide (NO), neural cell adhesion molecule (NCAM), and interleukins [14]. Imaging studies have identified brain structures that are associated with AB, such as the prefrontal cortex, amygdala, hypothalamus, hippocampus, septal nuclei, and periaqueductal gray matter (PAG) [12].

Treatment of AB is versatile, including drugs and non-pharmacological interventions. Because of the diverse and complex etiology, as well as different comorbidities, the choice of intervention and type of drug treatment may vary considerably between individual patients. AB in conjunction with acute psychosis or mild depression, for instance, needs different treatment approaches [11]. A plethora of drugs may be used to treat AB. Second-generation antipsychotic drugs have been used, based on their ability to modulate several receptors involved in AB, such as 5-HT, DA, NMDA, NE, and GABA receptors [13]. Benzodiazepines, being allosteric agonists at GABA A receptors, have also been used. However, they may elicit paradoxical reactions, i.e., reinforced AB [12]. Selective serotonin reuptake inhibitors (SSRI), β-adrenergic blockers, psychostimulants (e.g., amphetamine), lithium, and AEDs like valproate, lamotrigine, gabapentin, and TPM have all been shown to be effective [8, 13]. Nevertheless, the most promising treatments will be those that take underlying, specific processes into consideration [11].

3. Aggressive Behavior as an Adverse Effect of AEDs

It has been estimated that up to 50% of AED users experience adverse reactions, leading to discontinuation of the culprit drug in up to 20% of all cases [15–17]. Generally, most newer
AEDs have better tolerability profiles than the older ones [17]. Many adverse effects are dose-dependent and often involve the central nervous system, such as dizziness, sedation, ataxia, nystagmus, and impaired cognitive functions.

AEDs may frequently induce PBAR, including depression, hostility/aggression, anxiety, insomnia, nervousness/irritability. Many adverse effects are dose-dependent and often involve the central nervous system, such as dizziness, sedation, ataxia, nystagmus, and impaired cognitive functions.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability</td>
<td>Higher prevalence in children and adolescents than in adults: agitation (3.4%), mood swings (2.1%), affect lability (1.7%), aggression (8.2%), abnormal behavior (5.6%)</td>
</tr>
<tr>
<td>Suicide attempt, suicidal ideation, psychotic disorder, abnormal behavior, hallucination, anger, confusion, panic attack, affect lability/mood swings, agitation</td>
<td></td>
</tr>
<tr>
<td>Completed suicide, personality disorder, thinking abnormal</td>
<td></td>
</tr>
<tr>
<td>Aggression, anger, anxiety, confusion, irritability</td>
<td>Aggression more frequently observed in adolescents than in adults</td>
</tr>
<tr>
<td>Suicidal ideation, suicide attempt</td>
<td></td>
</tr>
<tr>
<td>Irritability, bradyphrenia, insomnia, expressive language disorder, anxiety, confusion, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behavior</td>
<td>Irritability and expressive language among the most common adverse effects (&gt;5%)</td>
</tr>
<tr>
<td>Suicidal ideation, suicide attempt, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido decreased, restlessness, crying, dysphoria, euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia, flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood</td>
<td>Higher prevalence in children than in adults (&gt;2 times): suicidal ideation, abnormal behavior, aggression</td>
</tr>
<tr>
<td>Mania, panic disorder, feeling of despair, hypomania</td>
<td></td>
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</tbody>
</table>

*Very common: ≥1/10, common: ≥1/100 to <1/10, uncommon: ≥1/1000 to <1/100, rare: <1/1000.

Table 1 provides an overview of various PBAR of LEV, PER, and TPM and their frequencies. Aggression and irritability are categorized as “common” adverse effects in their respective summary of product characteristics (SPC), meaning that they occur with a frequency of 1–10% [24–26]. Some studies report even higher frequencies, e.g., up to 16% for LEV [27]. TPM on the other hand shows the broadest spectrum of PBAR, including anxiety, agitation, aggression, depression, and psychosis [28]. The SPC for BRV states irritability as common and aggression as uncommon [29].
However, newer studies report higher frequencies, although still lower than for LEV [5, 6]. It is difficult to predict at which point in time PBAR will become manifest, since data from clinical studies are scarce and not uniform (Tables 2–4). Most studies merely report that PBAR occurred during the study period, and only a few studies state a time interval from start of treatment until the adverse effect emerged. Dinkelacker et al. [30] report an interval of 3.6 months from start with LEV to the recognition of PBAR. Similarly, Mula et al. [31] report an average delay of 88 days for mainly aggression, agitation, anger, and hostile behavior. Other studies state a much shorter interval of less than one month [32, 33]. For PER, various time intervals have been reported: within six weeks [34], three months [35, 36], or even six months [36, 37]. For TPM, Mula et al. [38] state an interval of 60 days for the emergence of affective disorders and aggression, even later for psychosis. However, it is difficult to sort out to what extent the delayed reactions might be associated with a gradual dose increase.

People with epilepsy seem to be more susceptible to PBARs from AEDs, particularly LEV and PER, since the prevalence of such reactions is lower when these drugs are used for non-epilepsy conditions (Tables 2 and 3) [4, 21]. Moreover, some data suggest that the incidence and clinical characteristics of AB depend not only on previous psychiatric history but also on age, sex, type of epilepsy, and AED dose [28]. This is discussed in Section 5.

Adverse reactions involving the CNS are often, but not always, dose-dependent, and it seems that the risk for PBAR can be reduced by low initial doses and slow titration [39–42]. This applies particularly to PER, since many studies found that adverse effects primarily occur with doses of 8 or 12 mg/day. In phase III clinical studies, the overall rate of psychiatric TEAEs was 17.2% (8 mg) and 22.4% (12 mg) (placebo: 12.4%) [34, 43–48]. Regarding LEV, the literature is more diverse. Some studies suggest that adverse reactions to LEV are mostly dose-independent, as they may occur at any dose and despite slow titration, while others found that the likelihood of LEV being discontinued or lowered was higher when it was initiated at a high dose [49–53]. With TPM, slow titration may reduce the risk, although adverse reactions may occur at any dose. PBAR induced by TPM usually resolve upon dose reduction [38, 50, 54–56].

4. Possible Neuropharmacological Mechanisms of AED-Induced Aggressive Behavior

4.1. Levetiracetam. Levetiracetam (LEV) is effective in focal onset seizures as well as in generalized onset tonic-clonic and myoclonic seizures [24]. LEV is a pyrrolidone derivative that has been developed from piracetam. It is presumed to act on presynaptic neurotransmitter release by binding to synaptic vesicle protein 2A (SV2A), a glycoprotein that is part of the membrane of presynaptic neurotransmitter-containing vesicles in neurons and neuroendocrine cells. SV2A and related isoforms (SV2B, SV2C) are expressed in several locations in the brain, especially in the cortex but also in subcortical regions such as thalamus, basal ganglia, and hippocampus. Reduced expression of SV2A may lead to a lower seizure threshold and epileptogenesis [84].

It is not clear exactly how LEV’s binding to SV2A results in antiepileptic efficacy, but it is assumed that this protein is involved in exocytosis of neurotransmitters and that this exocytosis is downregulated either via reduced calcium inward currents or other modulating mechanisms [85]. The recently introduced AED, BRV, is a derivative of LEV/piracetam and has a higher affinity to SV2A, although it has already been shown that BRV also acts as a sodium channel blocker [86].

LEV also increases tissue concentrations of GABA, neutralizes the action of negative modulators of the GABAA receptor, and reduces the excitatory action of glutamate by modulation of AMPA receptors [84, 87–92]. Several studies suggest that LEV modulates neuronal cell function via additional pharmacological mechanisms including modulation of serotoninergic and α2-adrenergic signaling paths as well as μ-opioid receptors [93]. LEV also modulates intraneuronal calcium levels via inhibition of N-type calcium channels. Other MOAs associated with LEV are modulation of presynaptic P/Q-type calcium channels and potassium channels, as well as upregulation of glutamate transporters in glial cells [84, 91, 94]. It is not clear whether these MOAs occur on their own or as a consequence of the interaction with SV2A [84, 93].

The broad pharmacological effect of LEV makes it difficult to determine the exact cause of AB. The high rate of AB with LEV may not necessarily be related to SV2A, since it has been suggested that BRV, which has a 15–30 times higher affinity to SV2A than LEV, is associated with a lower incidence of AB than LEV [6, 22, 23, 95]. Interestingly, it seems that BRV does not modulate NMDA, AMPA, or kainate receptors [96, 97]. These findings suggest that LEV’s negative modulating effect on AMPA receptors contributes to increased AB. This idea is supported by the observation that piracetam (the predecessor of LEV) is not associated with increased AB. Piracetam improves neural and cognitive functions, presumably via positive allosteric modulation of the AMPA receptor [98, 99]. The interaction between NMDA and AMPA receptors and AB is discussed in more detail under Section 4.2.

5-HT (serotonin) and GABA have also been associated with AB [4, 32, 42, 100]. 5-HT is possibly the best-studied neurotransmitter in relation to AB, especially impulsive aggression [4, 12, 100, 101]. Several studies suggest that 5-HT modulates brain activity in the prefrontal cortex, which controls limbic system responses to stimuli, i.e., regulation of emotions. It has been speculated that reduced levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) are associated with impulsive aggression [101, 102]. However, the relationship between 5-HT and behavior is complex [4, 101]. The 5-HT-system consists of at least 14 different receptors with subtypes, both pre- and postsynaptic, with unique and partly antagonistic effects on aggression [4, 101]. Undoubtedly, 5-HT is involved in AB, but whether LEV might interfere with this mechanism is unclear. The relationship between GABA and AB is discussed under Section 4.3.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodtkorb et al. 2004 [57]</td>
<td>Cohort study, $t = 8.1$ months</td>
<td>$n = 184$ adults (mean age: 34.7 years), of which 56 have intellectual disability</td>
<td>PBAR (agression, irritability, mood swings, anxiety, restlessness, and psychotic symptoms) were among the most frequent adverse reactions. More frequent in patients with intellectual disability (23% vs. 10%).</td>
</tr>
<tr>
<td>Chen et al. 2017 [19]</td>
<td>Case-control, $t = 1–15$ years</td>
<td>$n = 922$ (2–18 years) with epilepsy; mono- or polytherapy</td>
<td>PBAR in 13.8%, leading to dose reduction or discontinuation in 11.2%. LEV with the highest frequency of PBAR (16.2%), leading to dose reduction or discontinuation in 6.7%.</td>
</tr>
<tr>
<td>Chen et al. 2017 [18]</td>
<td>Case-control, $t = \geq 12$ months</td>
<td>$n = 4085$ adults (mean age 41 years) with epilepsy; mono- or polytherapy of which LEV: 1890</td>
<td>Discontinuation due to PBAR in 19% using LEV (vs. 2–7% with LTG, OXC, TPM, and ZNS).</td>
</tr>
<tr>
<td>Chung et al. 2007 [50]</td>
<td>Cohort study, $t = 2$ years</td>
<td>$n = 828$ adults (mean age 38.5 years) (LEV: 196; LTG: 251; OXC: 97; TPM: 156; ZNS: 128)</td>
<td>No difference in neuropsychological tests after short-term treatment with LEV or PGB.</td>
</tr>
<tr>
<td>Ciesielski et al. 2006 [58]</td>
<td>Cohort study, $t = 2$ weeks</td>
<td>$n = 20$ (22–52 years) with epilepsy (LEV: 10, PGB: 10)</td>
<td>PBAR in 25.4% of 1393 patients using LEV (vs. 6.2% with placebo), including agitation (1.6% vs. 0.2%), emotional instability (3.0% vs. 0.2%), hostility (3.3% vs. 0.9%), and nervousness (7.3% vs. 1.8%). PBAR more common in epilepsy compared to non-epilepsy (cognition/anxiety) ($p = 0.022$).</td>
</tr>
<tr>
<td>Cramer et al. 2003 [32]</td>
<td>Review article, $t = \geq 2$ years</td>
<td>Total $n = 4179$ adults (epilepsy, cognitive disorders, and anxiety) of which LEV: 2871, placebo: 1308</td>
<td>Significant difference in total problem score between LEV (worsened) vs. placebo (improved). Significant worsening of aggression (LEV vs. placebo; $p = 0.013$). Based on questionnaires.</td>
</tr>
<tr>
<td>de la Loge et al. 2010 [59]</td>
<td>RCT, $t = 12$ weeks</td>
<td>$n = 98$ (4–16 years), of which 64 used LEV as add-on and 34 used placebo</td>
<td>33 patients that experienced irritability or aggression (representing 3.5% of all patients treated with LEV, vs. &lt;1% not on LEV). 24 patients: moderate or transient irritability, of which 10 had to reduce dose or discontinue. Nine (8 males) had severe aggressive symptoms; two of them required acute psychiatric intervention.</td>
</tr>
<tr>
<td>Dinkelacker et al. 2003 [30]</td>
<td>Case series, $t = 19$ months</td>
<td>$n = 33$ adults with epilepsy</td>
<td>PBAR in 13% of 769 patients with epilepsy using LEV in placebo-controlled studies (placebo: 6%), 6% (placebo: 4.1%) of elderly and 5.1% (placebo: 5.5%) of patients with anxiety reported PBAR.</td>
</tr>
<tr>
<td>French et al. 2001 [60]</td>
<td>Review article, $t = \geq 3$ years</td>
<td>$n = 3347$ adults (healthy subjects and patients with epilepsy or anxiety)</td>
<td>Increased frequency of PBAR with any AED. LEV among those AEDs with the highest frequency.</td>
</tr>
<tr>
<td>Guilfoyle et al. 2017 [61]</td>
<td>Case-control, $t = 1$ months</td>
<td>$n = 335$ children (mean age: 8.9 years) with newly diagnosed epilepsy, of which 37% started with LEV</td>
<td></td>
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</tbody>
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Table 2: continued.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halma et al. 2014 [62]</td>
<td>Meta-analysis</td>
<td>n = 727 (1 month–18 years) with epilepsy using LEV as monotherapy or add-on. 13 studies in total</td>
<td>Three RCTs: hostility (7.3%), nervousness (6.1%), and aggression (4.9%). Significantly increased risk for these adverse reactions (relative risk: 2.2 vs. placebo; 95% CI: 1.4–3.4). Ten observational studies: worsened and improved behavior with LEV. Add-on therapy associated with irritability (4.7%), hyperexcitability (4.4%), and aggression (2.7%); monotherapy associated with general behavior problems (19%) and irritability (2.6%).</td>
</tr>
<tr>
<td>Helmstaedter et al. 2008 [63]</td>
<td>Interview-based, t = 2,3–5 years</td>
<td>n = 466, of which 288 used LEV (men age: 38 years), 135 relatives, and 43 controls (using different AEDs)</td>
<td>37% reported a negative behavior change, of which aggression was most frequent.</td>
</tr>
<tr>
<td>Kanemura et al. 2014 [64]</td>
<td>Cohort study, t = 12 months</td>
<td>n = 12 children (mean age: 10.3 years) with epilepsy and pervasive developmental disorder</td>
<td>Of eight patients with improved seizure control, six had &gt;50% reduction in panic episodes or aggression.</td>
</tr>
<tr>
<td>Kang et al. 2013 [51]</td>
<td>Case-control, t = 29.3 months</td>
<td>n = 568 (mean age: 33 years) using LEV in mono- or polytherapy</td>
<td>Behavioral adverse reactions in up to 24%, of which irritability was most frequent.</td>
</tr>
<tr>
<td>Kowski et al. 2016 [65]</td>
<td>Case-control, t = 3 years</td>
<td>n = 841 patients with epilepsy (mean age: 44.7 years), of which 438 used monotherapy (different AEDs)</td>
<td>LEV with the highest frequency of anger, aggression, nervousness, and agitation</td>
</tr>
<tr>
<td>Labiner et al. 2009 [39]</td>
<td>RCT, t = 20 weeks</td>
<td>n = 268 patients with epilepsy (&gt;16 years) of which 132 used LTG and 136 used LEV as add-on</td>
<td>Patients on LEV: worsened anger-aggression subscore, while patients on LTG improved each week.</td>
</tr>
<tr>
<td>Lee et al. 2011 [33]</td>
<td>Cohort study, t = 24 weeks</td>
<td>n = 71 patients with epilepsy (mean age: 35.4 years)</td>
<td>Improvement of anxiety symptoms with LEV, but five patients (6.5%) discontinued LEV due to PBAR (nervousness, irritability, anxiety, hostility, depression, suicidal ideation, and attempted suicide).</td>
</tr>
<tr>
<td>Mbizvo et al. 2014 [66]</td>
<td>Meta-analysis</td>
<td>n = 1861 children and adults, 11 studies in total</td>
<td>Agitation in 0.82% on LEV vs. 0.14% on placebo. Irritability in 0.46% vs. 0% on placebo.</td>
</tr>
<tr>
<td>Mula et al. 2003 [52]</td>
<td>Cohort study, t = 8.3 months</td>
<td>n = 517 patients (mean age: 35.6 years) using LEV as add-on</td>
<td>PBAR in 10%, of which aggression was most frequent (3.5%).</td>
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<tr>
<td>Mula et al. 2004 [31]</td>
<td>Cohort study, t = 8.3 months</td>
<td>n = 118 patients with epilepsy and learning disabilities (mean age: 30.6 years)</td>
<td>PBAR in 15 patients (12.7%). Aggression most common (9 patients; 7.6%). Two patients (1.7%) experienced agitation, anger, and hostility.</td>
</tr>
<tr>
<td>Mula et al. 2007 [67]</td>
<td>Case-control, t = 2 years</td>
<td>n = 108 patients with epilepsy (mean age: 37.9 years) using LEV and TPM (not simultaneously)</td>
<td>PBAR in 13%.</td>
</tr>
<tr>
<td>Mula et al. 2015 [68]</td>
<td>Case-control, interview</td>
<td>n = 163 (mean age: 42 years)</td>
<td>9.8% reported that aggressive behavior «always» was a problem. No difference in score for behavior/aggression (LEV vs. placebo). Aggression occurred in 7.8%, irritability in 7.8% (sic), abnormal behavior in 3.9%.</td>
</tr>
<tr>
<td>Schiemann-Delgado et al. 2012 [69]</td>
<td>RCT, t = 48 weeks</td>
<td>n = 103 (4–16 years) of which 80 were from the de la Loge et al. (2010) study</td>
<td>LEV well tolerated regarding cognition, mood, and balance, but increased general tendency to feeling irritated (p = 0.029 vs. placebo).</td>
</tr>
<tr>
<td>Schoenberg et al. 2017 [70]</td>
<td>RCT, t = 10 weeks</td>
<td>n = 20 healthy elderly subjects, (mean age: 72.4 years) of which LEV: 9 and placebo: 11</td>
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</table>
4.2. Perampanel. Perampanel (PER) is licensed as add-on treatment for focal onset seizures and generalized onset tonic-clonic seizures in patients > 12 years [25]. It acts as a highly selective, noncompetitive antagonist on AMPA receptors, thereby reducing glutamatergic transmission. In contrast to competitive antagonists, noncompetitive antagonists will not be overcome by high synaptic glutamate concentrations. PER reduces calcium inward currents through AMPA receptors in cortical and subcortical brain regions. Some data suggest that it also acts on NMDA and kainate receptors [103]. PER is one of the newest AEDs, and presently, there is no evidence that it acts on other pharmacological targets.

Increased levels of glutamate are associated with increased AB, particularly impulsive aggression [4, 12, 104]. This is believed to be mediated by stimulation of glutamatergic receptors in the amygdala, hypothalamus, and periaqueductal gray matter [104]. Genetic modification of AMPA and NMDA receptors in mice leads to changes in AB [4, 104–106]. However, glutamate’s effect on behavior is complex and studies demonstrated that blocking of AMPA receptors can both decrease and increase AB [106, 107]. It has been demonstrated that phencyclidine, a NMDA antagonist, increases aggression at low doses, but decreases it at higher doses [108].

4.3. Topiramate. Topiramate (TPM) is effective against focal onset seizures and generalized onset tonic-clonic seizures [26, 109]. Additionally, it is effective as a prophylactic treatment of migraine [26, 109]. Topiramate has several MOAs. While none of them has been pointed out as the principal MOA, three of them have received most attention: blockade of voltage-dependent sodium and calcium channels, enhancement of GABA-dependent chloride inward currents, and antagonism at glutamatergic AMPA and kainate receptors [26, 109, 110]. These channels and receptors are all involved in aggressive behavior [4]. TPM also inhibits carbonic anhydrase types II and IV, although this MOA is not believed to contribute noteworthy to TPM’s antiepileptic effect [26, 110]. Some studies have shown that TPM has neuroprotective properties [111]. Being a fructose derivative, TPM is structurally unrelated to other AEDs (although it shares with zonisamide a sulfamate group) [26, 109, 110].

4.4. One Common Mechanism? Having reviewed the different pharmacological profiles of LEV, TPM, and PER, it is still not possible to conclude with certainty which MOA is responsible for the increased rate of AB in people treated with these drugs. Available data suggest that 5-HT, glutamate, and GABA play a major role in AB. Since all three AEDs have an inhibiting effect on glutamatergic transmission via the AMPA receptor, it appears most promising for future research to focus on this mechanism [18]. One caveat is that these MOAs are only the ones that we are currently aware of, but this may change. It cannot be ruled out that LEV, PER, and TPM exert part or most of their therapeutic and undesired effects via other MOAs that have not been discovered yet.

### Table 2: Continued.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shukla et al. 2016 [71]</td>
<td>Case-control, $t = 2.5$ years</td>
<td>$n = 445$ patients with epilepsy (mean age: 21 years) using LEV (114), OXC (151), or VPA (134), of which 292 were included</td>
<td>PBAR in 43 patients (irritability, compulsive symptoms, aggression, psychosis). 23 (20.2%) used LEV. LEV discontinued in 10 patients (9%).</td>
</tr>
<tr>
<td>Tekgul et al. 2016 [49]</td>
<td>Case-control, $t = \geq 12$ months</td>
<td>$n = 351$ (6 months–18 years: mean age: 9.9 years) using LEV in monotherapy</td>
<td>PBAR in 87%. Irritability (67%), hyperactivity (8%), and disturbed behavior (5%) were most common.</td>
</tr>
<tr>
<td>Weintraub et al. 2007 [27]</td>
<td>Case-control, $t = 13$ months</td>
<td>$n = 1394$ of which 521 patients (mean age: 43 years) used LEV</td>
<td>LEV with highest incidence (16%) of PBAR, leading to a discontinuation in 8%. Irritability in 9%, disturbed behavior in 3.5%.</td>
</tr>
<tr>
<td>White et al. 2003 [53]</td>
<td>Case-control, $t = 25$ months</td>
<td>$n = 553$ (mean age: 41.4 years)</td>
<td>7% discontinued LEV due to PBAR, mainly depression, and irritability. 1.8% were evaluated as a potential threat for themselves or others.</td>
</tr>
<tr>
<td>Wieshmann and Baker 2013 [72]</td>
<td>Case-control, interview</td>
<td>$n = 459$ (mean age: 41.6 years) of which 418 have epilepsy and 41 controls. 158 used LEV in monotherapy or add-on, 260 used other AEDs</td>
<td>49% of LEV users reported anger as a problem, vs. 3% using other AEDs, and 7% of controls.</td>
</tr>
<tr>
<td>Wieshmann and Baker 2017 [73]</td>
<td>Case-control, interview</td>
<td>$n = 380$ of which 329 (mean age: 39.8 years) have epilepsy using CBZ, VPA, LTG, or LEV in monotherapy, and 51 healthy controls</td>
<td>CNS-related adverse reactions more common with CBZ, VPA, LTG, and LEV vs. controls. Anger significantly more frequent with LEV (54% vs. 34% on CBZ, 33% on VPA, 31% on LTG, and 6% in controls).</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; $t$: observation time; PBAR: psychiatric and/or behavioral adverse reactions; CBZ: carbamazepine; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PGB: pregabalin; TPM: topiramate; VPA: valproate; ZNS: zonisamide.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biro et al. 2015 [35]</td>
<td>Case-control, ( t = 16 ) weeks–18 months</td>
<td>( n = 58 ) (mean age: 10.5 years) treated with PER</td>
<td>Aggression in 8 patients (13.8%). PER with increased risk of PBAR (incl. aggression, hostility, irritability, and anger). Occurrence of hostility and aggression independent of cotreatment with LEV or TPM.</td>
</tr>
<tr>
<td>Chung et al. 2017 [43]</td>
<td>Case-control, ( t = 29–142 ) weeks</td>
<td>( n = 1643 ) patients (≥12 years) with epilepsy using PER in monotherapy or with LEV and/or TPM</td>
<td>PBAR most common reason for discontinuation (aggression: ( n = 2 ); suicidal ideation ( N = 2 ); both combined: ( n = 1 )).</td>
</tr>
<tr>
<td>Coyle et al. 2014 [74]</td>
<td>Case-control, ( t = 19 ) months</td>
<td>( n = 47 ) patients with epilepsy (mean age: 31 years)</td>
<td>Irritability in 11.5% and aggression in 5.1%, leading to discontinuation of PER in 1.3% and 0.4%, respectively. 3.9% had ≥1 serious PBAR, of which 0.2% agitation, 0.2% abnormal behavior, and 1% aggression.</td>
</tr>
<tr>
<td>De Liso et al. 2016 [44]</td>
<td>Case-control, ( t = 7 ) months</td>
<td>( n = 62 ) children/adolescents (mean age: 14.2 years) using PER as add-on</td>
<td>Add-on treatment with 8 mg PER improved seizure control but worsened aggressive behavior which resulted in institutionalization of the patient.</td>
</tr>
<tr>
<td>Dolton and Choudry 2014 [75]</td>
<td>Case report, ( t = &gt;6 ) months</td>
<td>1 patient (37 years) with epilepsy, Tourette’s, moderately reduced cognitive function and demanding behavior</td>
<td>Higher incidence of aggression and hostility for PER vs. placebo in “narrow” and “broad” questionnaires (narrow: PER 3.0% vs. placebo 0.7%; broad: 11.8% vs. 5.7%), but not increased in non-epilepsy disorders.</td>
</tr>
<tr>
<td>Ettinger et al. 2015 [34]</td>
<td>Review of safety in phase I, II, and III clinical studies</td>
<td>( n = 9420 ) (12–65 years) with epilepsy, Parkinson’s, pain, MS, or migraine who received either PER or placebo</td>
<td>Irritability was the only individual adverse reaction with incidence ≥5% (PER: 11.1% vs. placebo 3.7%). Combined incidence of hostility and aggression: PER 18.5% vs. placebo 4.9%.</td>
</tr>
<tr>
<td>French et al. 2015 [76]</td>
<td>RCT, ( t = 32–54 ) weeks</td>
<td>( n = 162 ) patients (mean age: 28.4 years) with generalized epilepsy, of which PER: 81 and placebo: 81</td>
<td>PBAR in 50%, incl. irritability, aggression, increased sensitivity, and suicidal ideation/acts. This was also the main reason for discontinuation of PER.</td>
</tr>
<tr>
<td>Huber and Schmid 2017 [37]</td>
<td>Case-control, ( t = 2 ) years</td>
<td>( n = 26 ) patients (mean age: 30 years) with epilepsy and cognitive impairment of various degrees</td>
<td>Irritability in 11.5% and aggression in 5.1%, leading to discontinuation of PER in 1.3% and 0.4%, respectively. 3.9% had ≥1 serious PBAR, of which 0.2% agitation, 0.2% abnormal behavior, and 1% aggression.</td>
</tr>
<tr>
<td>Krauss et al. 2014 [77]</td>
<td>RCT, ( t = 1.5–2 ) years</td>
<td>( n = 1216 ) patients (≥12 years) with epilepsy, using 1–3 AEDs and PER as add-on</td>
<td>No difference in total score (behavior and competence) between PER and placebo, but aggression and hostility in 15 patients (17.6%) on PER vs. 2 (4.2%) on placebo.</td>
</tr>
<tr>
<td>Lagae et al. 2016 [78]</td>
<td>RCT, ( t = 20 ) weeks</td>
<td>( n = 133 ) (12–17 years) with epilepsy (PER: 85 and placebo: 48)</td>
<td>Aggression in 8.2% (vs. 0% on placebo).</td>
</tr>
<tr>
<td>Rosenfeld et al. 2015 [45]</td>
<td>RCT, ( t = 25–29 ) weeks</td>
<td>( n = 143 ) (12–17 years) with epilepsy of which PER: 98 and placebo: 45</td>
<td>Aggression was one of the most common reasons (6.6%) for dose changes or discontinuation of PER. Higher frequency of PBAR with PER, particularly irritability and aggression. Frequency of serious PBAR reported as low, but 3 cases of aggression and 1 of suicidal ideation.</td>
</tr>
<tr>
<td>Rugg-Gunn 2014 [46]</td>
<td>Review article, ( t = &gt;19 ) weeks</td>
<td>( n = 1450 ) patients of which 1008 on PER and 442 on placebo</td>
<td></td>
</tr>
</tbody>
</table>
advanced imaging. It seems that patients with dysfunction, as suggested by neuropsychological testing and often impaired. This has been associated with frontal lobe planning, execution of tasks, and behavioral control, are patients. Executive functions, e.g., problem-solving, and risk-seeking behavior are reported in a subset of these. Impulsiveness, quick and frequent mood changes, psychiatric comorbidity including substance and alcohol abuse personality disorders, psychosocial maladjustment, and psychiatric symptoms.

These brain regions are associated with regulation of emotions by its connections to the limbic system. Structural or functional abnormalities in the medial temporal lobe, like neuronal loss, synaptic reorganization, or changes in the hippocampus or the amygdala, are associated with a disposition for the development of psychiatric symptoms, including aggression [4]. The medial part of the temporal lobe contributes to the regulation of emotions by its connection to the limbic system. Structural or functional abnormalities in the medial temporal lobe, like neuronal loss, synaptic reorganization, or changes in the hippocampus or the amygdala, are associated with a disposition for the development of psychiatric symptoms, including aggression [4].

5. Biological Vulnerability

A wide range of clinical factors may interact to lay the ground for the development of AB induced by AEDs.

5.1. The Epileptic Disorder Itself. Neurological and psychiatric conditions may generally increase the vulnerability for PBAR [67]. This is in line with the observation that the rate of PBAR is lower in patients using AEDs for non-epilepsy conditions [4, 21]. It has been speculated that the increased vulnerability is due to structural and functional cerebral alterations.

Generalized onset seizures, particularly absence seizures, are associated with an increased risk of psychiatric and behavior-related symptoms, including anger, irritability, and aggression [18, 19, 24, 53]. It has been suggested that absence seizures have a cortical origin in the frontal lobe and involve the thalamus which may cause general functional impairment. These brain regions are associated with regulation of aggressive behavior [4, 18, 19, 112].

Juvenile myoclonic epilepsy (JME) is the most common form of idiopathic generalized epilepsy. It is associated with personality disorders, psychosocial maladjustment, and psychiatric comorbidity including substance and alcohol abuse [113, 114]. Impulsiveness, quick and frequent mood changes, and risk-seeking behavior are reported in a subset of these patients [114]. Executive functions, e.g., problem-solving, planning, execution of tasks, and behavioral control, are often impaired. This has been associated with frontal lobe dysfunction, as suggested by neuropsychological testing and advanced imaging [113, 114]. It seems that patients with JME are more vulnerable for PBAR induced by AEDs [113]. However, the clinical heterogeneity is pronounced, and psychosocial outcome and treatment responses vary widely in JME [114].

Besides generalized epilepsy, temporal lobe epilepsy (TLE) as well as is associated with psychiatric symptoms, including aggression [4]. The medial part of the temporal lobe contributes to the regulation of emotions by its connection to the limbic system. Structural or functional abnormalities in the medial temporal lobe, like neuronal loss, synaptic reorganization, or changes in the hippocampus or the amygdala, are associated with a disposition for the development of AB [4, 34, 115]. A previous history of febrile seizures or status epilepticus is often involved [4, 67, 115]. Brodie et al. [4] suggest that the structural changes seen with TLE may lead to growth of immature GABAergic neurons that convey excitation instead of inhibition, as seen in the brain of newborns. Hence, AEDs that reinforce GABA, i.e., LEV or TPM, would increase neuronal excitation instead of decreasing it [4]. Similar paradoxical effects may take place in the glutamatergic system, which implies that AEDs that normally inhibit glutamatergic signal transmission (LEV, PER, and TPM) might instead have a facilitating effect [4]. How these changes might affect the propensity to PBAR is not clear.

5.2. Psychiatric Comorbidity. The relationship between structural anomalies in the brain and PBAR is further illustrated by the fact that AB is frequently seen in patients with central nervous pathology, e.g., due to trauma or infection [116].
The concept of the interictal dysphoric disorder means that patients with epilepsy may exhibit the following psychiatric symptoms between seizures: depressed mood, reduced energy, pain, insomnia, anxiety, mood swings, and outbursts of irritability and AB irritability [117]. Patients with epilepsy may also present atypical behavioral symptoms that occur peri-ictally, i.e., before, during, or after an epileptic seizure [32, 117]. Prodromal and immediate postictal symptoms often manifest with dysphoric, emotional, and behavioral symptoms [118]. Postictal psychosis is a potentially dangerous complication of chronic epilepsy usually occurring with a lucid interval within one week after a cluster of (usually tonic-clonic) seizures. It may be associated with religious, paranoid, and persecutory ideas causing pronounced aggressive behavior [119]. A case of homicide was recently reported during postictal psychosis and was thought to be promoted by a preceding treatment switch from carbamazepine to LEV [120]. Furthermore, psychiatric symptoms that emerge after seizure control may represent an entity on its own, called “alternative psychosis” (see chapter 6.3). The above-mentioned phenomena illustrate how difficult it can be to distinguish between AED-induced PBAR and endogenous as well as seizure-related psychiatric and behavioral symptoms.

5.3. Genetic Influence. Since patients with difficult-to-treat epilepsy and a personal or family history of psychiatric disorders have a higher risk of PBAR, the question of a genetic predisposition has been discussed [4, 18, 67, 68]. Recently, numerous copy number variations have been uncovered as important risk factors for the development of multiple neuropsychiatric disorders [121]. Such chromosomal rearrangements may underlie a broad phenotype spectrum, ranging from normal development to mild learning- or intellectual disabilities, epilepsy, and psychiatric diseases, such as autism spectrum disorders and schizophrenia, often in combination [122–124]. The epilepsy is frequently of generalized type [121]. Conceivably, this vulnerable group of patients may harbor a particular susceptibility to develop complex PBAR from AEDs. Moreover, an association study by Helmstaedter et al. investigated LEV as a model AED for PBAR and found several genetic polymorphisms that are associated with reduced dopaminergic activity in patients having the most pronounced reactions [125]. However, as there are no further

Table 4: Studies reporting psychiatric and behavioral adverse reactions to topiramate.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. 2017 [18]</td>
<td>Case-control, t = ≥1 years</td>
<td>n = 4085 adults (mean age: 41 years) with epilepsy on ≥1 AED, of which TPM: 639</td>
<td>PBAR in 17.2%, leading to dose reduction or discontinuation in 13.8% (all patients) and 6.3% (TPM users).</td>
</tr>
<tr>
<td>Chung et al. 2007 [50]</td>
<td>Case-control, t = 2 years</td>
<td>n = 828 adults (mean age 38.5 years) on different AEDs (LEV: 196, LTG: 251, OXC: 97, TPM: 156, ZNS: 128)</td>
<td>TPM with the highest rate of discontinuation (55.8%), but only few due to PBAR (5 of 156 patients).</td>
</tr>
<tr>
<td>Endoh et al. 2012 [54]</td>
<td>Case-control, t = 17.6 months</td>
<td>n = 58 children with epileptic spasms, of which 33 used TPM</td>
<td>5 of 33 patients (15.2%) developed irritability.</td>
</tr>
<tr>
<td>Grosso et al. 2005 [81]</td>
<td>Cohort study, t = 11 months</td>
<td>n = 59 children &lt; 2 years (mean age: 13 months) on TPM</td>
<td>Irritability is one of the most common adverse reactions.</td>
</tr>
<tr>
<td>Kanner et al. 2003 [82]</td>
<td>Cohort study, t = 10.5 months</td>
<td>n = 596 patients (mean age: 36.1 years) with epilepsy using TPM as monotherapy or add-on</td>
<td>PBAR in 12.6%, incl. aggression (10.7%), irritability (5.7%), and depression (5%). TPM discontinued in 27% with these adverse reactions.</td>
</tr>
<tr>
<td>Lee et al. 2011 [55]</td>
<td>Cohort study, t = 17.2 weeks</td>
<td>n = 28 children (2-18 months) with infantile spasms using TPM</td>
<td>Irritability in 4 patients (14.3%; most common adverse reaction).</td>
</tr>
<tr>
<td>Mula et al. 2003 [38]</td>
<td>Cohort study, t = ≥6 months</td>
<td>n = 431 patients (mean age 35.8 years) with epilepsy using TPM</td>
<td>PBAR in 24% (agression: 5.6%).</td>
</tr>
<tr>
<td>Mula and Trimble 2003 [56]</td>
<td>Cohort study, t = ≥6 months</td>
<td>n = 103 patients on TPM</td>
<td>Mood symptoms in almost half of patients. Aggression is the second most common (23%), resolved after dose reduction or discontinuation of TPM.</td>
</tr>
<tr>
<td>Mula et al. 2007 [67]</td>
<td>Case-control, t = 2 years</td>
<td>n = 108 patients with epilepsy, treated with LEV and TPM (consecutively)</td>
<td>PBAR in 30%</td>
</tr>
<tr>
<td>Reith et al. 2003 [83]</td>
<td>Case-control, t = 309 days</td>
<td>n = 159 &lt; 18 years (mean age: 8.1 years) with epilepsy using TPM; follow-up of n = 127 of these</td>
<td>Aggression or psychosis treatment-limiting in 10 of 127 patients (7.9%).</td>
</tr>
<tr>
<td>Weintraub et al. 2007 [27]</td>
<td>Case-control, t = 13 months</td>
<td>n = 1394 of which 112 patients (mean age: 41 years) used TPM</td>
<td>PBAR in 6.3% on TPM, which was lower than the mean frequency of all AEDs (8.4%).</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial, t: observation time; PBAR: psychiatric and/or behavioral adverse reactions; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; TPM: topiramate; ZNS: zonisamide.
such studies, it is not clear whether these findings apply to other AEDs besides LEV [4, 125].

5.4. Intellectual Disability. From a lifetime perspective, people with intellectual disability are among the most drug-exposed groups in society. Epilepsy is the most common comorbidity in these individuals. They may not be able to report and describe adverse reactions from AEDs in the form of slowing of central information processing (114). Symptoms of overdosing, such as sedation, ataxia, or blurred vision, may even occur unnoticed by the caregivers [68, 84, 126]. Such unspecified adverse reactions are not uncommon with LEV, PER, and TPM (Table 1) and may be indirectly expressed as disturbed behavior and interpreted as specific pharmacodynamic effects [57, 127, 128]. It is also well-known that sedating drugs can paradoxically induce hyperactivity, especially in children [57]. TPM, in addition, can impair language function and reduce verbal fluency [128, 129]. This may be more pronounced in patients with lower educational levels, suggesting an impact of baseline cerebral performance [129]. Impaired ability to express oneself may trigger AB. Moreover, these patients often use AED polytherapy and other drugs targeting the brain, which may cause pharmacodynamic interactions and further increase the risk of disturbed behavior [28, 115].

In contrast, the “release phenomenon” denotes challenging conduct in patients disabled by a previously severe drug-resistant seizure disorder who obtain seizure control with newer drugs with less impact on alertness and cognition. This occurs usually in patients with intellectual disability, who may express increased vigilance and self-assertion as AB. A more demanding behavior should not invariably be interpreted as a sign of drug toxicity [114].

6. Other Potential Mechanisms

6.1. Hormonal and Biochemical Aspects. Various steroid hormones modulate AB, and studies have shown an association between high CNS levels of testosterone and impulsive-aggressive behavior [14, 130–132]. Testosterone may interact with the serotonin system and increase neuronal activity in brain regions involved in AB, such as the amygdala, hypothalamus, and periaqueductal gray matter (PAG) [130, 131]. Low levels of serotonin together with high levels of testosterone seem to play an important role in aggression [130]. Synthetic testosterone analogues have been shown to alter the expression of GABA_A and DA receptors and increase levels of vasopressin, substance P, and stress hormones [133]. Not surprisingly, aggressive behavior is much more frequently seen in male than in female patients with epilepsy [134, 135]. However, while women show less aggression, they tend to be more irritable than men [136].

It has been suggested that LEV inhibits aromatase, an enzyme that converts testosterone to estradiol [137, 138]. This would imply that patients using LEV may have higher levels of testosterone (and, possibly, reduced levels of estradiol). This could, at least partially, explain the increased prevalence of AB in patients using LEV. Birger et al. (2003) demonstrated that administration of testosterone in rats increased the expression of 5-HT_2A receptors and other 5-HT binding sites and that this most probably was an effect mediated by estradiol [130]. Inhibition of aromatase by LEV could therefore produce a dual negative effect on the serotonin system: increased testosterone levels may downregulate 5-HT, and decreased estradiol produces fewer 5-HT receptors and binding sites.

Stress is a trigger for both epilepsy and psychiatric disorders, and there is a significant overlap of the neural networks involved in stress and aggression [139, 140]. It is possible that AEDs directly or indirectly affect those hormones of the hypothalamus-pituitary-adrenal gland axis that are involved in regulation of stress responses [139].

Brodie et al. [4] point out that TPM, a carbonic anhydrase inhibitor, can induce metabolic acidosis, which is associated with aggression and irritability [4]. Interestingly, this pharmacologic characteristic is shared by zonisamide, an AED that is also associated with an elevated risk of PBAR [18].

6.2. Epigenetics. Epigenetics explains how dynamic environmental factors can affect the expression of genes and the pathophysiology of disease states without changing the genetic code [141]. In recent years, much attention has been directed toward AEDs and their impact on crucial epigenetic processes such as histone acetylation and DNA methylation [4, 12, 142]. Histones are proteins that are bound to the DNA. Their acetylation state affects the accessibility of the DNA and, thus, gene transcription and expression [142]. Acetylation is controlled by two enzymes called histone acetyltransferase (HAT) and histone deacetylase (HDAC). While little is known about the exact mechanisms, an association between HDAC and behavior has been found, including AB [142].

Valproate, a broad-spectrum AED and a mood stabilizer, possesses several MOAs, including inhibition of HDAC [4, 12, 13, 142, 143]. This contributes to increased expression of reelin and GAD67 in cortical GABAergic interneurons which may reduce aggression, as downregulation of reelin and GAD67 has been observed in patients with schizophrenia and bipolar disorder. These patients often show more anger and aggression than the general population [12, 142]. It has also been found that TPM and the main metabolite of LEV inhibit HDAC, but for now little is known how that may affect AB [143].

Further epigenetic mechanisms associated with AEDs and aggression are modulation of the serotonin system in the amygdala and the prefrontal cortex, as well as monoamine oxidase A activity [4, 142]. By now, it is not known whether PER exerts epigenetic effects.

6.3. Forced Normalization and Alternative Psychosis. “Forced normalization” (FN) is an EEG phenomenon [32, 115] that was first described by Landolt in 1953. He observed that patients with epilepsy developed psychiatric symptoms, mainly psychosis, when their EEG became normal and seizure control was achieved [144]. In 1965, Tellenbach introduced the term “alternative psychosis” which is the clinical counterpart of FN [115]. Later, “alternative” phenomena
have been expanded to include other psychiatric symptoms as well, e.g., depression, anxiety, hypomania/mania, and aggression [4, 115, 145]. Hence, it is possible that the psychiatric adverse reactions seen with AEDs not necessarily are direct pharmacological effects, but sometimes a neurophysiological consequence of improved seizure control.

Although the concept of FN/alternative psychosis was long ago acknowledged, its underlying mechanisms are essentially unknown [56, 146, 147]. It is thought to be related to the antagonism between epilepsy and psychosis, as epileptic seizures occasionally abort psychiatric symptoms (which also is the rationale for treating psychiatric conditions with electroconvulsive therapy) [148]. It has been speculated that some patients with epilepsy have a preexisting imbalance of neurotransmitters that would cause psychiatric symptoms would they not be prevented by recurrent epileptic seizures that lead to stabilization. A related possible explanation is the kindling phenomenon, where repeated stimulation of the limbic system, mainly the amygdala, is supposed to induce behavioral changes [146, 147, 149].

It has been reported that alternative psychosis occurs in relation to the introduction of new AEDs, and both LEV and TPM are examples [41, 67, 146, 149]. It is, however, important to understand that alternative psychiatric symptoms are not limited exclusively to drug treatment as it also may occur when seizure control is achieved by other methods, e.g., surgery [42, 115, 147]. From this, it follows that this clinical phenomenon does not depend on one distinct pharmacologic mechanism [32, 67]. Moreover, the concept of FN/alternative psychosis alone does not fully explain AB with AED use, since several studies have shown that PBAR also occurs in patients who do not become seizure-free [28, 32, 67]. Some studies also report that AB may be associated with deteriorated seizure control, which again illustrates the complex relationship between epileptic activity and behavior [56]. In clinical practice, it is important to clarify if psychiatric symptoms in patients using AEDs are adverse drug reactions, a consequence of seizure control, seizure breakthrough or an expression of a more complex, endogenous aptness for psychiatric disorders [4, 67].

6.4. Aggression Induced by Other Drugs. To identify possible mechanisms by which AEDs may induce AB, it could be useful to look at other drugs that also have the potential to induce this adverse reaction. Interestingly, several drugs used to treat aggression have been reported to induce AB. Among those are benzodiazepines, antidepressants, central stimulants [150–152], and AEDs, among them TPM [153]. Benzodiazepines increase the inhibitory actions of GABA via allosteric modulation of the GABA<sub>A</sub> receptor, thereby increasing its affinity for GABA [12, 150]. While most adverse reactions to sedative drugs are predictable, some patients may develop paradoxical reactions such as increased irritability, aggression, hostility, and impulsivity. Usually, this occurs in children, in elderly patients, and in patients with intellectual disability [150]. The paradoxical reactions are presumably due to disinhibition of behavioral networks that normally are balanced. This is based on the theory that GABA plays a role in AB, yet it is speculative [4, 150]. It has been found that the risk of AB is doubled in children and adolescents using antidepressants (SSRI, SNRI) that increase the amount of 5-HT and NA in synaptic clefts [151]. These monoamines are involved in AB [4]. Among central stimulants, particularly amphetamine and its derivatives are associated with irritability [152]. Amphetamines both increase the release and inhibit the reuptake of NE and DA in the synapse. In higher doses, they also inhibit 5-HT. High levels of NA and DA and low levels of 5-HT have been suggested to promote aggression and irritability [4, 152].

Other drugs that can induce AB are antihistamines, statins, and anabolic steroids [154–156]. In children, second-generation antihistamines can produce aggression, agitation, and hyperactivity [154]. Antihistamines act primarily as antagonists at the histamine H1 receptor. As mentioned above, low levels of 5-HT may promote AB, and it has been shown that histamine and H1 receptors in the brain can modulate AB via the 5-HT system [14]. Statins are another class of drugs that may induce increased irritability, which suggests a relationship between lowered cholesterol and AB [155]. These drugs are commonly used in combination with AEDs in elderly patients with vascular epilepsy.

It is not surprising that AB is a common adverse reaction to anabolic-androgenic steroids (AAS) [133, 156, 157]. Studies have shown that AAS not only increase AB temporarily, but also may lead to psychiatric long-term consequences as their use in or close to puberty may induce permanent changes in the developing brain [133, 156, 157]. AAS has been shown to modify the expression of cerebral androgen, GABA<sub>A</sub>, and DA receptors, as well as affect the 5-HT system and the levels of neuroactive substances, e.g., vasopressin, substance P, and stress hormones [133]. Carrillo et al. found that AAS reinforce glutamatergic connections between the hypothalamus and the stria terminalis. Their study supports that glutamate and vasopressin are involved in AB [158].

This review of AB induced by drugs that are not AEDs reveals some pharmacological similarities: (1) the modulation of GABAergic neurotransmission, demonstrated for both LEV and TPM and (2) inhibition of glutamatergic neurotransmission, particularly via the AMPA receptor—this has been demonstrated for LEV, PER, and TPM—and (3) modulation of the 5-HT system, which has been shown for LEV. Possible effects of AEDs on androgen and DA receptors as well as on neuroactive substances are poorly studied, but this does not mean that they do not exist. It must also be kept in mind that PER is one of the newest AEDs on the market. Chances are good that it may have pharmacological properties that have not yet been discovered. Likewise, all other drugs discussed here including LEV and TPM may possess unknown MOAs that contribute to their clinical effects.

7. Future Perspectives

Since little is certain and much is speculative regarding AB associated with AED treatment of epilepsy, and since it represents a significant clinical problem, further study on this topic is desirable. Studies on the pharmacological MOAs of AEDs and how they are related to AB would be particularly useful. This includes the search for yet unknown MOAs.
New technologies like pharmacological magnetic resonance imaging (phMRI) may help to identify the sites of AED action in the brain [159]. This could be related to what is known about the etiology and the pathophysiology of AB. As LEV, PER, and TPM share an inhibiting effect on glutamatergic transmission via the AMPA receptor, the latter may represent a promising starting point [18]. Possible AED effects on hormones like testosterone, oxytocin, and stress hormones as well as on neuroactive substances like vasopressin or substance P deserve further research, e.g., by concentration measurement in CSF or brain tissue. The relation between epigenetic factors and AB is another promising area of future research [4, 142]. It is also desirable to develop instruments and clinical routines that help clinicians to define whether psychiatric symptoms in the individual patient are an adverse reaction to AEDs, a consequence of achieved seizure control, the seizure disorder itself and its underlying cause, or the manifestation of endogenous psychiatric conditions [4, 67]. Moreover, further clinical research attempting to identify vulnerability factors may be helpful in order to minimize the incidence of these drug effects.

8. Summary and Conclusion

LEV, PER, and TPM are associated with a higher risk of AB than other AEDs. They have various pharmacological MOAs, some of which interfere with neurotransmitters involved in AB. However, it is not clear which of them is the main one responsible for the increased prevalence of AB. In this context, it is important to note that the MOAs we know of today do not necessarily represent the complete and final spectrum of pharmacological effects of these drugs. Future research might unveil additional MOAs. There are indications that particularly 5-HT, glutamate, and GABA are involved in aggression, and the AMPA receptor looks like the most promising target. Other mechanisms by which drugs may induce AB include modulation of testosterone levels and of various neuroactive substances. Little is known about the role of epigenetics in aggression, but it has already been shown for some AEDs that they do interact with epigenetic mechanisms such as histone acetylation and DNA methylation.

The biological vulnerability to PBAR from AEDs is multifaceted. A range of mechanisms and clinical predisposing factors may interact, including the phenomenon of alternative psychosis. Figure 1 illustrates the complex and multifactorial background of AB in people with epilepsy. Drug related, epilepsy-related, and patient-related elements must be carefully evaluated in each case. Challenging behaviors from non-AED-related causes should be excluded. Consideration of the epilepsy type and etiology and the previous personal or familial psychiatric history should receive particular attention. A low total drug burden and a slow dose titration are prerequisites for best possible risk reduction. Remarkably, PBAR may first be recognized clinically several weeks or months after starting the culprit drug. Of utmost importance is information to the patients, relatives, or caregivers about potential PBAR, and the possibility of their delayed onset. Patients starting AED treatment, particularly with LEV, PER, and TPM, need long-term and comprehensive clinical monitoring with awareness of emergent adverse behavior.

**Figure 1:** Summary of factors involved in aggressive behavior associated with antiepileptic drug treatment of epilepsy.
Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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