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Underestimated Aspects of Epilepsy Treatment: Forced Normalization and Seizure Aggravation by Antiepileptic Drugs

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ABSTRACT

After a detailed literature review, modern data about two underestimated aspects of epilepsy treatment - forced normalization and seizure aggravation by Antiepileptic Drugs **(AEDs)** - were summarized.

Forced Normalization **(FN)** is a phenomenon, characterized by a manifestation of some kind of incidental behavioral disorder in patients with epilepsy in association with a relative **EEG** normalization. The pathogenesis of this condition remains unresolved. The most important hypothesis assumes that, during **FN**, the epilepsy is still active subcortically, perhaps with spread of discharge along unusual pathways. The main risk factors of **FN** include: usage of some **AEDs**, neurophysiological factors associated with impaired balance of the glutamatergic, dopaminergic and **GABA**-ergic activity and some special clinical characteristics of patients. The most typical manifestations of **FN** include behavioral disturbance, psychosis, dysphoric and conversion symptoms. The diagnosis **FN** is based on the modern diagnostic criteria proposed by Krishnamoorthy and Trimble. Although there is no consensus about the therapeutic approach, most investigators recommend reassessment of the type and dose of **AEDs** and a possible brief course of treatment with antipsychotics and antidepressants.

Seizure aggravation by **AEDs** is defined as a paradoxical reaction when an **AED** increases the frequency and/or severity, and/or changes the pattern of a seizure type against it is usually effective, or when it leads to the onset of new types of seizures, or the occurrence of status epilepticus. The main mechanism of aggravation is the occurrence of inverse pharmacodynamic effect. This phenomenon occurs in patients treated by **AEDs** with a single mechanism of action - **GABA**ergic enhancement or blockade of Na^+ channels. Detailed information about the role of **AEDs** for different seizure type aggravation and SE induction was presented. Recommendations about an adequate diagnostic and therapeutic approach with the purpose of preventing from seizure aggravation were summarized.

Key words: Epilepsy; Forced normalization; Diagnostic criteria; Seizure aggravation; Antiepileptic drugs

Abbreviations: AED – antiepileptic drug, BDZ – benzodiazepines, BECTS - benign epilepsy with centrotemporal spikes, CBZ – Carbamazepine, CPS – complex partial seizures, CZP – Clonazepam, EEG – electroencephalography, ESM – Ethosuximid, IGE – idiopathic generalized epilepsies, FN – forced normalization, GABA - gamma aminobutyric acid, GBP - Gabapentin, GTCS – generalized tonic-clonic seizures, JME – juvenile myoclonic epilepsy, LEV – Levetiracetam, LTG – Lamotrigine, OCBZ – Oxcarbazepine, PB – Phenobarbital, PGB – Pregabalin, PHT – Phenytoin, PSSG – partial seizures with secondary generalization, SPS – simple partial seizures, RTG – Retigabine, SE – status epilepticus, TGB – Tiagabine, TPM – Topiramate, VGB – Vigabatrin, VPA – Valproate, ZNS - Zonisamide

Forced normalization and seizure aggravation by **AED**s are serious, although not frequent problems in patients with epilepsy. Both of them remain underestimated in clinical practice. Their understanding, however, is important for recognition, differential diagnosis purposes, and adequate, personalized, and multi-discipline approach.

FORCED NORMALIZATION

In spite of the considerable number of described patients with epilepsy and Forced Normalization **(FN)** in literature, the debate about the pathogenesis of this phenomenon still continues and specific diagnostic and therapeutic difficulties have emerged.

History of the Term “Forced Normalization”

The term “transformed epilepsy” was first used in 1875 to describe the manifestation of psychiatric symptoms following complete seizure control [1]. This concept was adopted in 1950s, when Landolt presented cases with epilepsy and psychotic episodes following seizure control and **EEG** normalization [2]. He introduced the term “paradoxical” or “forced normalization”, which means the manifestation of some kind of incidental behavioral disorder in patients with epilepsy in association with a relative **EEG** normalization [3]. With the purpose of avoiding of the absolute necessity of **EEG** recording, Tellenbach introduced the term “alternating psychosis” in

1965 to describe the lack of recovery or inactivation of the disease [4]. In fact in cases with **FN** epileptic discharges do not completely stop, but change their model of repetition, which generates psychopathological symptoms.

FN Pathogenesis

The pathogenesis of this condition has given rise to some debate but remains still unresolved. Older observations indicated a "biological antagonism" between productive psychotic symptomatology and epileptic seizures, which led to the therapy of psychoses with artificially induced convulsions. [5].

The most important and comprehensive hypothesis basically assumes that, during **FN**, the epilepsy is still active subcortically, perhaps with spread of discharge along unusual pathways [5]. This activity is supposed to provide energy and, possibly, some of the symptoms included in the psychotic syndrome. A critical clinical condition results, usually with a dysphoric symptomatology, where a development towards psychosis is impending. [6].

Bcause of the ongoing epileptic activity during **FN**, the differences with respect to other psychotic conditions in epilepsy are probably subtle rather than fundamental. Thus, it could be that ictal psychosis is characterized by a direct expression of epileptic activity, whereas in postictal psychosis a momentum of exhaustion may be added; moreover, in **FN** the prevailing pathogenic factor could be an abnormally high level of balance between excitatory and inhibitory processes [6]. It was established that in **FN**, the **EEG** deep structures of the lymbic system may show active foci of epileptical bioelectrical activity. This picture was suggested as a result of dissociated inhibitory influences of the brain stem [7]. It was also suggested a possible hypothetical relationship between psychosis and epilepsy regarding the mesolimbic dopaminergic system and kindling of this system with epileptic discharge in temporal-limbic circuits which could induce a psychotic state in some patients [8]. This would also easily explain the amelioration of acute psychotic activity with neuroleptic agents [8].

FN Risk Factors

The first group of risk factors includes some antiepileptic drugs. Ethosuximid seems to be the drug with the highest hazard because of the associated sleep disorders (decreased duration of slow-wave sleep, significant increase of stage 1 and moderate increase of stage 2 [6,9]. The rapid up-titration of **AEDs** is also a predisposing factor for **FN** [10]. Table 1 presents the main **AEDs** and their role for **FN** precipitation described in literature. **FN** has been also observed after surgical treatment – anterior temporal lobectomy [11], and after vagus nerve stimulation [12].

Table 1: Role of AEDs for FN precipitation.

AED	Role for FN precipitation	References
ESM	Да	10, 13, 14
VPA	Yes	13, 15
CBZ	Yes	13
PB	Yes	10, 16
PHT	Yes	10, 16
CZP	No data	-
OCBZ	No data	-
LTG	Yes	17, 18
TPM	Yes	10
VGB	Yes	10
TGB	Yes	19
GBP	No data	-
LEV	Yes (even in cases with slow up-titration)	10, 20, 21
PGB	No data	-
ZNS	Да	22
LCM	No data	10
RTG	No data	-

It has been described the role of some factors which may result in seizures, behavioral disturbance and **FN** [23]. Some investigators have emphasized the importance of the kindling phenomenon [23,24], the phenomenon of long-term potentiation [24] and the channel disorder paradigm [24] for **FN** precipitation.

Patients with frequent diurnal seizures (typically focal limbic seizures), repeated experience of ictal sudden, unexpected loss of consciousness [6], sleep disorders, preceding psychiatric disease [10] or brain dysfunction [25] are more likely to be diagnosed with **FN**.

Clinical Manifestations of FN

The frequency of **FN** in people with epilepsy is 1% [26] and explains about 15% of psychoses [13]. This phenomenon may be observed as a rare complication in patients with generalized epilepsies [6], here included refractory myoclonus epilepsy [14], and focal epilepsies [6]. **FN** is commonly described in adult patients with persisting absence seizures, well controlled by **ESM** [6, 26].

Psychotic episodes are most typical, catatonic psychosis has been also observed [27]. Tellenbach described a prodromal period with insomnia, anxiety, irritability, aggressiveness, withdrawal from contacts and habitual activities. **BDZ** application in this period may prevent from psychosis evolution through coping of insomnia [6].

Apart from psychotic episodes, the clinical manifestations of **FN** comprise dysphoric states,

hysterical and hypochondriacal syndromes, affective disorders [6,27], akinesia, apathy [20], behavioral disturbance with easy irritability and anger outbursts, verbally and physically abusive behavior towards everyone in the family, and throwing away utensils and valuable things out of the house, unusual stubbornness regarding accountability of household expenses [15], mania [14], stereotypic behavior [22], communication problems [22], paranoid hallucinations [26], dysgraphia [28]. Anzelotti et al described non-epileptic seizures presented with confusion, abdominal pain, asthenia, brief and repetitive tonic jerks of the trunk unaccompanied by loss of consciousness, which lasted about 50 seconds, followed by drowsiness for 10-15 minutes, without ictal **EEG** abnormalities [10].

Diagnostic Criteria for FN

The modern diagnostic criteria for **FN** proposed by Krishnamoorthy and Trimble have been accepted in clinical practice (Table 2).

Table 2: Primary and supportive diagnostic criteria for FN.

Primary (essential) criteria
1. Established diagnosis of epilepsy based on clinical history, EEG and imaging.
2. Presence of a behavioral disturbance of acute/subacute onset characterized by one or more of the following:
Psychosis with thought disorder, delusions, hallucinations
Significant mood change, hypomania/mania or depression
Anxiety with depersonalization, derealization
Hysteria: motor, sensory, abasia.
3A. Reduction in the total number of spikes counted in a 60-min awake EEG recording with a 16-channel machine, using standard 10-20 electrode placement, by over 50% compared to a similar recording performed during a normal state of behavior,
OR
3B. Report of complete cessation of seizures for at least 1 week, corroborated by a relative or carer.
Supportive criteria:
Recent change (within 30 days) of pharmacotherapeutic regimen
Report of similar episodes of seizure cessation and behavioral disturbance in the past, from close relative or carer, or general practitioner, or documentation of this in hospital records with or without EEG evidence. This may or may not be linked with an AED.

To make the diagnosis:

Primary criteria 1, 2 and 3A OR primary criteria 1, 2 and 3B and one supportive criterion [23].

Therapeutic approach in cases with **FN**

There is no consensus in literature whether **AED** termination is obligatory in patients with diagnosed **FN** [26]. Some investigators recommend dose reduction of **AEDs** [17,29], others-AED substitution [10], switching to monotherapy, slow up-titration to low doses of **AEDs** [29]. Serotonin reuptake inhibitors such as Fluvoxamine [22] or antipsychotics for a short period of time (3 months) such as Risperidone [15] may be additionally prescribed.

SEIZURE AGGRAVATION BY AEDS

Seizure aggravation by **AEDs** is a common and serious problem in medical practice. It was first recognized in the early 1990s [30]. It is probably more common in children than in adults, especially among mentally retarded children with mixed seizure disorders [31]. Unfortunately, this phenomenon receives poor attention in clinical trials and most reports describe single cases or small case series suggesting idiosyncratic reactions. However, there is sufficient evidence that a steadily increasing number of **AEDs** used in certain epilepsies may consistently cause worsening of seizures [32].

Definition

Seizure aggravation by **AEDs** is defined as a paradoxical reaction when an **AED** increases the frequency and/or severity, and/or changes the pattern of a seizure type against it is usually effective, or when it leads to the onset of new types of seizures, or the occurrence of status epilepticus. This is typically observed in the usual doses and normal serum levels, and in the absence of any other clinical features suggesting of an encephalopathy or sedation. The clinical improvement after dose reduction supports the diagnostic hypothesis [32, 33].

Aggravation is usually idiosyncratic, but it can be partly related to specific syndromes. It is difficult to predict aggravation of seizures in individual patients.

Pathophysiology

The pathophysiology of seizure aggravation is still poorly understood. The main mechanism of aggravation however, is the occurrence of inverse pharmacodynamic effect. This phenomenon occurs in patients treated by **AEDs** with a single mechanism of action - **GABA**ergic enhancement (**VGB, TGB, GBP**) or blockade of Na^+ channels (**CBZ, OCBZ, PB, PHT, LTG**). **AEDs** with multiple mechanisms of action are less likely to aggravate seizures [33].

Among cellular mechanisms by which **AEDs** may precipitate seizures, the **GABA** system is the most extensively studied. From a pathophysiological point of view, the facilitation or suppression of seizures depends on the balance between the inhibitory and excitatory activities of the thalamocortical network. The structure that plays a pivotal role in the activation of cortical sensorimotor areas (and consequently in the synchronisation of the epileptic discharge) within this network is the ventrobasal nucleus of the thalamus, which enhances **GABA**ergic action. The facilitating activity of this nucleus is normally inhibited by the **GABA**-mediated activity of the reticular nucleus of the thalamus. Although **GABA**ergic drugs are presumed to enhance **GABAA** transmission of the ventrobasal nucleus, it does not have a similar effect on the reticular nucleus. This different effect results in an imbalance in **GABA** transmission, hyperpolarization of the thalamocortical neurons, deinactivation of calcium T-channels. In this model, **GABA**ergic drugs, carbamazepine, and oxcarbazepine enhance oscillatory thalamocortical activity, increase slow-wave discharges and clinical seizures [30,34-36]. **AEDs** acting as voltage-dependent

sodium channel blockers enhance membrane stabilization, which may indirectly increase hypersynchronization of neuronal discharges in the thalamocortical network with already intensified oscillatory activity [36, 37].

Risk factors

Risk factors for worsening of seizures are epileptic encephalopathy, polytherapy, high frequency of seizures, and cognitive impairment [38].

Seizure types and epilepsy types aggravated by AEDs

Table 3 presents information about the role of **AEDs** for seizure type aggravation and **SE** induction.

Table 3: Role of AEDs for seizure aggravation and SE induction.

AEDs	Seizure type						SE	References
	Absences	Myoclonic	GTCS	SPS/ CPS/PSSG	Atonic	Tonic		
CBZ	+	+		+	+	+	+	36, 39-45
OCBZ		+		+			+	30, 46
VPA	+	+	+	+				47-50
PHT	+	+	+	+			+	36, 42-44, 51
TPM	+							39, 52
VGB	+	+		+		+	+	42, 43, 51, 53, 54
LTG	+	+	+			+	+	32, 56-61
GBP	+	+					+	42, 43, 62
TGB	+	+	+	+			+	34, 43, 63, 64
LEV	++	+	+	+			+	31, 65-68
BDZ		+				+	+	42, 69
PB	+	+				+		42, 51
ESM	+	+	+					70, 71
LCM		+						72, 73
PGB	+	+						74, 75
ZNS				+				76, 77
RTG								No

For some epilepsies the choice of **AEDs** may be inappropriate and its occurrence may be fairly predictable. This is best documented for the use of **CBZ** in **IGE** and myoclonic epilepsies, although exacerbation is possible in other epilepsy syndromes (childhood occipital epilepsy, symptomatic generalized epilepsies) as well [36,39,42,65]. **CBZ** was found to exacerbate all types of absence seizures (absences in patients with juvenile absence epilepsy, childhood absence epilepsy, absences with myoclonic jerks in **JME**, absences with eyelid myoclonus, Lennox-Gastaut syndrome and **BECTS** [39,41,43,78,79]. In the latter case, **CBZ** exacerbated absence, atonic and myoclonic seizures, in parallel with worsening of **EEG** features into a state of electrical status

epilepticus during sleep [41,43]. There is a case report of deterioration due to **CBZ** administration in childhood occipital epilepsy which was manifested by seizure aggravation, behavior and cognition changes, with occurrence of long-term bilateral discharges, and posterior sharp and slow-wave high amplitude complexes recorded by **EEG** [65].

OXC was shown to have a paradoxical response in patients with **BECTS** [78] and juvenile idiopathic generalized epilepsies [80].

Evidence for seizure aggravation with **PHT** is less robust than for **CBZ** [43]. Seizure deterioration and ataxia with **PHT** treatment were described in patients with progressive myoclonus epilepsy [81]

Benzodiazepines were occasionally reported to precipitate tonic seizures or aggravate tonic seizures, especially when given intravenously to control other seizure types in patients with Lennox-Gastaut syndrome [51].

The possibility of aggravation of some seizure types by **LEV** treatment was highlighted by some reports [65, 67] Four patients, two with cryptogenic focal epilepsy, another with Lennox-Gastaut syndrome, and another with Dravet syndrome, who experienced seizure aggravation (here included sudden development of apnoeic attacks) and negative myoclonus, associated with continuous spikes and waves during slow sleep, induced by **LEV**, were presented [31,68]. In 14 adults and 19 children **LEV** was associated with an increase in seizure frequency. Such a paradoxical effect appeared most often in mentally retarded patients during the first 2 months of treatment, and on relatively high doses [31].

LTG was associated with seizure aggravation in several type of epilepsies, including worsening of myoclonic, tonic, and tonic-clonic seizures in cases of severe myoclonic epilepsy of infancy [43,58], new onset of absence seizure in **BECTS** and transient cognitive impairment [56,82,83], and exacerbation of myoclonus in **JME** [59,84].

VGB was reported to aggravate absences [55], to induce atypical absence and tonic seizure in children with Lennox-Gastaut syndrome and myoclonic epilepsies [53], and the new appearance of myoclonic seizures in children with partial epilepsies [54]. It is paradoxical that **VGB** is effective in patients with West syndrome, but is contraindicated in other generalized epilepsies [42].

Seizure aggravation by **LCM** was described in three patients with Lennox-Gastaut syndrome resistant to conventional **AEDs** [72].

Two reports were found in literature about seizure aggravation by **LCM**: a patient who de novo developed almost continuous epileptic negative myoclonus, triggered by the addition of **LCM** to **CBZ** [24] and three patients with Lennox-Gastaut syndrome resistant to conventional **AEDs** [72].

The lowest risk of seizure aggravation appears to be with **VPA** [38, 85]. The number of reported cases of seizure aggravation in patients taking the drug in the literature is low – in a few patients with childhood absence epilepsy [48,49] or juvenile absence epilepsy [50]. Aggravation

of absence seizures with **VPA** was detected in eight children [48]. A paradoxical effect of **VPA** was also observed in a 3-year-old girl with cryptogenic localization-related epilepsy. On admission she experienced two types of seizures that were confirmed by ictal **EEGs**: **CPS** and combined seizures that began with repetitive myoclonic seizures immediately followed by a complex partial seizure. In the process of introduction and increase in the dosage of **VPA**, an aggravation of epileptic discharges, especially a dramatic increase in diffuse spike-waves during sleep, was observed. In the same period of time, myoclonic seizures not followed by **CPS** newly appeared, and there was an increase in the frequency of **CPS** and combined seizures [47].

Patterns of seizure aggravation

There are two main patterns of seizure aggravation by **AEDs**: seizure aggravation due to generic substitution or increasing the dose of **AEDs** and status epilepticus induction.

Seizure aggravation due to generic substitution was observed in cases treated with **TPM, VPA, CBZ, LTG, LEV** [39]. Seizure aggravation due to increasing the dose of **AEDs** was associated with resistant epilepsy and poor prognosis [39].

SE precipitation by **AEDs** is usually seen in cases with **IGE** inappropriately treated with drugs well known to exacerbate absences and/or myoclonic seizures. Fortunately, **SE** in this context has a good prognosis [66]. Bouts of absence or tonic-clonic status epilepticus and seizures in subjects with **IGE** treated with **PHT** or **CBZ** at therapeutic concentrations were considerably more frequent and proved intractable to treatment with **VPA** or **BDZ** compared with a cohort of subjects also with **IGE**, but naive to, or receiving subtherapeutic or therapeutic doses of other agents [44]. There was a report in literature about two adolescents with **IGE** in whom non convulsive **SE** with typical **EEG** abnormalities, triggered by **CBZ**, presented as affective and dissociative disorders [45]. Seven patients with absences or **GTCS** with induced typical or atypical absence **SE** by increase of the dose of **CBZ** or **CBZ** and **PHT** were also described [36].

Myoclonic **SE** was induced in a patient with **JME** by **OCBZ** [30].

Non convulsive **SE** in children with partial epilepsy [63, 64] and absence status in **IGE** [34] was triggered by **TGB**.

Precipitation of tonic **SE** was reported in patients with generalized epilepsies treated with **BDZ** [42].

Case reports about aggravation of absence seizures by **LTG** leading to absence status epilepticus in a child [32], myoclonic SE following high-dosage **LTG** therapy in a girl with Lennox-Gastaut syndrome [60], and three other patients, who developed absence SE with myoclonic components when switched from **VPA** [61], were found in literature.

SE was induced by **LEV** in three adults and four children and was most related to high or rapidly escalating doses [31,66].

A life threatening myoclonic **SE** after administration of **GBP** in a patient with benign adult familial myoclonic epilepsy was reported [62].

VGB was reported to aggravate absence status or to induce partial or generalized **SE** in patients with symptomatic or generalized epilepsy [51, 55].

Diagnosis

Before attributing exacerbation of seizures to an **AED**, alternative explanations should be excluded:

- Paradoxical intoxication (toxic serum concentration of the new drug),
- Spontaneous fluctuation of seizure frequency as a part of the natural course of epilepsy,
- The presence of known seizure aggravators (sleep deprivation, alcohol, psychotropic medication),
- Progression of brain disease and/or epilepsy,
- Drug resistance development,
- Low serum concentrations due to tapering-off comedication, pharmacokinetic interaction with the new drug or irregular compliance,
- Maladjustment to the disease,
- Comorbid illness,
- Development of tolerance,
- Inappropriate use of an **AED**,
- Non-epileptic seizures [31,86,87].

The risk of incorrectly blaming a drug for seizure aggravation can be minimized by establishing baseline seizure frequency over a period long enough to encompass the extremes of seizure fluctuation and by educating the patient that a temporal relationship may not be a causal relationship. The patient is recommended to continue the drug long enough to establish if the aggravation is transient. If the drug is stopped, rechallenge should be considered [86].

RECOMMENDATIONS

In practice it is impossible to avoid seizure aggravation completely. However, with careful diagnosis of the epileptic syndrome, adequate **AED** choice, slow **AEDs** titration, keeping a seizure diary, ensuring compliance and appropriate lifestyle, aggravation of seizures can be minimized [39, 42].

Seizure aggravation by **AEDs** should be always considered when there is an unexpected increase in seizure frequency and/or new seizure type following a change in drug treatment [51].

Patients are usually aware of aggravation before their doctors, therefore they should be listened carefully whenever they express a 'dislike' for an **AED**. Awareness of the problem "seizure aggravation with **AEDs**" will be helpful for its prevention through a considered and flexible approach to treatment of patients with epilepsy.

In case of hesitation about the seizure type, a broad spectrum **AED** should be used. Na^+-channels modulating **AEDs** and **GABA**ergic drugs seem to be more prone to aggravating seizures, therefore it is best to be avoided in the initial management of **IGE**.

CBZ is contraindicated in patients with absence epilepsy and infantile or juvenile myoclonic epilepsy and should be used with caution in patients with a mixed seizure disorder, particularly with a combination of tonic-clonic, atonic, absence seizures and /or generalized bilaterally synchronous spike-and-wave **EEG** discharges [51].

VGB, PHT, TGB, GBP may have some of the adverse events of **CBZ** on absence and myoclonic seizures and should be used cautiously in these patients [51].

Before a precise syndrome diagnosis can be made in children, the wisest therapeutic approach is monotherapy initiation with **VPA** (provided no risk factors for hepatotoxicity are present), which is as effective as other type of treatment and has the lowest potential of worsening seizures [51].

Information about some new **AEDs (ZNS, LCM, RTG)** is generally insufficient or lacking to allow definite statements about the potential to exacerbate specific seizure types.

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