Clinical characteristics of forced normalization and alternative psychosis with special consideration of the new anticonvulsants

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SUMMARY

Background. In the case of an alternative psychosis (AP) or forced normalization (FN), the patient alternates between periods of clinically manifest seizures and normal behavior, and other periods of seizure freedom or significant seizure reduction accompanied by psychosis or behavioral disturbances. In clinical practice and in the literature, the terms AP and FN are mostly used synonymously despite small differences. FN of the EEG is not only common to interictal mental disturbances but may also occur in the case of pre-ictal and postictal mental disturbances.

Aim. To update the 2007 review on “Alternative Psychoses of Epilepsy” in this journal with special consideration of the new anticonvulsants.

Material and Methods. We conducted a literature research from 1987 (in this year a psychosis, triggered by the first “new” anticonvulsant vigabatrin in a patient with epilepsy was reported for the first time) up to September 2019.

Discussion. AP/FN are rare events; only 10% of epileptic psychosis are AP/FN. AP/FN respectively occur with both generalized and focal epilepsy; in recent years, patients with focal epilepsy predominate. AP/FN generally present with behavioral disturbances of acute or subacute onset associated with thought disorder, delusions, hallucinations, significant mood change, or anxiety with depersonalization and derealization symptoms. The reports on EEG findings in patients with AP are inconsistent. In the case of FN, the EEG is by definition normal or substantially improved. The most prominent risk factor for the development of an AP/FN is the anticonvulsant medication. The following anticonvulsants have not been observed until now as triggers of an AP/FN in the literature reviewed by us: Acetazolamide and sulthiame (“old” anticonvulsants) and the “new” anticonvulsants brivaracetam, eslicarbazepine, pregabalin, retigabine, rufinamide, stiripentol. The treatment is based on 3 strategies: Reduction or complete cessation of anticonvulsants, change of anticonvulsants and administration of antipsychotic drugs.

Conclusion. The risk of an AP/FN is probably different for the individual drugs. At the current level of experience, gabapentin, pregabalin, oxcarbazepine or eslicarbazepine can be the first alternative if an AP/FN was triggered by another anticonvulsant in a patient with focal epilepsy. In generalized epilepsy, especially in patients with absences, valproic acid remains the first alternative.

Key words: alternative psychosis • forced normalization • epilepsy • anticonvulsants
BACKGROUND
In 2007, we published a review "Alternative psychoses of epilepsy" in *Epileptologia* (Fröscher and Steinert, 2007). In May 2019, Professor Jerzy Majkowski in his capacity of Editor-in-Chief, proposed an update of this review and we agreed to do so in mid-2020. Professor Majkowski always had a special interest in psychiatric disturbances in epilepsy, and he himself published on the subject of forced normalization (FN; Majkowski, 2005). We are deeply moved that Professor Majkowski passed away two months later.

Since the 18th century the phenomenon of the alternation of seizures and psychiatric disturbances has been recognised in some patients. This phenomenon was characterized as "forced normalization" (of the EEG) by Landolt (1955). Landolt was an expert in epileptology and electroencephalography (EEG) and focused more on the changes of the EEG than on the clinical presentation. Ten years later Tellenbach (1965), a psychiatrist, coined the term “Alternativpsychose”, in English alternative/alternating psychosis.

According to the proposal of a commission of the ILAE “alternative psychosis” has been defined as follows: The patient alternates between periods of clinically manifest seizures and normal behavior, and other periods of seizure freedom accompanied by a behavioral disturbance. The behavioral disturbance is often accompanied by paradoxical normalization of the EEG (forced normalization). The behavioral disturbance is polymorphic with paranoid and affective features. If EEG confirmation is available, the diagnosis should be qualified further as “with forced normalization of the EEG”. The diagnosis of AP should be made in the absence of the EEG (Krishnamoorthy et al., 2007).

Krishnamoorthy and Trimble (1999) proposed criteria for FN including an established diagnosis of epilepsy and the 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), with concomitant reduction of epileptic activity in the EEG, and/or complete cessation of clinical seizures for at least 1 week. The expected EEG changes are very detailed (reduction in the total number of spikes counted in a 60-min. awake EEG recording by over 50% compared to a similar recording performed during a normal state of behavior and others. However, other EEG findings than spikes (such as focal slow activity) are not discussed.

Other names for the alternation between periods of clinically manifest seizures and normal behavior are the following: para-ictal psychosis (Agrawal and Mula 2019), paradoxical normalization (Wolf, 1991) and Landolt’s phenomenon (Mula, 2010). Also, in 2019, there are no generally agreed diagnostic criteria for AP and FN (Agrawal and Mula, 2019). The terms AP and FN are not used in the ICD-10 (International Statistical Classification of Diseases and Related Health Problems) and DSM-5 (Diagnostic and Statistical Manual of Mental Disorders). Unfortunately, in both classification systems AP and FN are not distinguished from non-alternating psychoses and behavioral disturbances in patients with epilepsy.

The terms AP and FN are frequently used synonymously, although this is inaccurate.

FN always comprises mental disturbances (Krishnamoorthy and Trimble, 1999; Landolt 1955), however, a "forced normalization" of the EEG is not only common to interictal mental disturbances but may also occur in the case of pre-ictal and postictal mental disturbances (Fröscher and Steinert, 2019). An alternative psychosis (or other alternative mental disturbances), however, may occur without normalization of the EEG or even with a deterioration of the EEG. The drawback of the term "alternative psychosis" is the restriction to psychotic phenomena, not covering other mental disturbances such as mood disorders or anxiety, which may appear alternatively. However, the somewhat vague terms AP and FN have become integral parts of medical nomenclature. In the international literature, the term FN seems to be used more often than AP.

When we evaluated the case reports on AP and FN published in the years 1987–2017 a joint evaluation was possible without difficulties (we only had to exclude 3 cases of FN that were associated with postictal psychoses (Fröscher and Steinert, 2019). The remaining 66 patients, all of whom had been published as AP or FN, had "alternative" mental disturbances (mostly psychoses). The EEG-findings were reported only in 43 of the 66 patients. In 40 of these 43 patients, the clinical syndrome corresponded to both the AP and the FN concept; only in 3 patients the EEG findings remained unchanged during the period of mental disturbances compared to the period prior to these disturbances.
MATERIAL AND METHODS
For this update we conducted a literature research from 1987 (in this year a psychosis, triggered by the new anticonvulsant vigabatrin in a patient with epilepsy was reported for the first time) up to September 2019 with the terms “alternative psychosis of epilepsy (AP), forced/paradoxical/spurious normalization, Landolt’s phenomenon”. The following databases were searched: Medline (inclusive Epub ahead of Print, In-Process & Other Non-Indexed Citations, Daily Medline), Embase, Psycinfo und Psynex.

RESULTS AND DISCUSSION
Clinical syndrome
Epidemiology
As already stated in 2007 (Fröscher and Steinert, 2007), AP and FN were rarely diagnosed phenomena. The hope that they would become even rarer with the declining prescription of “old “anticonvulsants such as phenobarbital and phenytoin has not been realized. In addition to the cases provoked by anticonvulsants, there are now cases provoked by epilepsy surgery or vagus nerve stimulation.

In the literature the frequency of psychotic episodes of any type in patients with epilepsy is estimated at 0.5–10% (Fröscher and Steinert, 2019). According to Schmitz (2012), only 10% of epileptic psychoses are alternative psychoses, according to Mula (2010) the prevalence of FN is estimated at approximately 1% of patients with intractable epilepsy.

Type of epilepsy
AP and FN, respectively, occur with both generalized and focal epilepsy. In earlier studies on psychoses with epilepsy there was a significant correlation between generalized idiopathic epilepsies and psychoses with FN as a consequence of the high risk associated with a treatment with ethosuximide (Wolf, 1991). In recent years, more patients with a focal, particularly a temporal lobe focus, have been observed with the development of alternative psychiatric disturbances (Calle-López et al., 2019; Fröscher and Steinert, 2019; Krishnamoorthy and Trimble, 1999). In the review of Fröscher and Steinert (2019), 47 out of 60 patients had a focal epilepsy (41 focal, 6 focal and generalized). The most frequent type of seizures were complex focal seizures. AP/FN is rare in patients with mainly generalized tonic-clonic seizures and in extra-temporal lobe epilepsy (Agrawal and Mula, 2019).

Age and gender
Alternative psychoses may occur in every period of life. Even in children aged 2 or 3 years, psychiatric symptoms have been associated with abrupt seizure cessation and normalization of the EEG (Amir and Gross-Tsur, 1994). In older age AP/FN are rarely observed (Fröscher and Steinert, 2019).

An association of AP/FN with gender was not confirmed in the older literature (Schmitz and Trimble, 2005); however, two recent reviews report a higher incidence in women (Calle-López et al., 2019; Fröscher and Steinert, 2019). In the cases reported by Fröscher and Steinert (2019), women were affected more than twice as often as men; as a cause of this gender discrepancy a higher dose of anticonvulsants on average per body weight has been considered.

Clinical presentation
With regard to the clinical presentation, no new findings have emerged in recent years. The clinical presentation is nonspecific and there are no generally agreed diagnostic criteria for AP/FN (Agrawal and Mula, 2019). AP/FN generally presents with behavioral disturbances of acute or subacute onset, associated with thought disorder, delusions, hallucinations, significant mood change (hypomania or depression), and anxiety with depersonalization or derealization symptoms. It is associated with a reduction in the total number of spikes and/or clinical report of complete cessation of seizures for at least one week (Agrawal and Mula, 2019; Krishnamoorthy and Trimble, 1999). In our review of 66 patients with AP/FN, in 39 of these patients the mental symptoms were described as “psychosis”; 19 of these patients had hallucinations (auditory, visual, olfactory, tactile), 15 patients had delusional ideas. The remaining 27 patients had the following symptoms as alternative phenomena (with decreasing frequency): aggressiveness, irritability, depression, “behavioral disturbances”, sleep disturbances (in most cases insomnia), agitation/restlessness, fits of rage, anxiety, pseudo-seizures (Fröscher and Steinert, 2019).

Calle-López et al. (2019) analyzed 77 cases of FN. Patients presented psychosis (86.4%), mood disorders (25.8%), and dissociation (4.5%) as the main manifestations. In the psychosis group, persecutory (52.6%) and reference (47.3%) delusions were frequent. In general, delusions were more common in patients with temporal lobe epilepsy in comparison to patients with extratemporal and generalized epilepsies.
The psychoses usually occur in a state of clear consciousness. While some authors suggested that psychotic episodes in patients with epilepsy are indistinguishable from those of "classic" schizophrenia, other studies observed a minor severity and a better response to therapy in alternative psychoses (Kanner, 2000; Klosterkotter and Penin, 1989; Schmitz and Trimble, 2005).

**EEG findings**

The reports on EEG findings in patients with AP/FN are inconsistent. For example, Köhler (1975) rarely found a normal or normalized EEG during a AP/FN. Krishnamoorthy and Trimble (1999), however, in cases of FN proposed the following EEG findings as "primary criteria": Reduction in the total number of spikes counted in a 60 minute 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.

The review of Calle-López et al. (2019) only included publications which fulfilled these criteria; data on the variety of EEG findings in cases of alternative mental disturbances are therefore not presented. Case reports on an AP/FN communicated in the literature often do not take into account the stringent criteria of Krishnamoorthy and Trimble (1999) or only cite incomplete EEG findings. In our own review (Fröscher and Steinert, 2019) we included cases of AP even with missing or incomplete EEG findings as completely as possible, in order to detect triggering anticonvulsants. In most cases of AP where EEG findings had been reported, an improvement or normalization of these findings had been observed.

**Clinical course**

Usually AP/FN evolve within days, months or even years after cessation or marked reduction of seizures. The duration of an AP/FN amounts to some days up to many months (Fröscher and Steinert, 2007). In the study of Calle-López et al. (2019), the mean duration of FN episodes was 111 ± 384 (1–2880) days; FN lasted more than 3 weeks in 42% of patients. In the study of Fröscher and Steinert (2019), the mean duration of an AP/FN episode was one month (3 days – several years, n = 35 patients); obviously the duration is very different. An AP/FN episode may be terminated spontaneously, by spontaneous seizures, by seizures induced by reduction of the anticonvulsant medication or by antipsychotic drugs (see below, treatment).

The development of a chronic psychotic state is considered to be a rare event. There are, however, some patients who alternate repeatedly between periods with seizures and seizure-free periods with mental deterioration (Fröscher and Steinert, 2007). In the case series reported by Fröscher and Steinert (2019), at least 12 out of 66 patients had repeated episodes of an AP/FN. In the study of Calle-López et al. (2019), psychiatric symptoms could be controlled completely in 65% of the cases; 27% of the patients persisted with few mild psychiatric symptoms and 6% of the patients continued showing severe behavior disturbances despite treatment. The treatment that had induced FN made a difference for the clinical course. The majority (87.5%) of FN cases triggered by anticonvulsants presented complete resolution of the symptoms with the drug withdrawn, in comparison to the cases triggered by vagus nerve stimulation and surgery. Fifty percent of FN cases triggered by vagus nerve stimulation and 28.5% of FN cases triggered by surgery had a complete clinical resolution. In the surgical cases the trigger was irreversible and antipsychotic drugs were not completely effective. Among the vagus nerve stimulation-cases there was one successful case, which improved after a change in the pulse intensity of stimulation.

In our group of patients with an anticonvulsant-triggered AP/FN (n = 47; Fröscher and Steinert, 2019), the mean of the interval between onset of epilepsy and the first episode of AP/FN was 15 years (range: several weeks up to 43 years).

**Differential diagnosis**

In seizure-free patients with a psychosis, an iatrogenic effect of anticonvulsant drugs has to be considered. The clinical differentiation between AP/FN and a toxic reaction to anticonvulsants can be difficult if a seizure-free state followed the introduction of an anticonvulsant (Kanner and Rivas-Grajales, 2016). The probability of an AP/FN is supported if the EEG course shows a “forced” normalization. An improvement of psychiatric disturbances in these patients by spontaneous seizures also supports the diagnosis of an AP/FN (Marchetti et al., 2003). AP/FN becomes a less likely explanation if the symptoms resolve when the patient is transitioned to an alternative drug and remains seizure-free with a normal EEG (Bui et al., 2014).

**Risk factors, especially anticonvulsants**

Risk factors for the development of drug-induced AP/FN include a long-lasting focal epilepsy with phar-
macoresistance, a history of status epilepticus, psychosis, psychiatric disturbances, mental retardation and unfavourable psychosocial factors (Fröscher and Steinert, 2001; Majkowski, 2005). FN/AP seem to be more frequent in patients with temporal lobe epilepsy (Calle-López et al., 2019). The most prominent risk factor is probably the anticonvulsant medication. Several authors report that AP/FN has been described with all anticonvulsants, suggesting that this is not a drug-specific phenomenon but instead linked to the neurobiological mechanism underlying seizure control. In fact, as highlighted above, cases of an AP/FN have been described with vagus nerve stimulation and after epilepsy surgery (Agrawal and Mula, 2019).

During the period when only the older anticonvulsants were available, and the succinimides were the treatment of choice for the treatment of absence seizures, they were most often associated with the development of an AP/FN. The new anticonvulsants do not seem to bear an equal risk.

AP/FN gained renewed attention when, since 1990, a number of cases had been observed that had been triggered by the new anticonvulsant vigabatrin. Most other new anticonvulsants have also been reported to trigger an AP/FN in the following years.

In the period from 1987 to 2017, we reported 66 published AP/FN cases (Fröscher and Steinert, 2019). Only 15 out of 66 patients were treated with monotherapy, reducing the accountability to single components. The most commonly triggering anticonvulsants were (with decreasing frequency): vigabatrin, levetiracetam, ethosuximide, carbamazepine, valproic acid.

Once to three times the following anticonvulsants were described as triggers: lamotrigine, phenytoin, topiramate, zonisamide, ACTH (corticotropin), clonazepam, lacosamide, methsuximide, phenobarbital, primidone, midazolam, perampanel, sirolimus (reduces seizure frequency, Wiemer-Kruel et al., 2009). Not yet considered in our review was the report of Kiteva-Trenchevska (2018) on 4 cases of an AP/FN triggered by levetiracetam.

In 4 retrospective studies, another 176 alternative episodes were reported, but some details are missing. In these studies, the most common triggering anticonvulsants were (with decreasing frequency): vigabatrin, carbamazepine, phenytoin, phenobarbital, topiramate, valproic acid, zonisamide, lamotrigine. Gabapentin and oxcarbazepine are mentioned twice, tiagabine once as triggering anticonvulsants.

In the study of Calle-López et al. (2019), the triggering anticonvulsants were (with decreasing frequency): levetiracetam, vigabatrin, carbamazepine, lamotrigine, ethosuximide, lacosamide, valproic acid and once topiramate and phenytoin. The cases reported in this study partly correspond to the cases of our review. Other than in our review (Fröscher and Steinert, 2019), Calle-López et al. (2019) included cases reported since 1953 (the year of the first publication on FN by Landolt (1953)); however, only papers were included that fulfilled the FN criteria established much later by Krishnamoorthy and Trimble (1999). As a result, pre-1999 publications are probably under-represented. This may explain why phenytoin-triggered episodes are rare and phenobarbital/primidone-triggered episodes are absent.

In various reviews, the following additional anticonvulsants are reported as triggers of an AP/FN: Bromides, clorazepate, felbamate, mephenytoin, phenytoin (Fröscher and Steinert, 2019). Recently, an episode of FN likely triggered by cannabidiol was reported for the first time (Sands et al., 2019). To date the following anticonvulsants have not been reported as triggers of an AP/FN in the literature reviewed by us: acetazolamide and sulthiame (“old” anticonvulsants) and the “new” anticonvulsants brivaracetam, eslicarbazepine, pregabalin, retigabine, rufinamide and stiripentol. The frequency of case reports for individual drugs is rather limited in predicting the extent of the risk of an AP/FN by specific drugs. Of course, the frequency of reports depends on the frequency of prescriptions and the time a drug was licensed for clinical use. Noteworthy, however, is the number of communications relating to VGB that were published within a few years of introduction. The frequent mention of levetiracetam is at least partially related to the frequent prescription of this widely used anticonvulsant. In 2013, levetiracetam was the most widely prescribed anticonvulsant in Germany, followed by lamotrigine (Willems et al., 2018). At the current level of experience, gabapentin, pregabalin, oxcarbazepine or eslicarbazepine can be considered the first alternative anticonvulsant if an AP/FN was triggered by another anticonvulsant in a patient with focal epilepsy (Fröscher and Steinert, 2019). For brivaracetam, lacosamide and perampanel the short time of clinical experience does not allow a general recommendation. In generalized epilepsy, especially in patients with absences, valproic acid remains the first alternative anticonvulsant of choice.
Treatment
The treatment of an AP/FN has changed from previous recommendations only insofar as more anticonvulsants are available as an alternative. Three strategies, which do not exclude each other, may be used:

1. Reduction or complete cessation of anticonvulsants.
2. Change of anticonvulsants: if strategy 1 does not work and the desirable balance cannot be found, the anticonvulsant has to be changed. In some patients the change of the anticonvulsant, for example from ethosuximide to valproic acid (Wolf et al., 1984), may be sufficient. In this case there is a substance-specific effect, an effect that Kanemoto et al. (2001) also report. These authors describe patients, who became psychotic after seizure control with zonisamide or phenytoin, but not after seizure control by other anticonvulsants. In other cases, it is not the substance-specific effect that is decisive, but the fact of seizure suppression, regardless of which therapeutic measure is in use. In such patients AP/FN was not only triggered by seizure suppression by anticonvulsants but also by vagus nerve stimulation (Anzellotti et al., 2014) or epilepsy surgery (Kanemoto et al., 2012).
3. Antipsychotic drugs: if the reduction or change of anticonvulsants is not effective, antipsychotics and in a few cases, antidepressants are recommended. Antipsychotic drug use does not predict complete remission of psychiatric symptoms in comparison with the withdrawal of anticonvulsants (Calle-López et al., 2019; Fröscher and Steinert, 2019). The development of a chronic psychotic state is considered to be a rare event. There are, however, some patients who alternate repeatedly between periods with seizures and seizure free periods with mental deterioration (Fröscher and Steinert, 2019).

Limitations
The major limitation of this approach is that the collected case reports do not represent a clinical sample and might not be representative for the incidence of AP/FN cases under naturalistic treatment conditions. A publication bias is possible in several respects. Case reports are published by physicians who are interested in research and those might be the same physicians who are interested in collecting experiences with newer anticonvulsants. In addition, new observations, such as observation of AP/FN under treatment with recently introduced anticonvulsants, will be submitted and accepted for publication with higher probability than well-known phenomena. For these reasons, the incidence of AP/FN under newer anticonvulsants in relation to the older ones might be overestimated in this review.

CONCLUSION
Phenomena of AP and FN in patients with epilepsy are rare events. However, knowledge of these syndromes is important to be able to initiate correct treatment quickly. AP/FN are triggered by suppression of seizures both by anticonvulsants as well as by other treatment measures such as epilepsy surgery and vagus nerve stimulation. The risk of an AP/FN is probably different for the different drugs. At the present level of experience, gabapentin, pregabalin, oxcarbazepine or eslicarbazepine can be considered the first alternative choice if an AP/FN is triggered by another anticonvulsant in a patient with focal epilepsy. For brivaracetam, lacosamide and perampanel the limited experience of their clinical use does not allow a general recommendation to be made. In generalized epilepsy, especially in patients with absences, valproic acid remains the first alternative choice.

CONFLICT OF INTEREST DISCLOSURE
The authors declared no conflict of interest.

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