Chapter

Cognitive and Psychological Side Effects of Antiepileptic Drugs

Katja Eva Brückner

Abstract

Among well-known side effects such as dizziness, nausea, headache and diplopia medical treatment of epilepsy may cause side effects on cognition, mood and behavior. In special constellations this can profoundly affect compliance with the medication as well as quality of life. Some patients are more vulnerable to side effects than others. Side effects can have profound impact on the development and future life of a patient. Some antiepileptic drugs (e.g. topiramate, zonisamide) show a more severe side effect profile than others (e.g. lamotrigine, levetiracetam). Thus, in the treatment of epilepsy, it is crucial to consider such possible side effects – especially in the beginning of or while changing the medical treatment. Specific neuropsychological examinations can monitor side effects on cognitive functions like concentration, memory or speech function. If this is not possible in an ambulant setting, specific screening instruments and repeated and precise interviews of patients and/or relatives can help to discover potential side effects. Because most side effects can be reversible, dosage modification or drug replacement is required as soon as incompatibilities are discovered.

Keywords: epilepsy, antiepileptic drugs, cognitive side effects, psychological side effects

1. Introduction

As one of the most common chronic neurological disorders, epilepsy affects many people across all population groups and ages. A prevalence rate of 0.5–1% of the population has been assumed [1]. More recent studies on large cohorts report even significantly higher rates: there is evidence of a prevalence rate of 1.2% of active epilepsy in the population [2]. Active epilepsy means that people diagnosed with "epilepsy" have had a seizure within the last 12 months, have seen a doctor because of their epilepsy, and/or have been treated with anticonvulsant medication. Before starting therapy, it must be clarified whether epilepsy is actually present. 20–30% of all patients with non-epileptic seizures are incorrectly diagnosed with epilepsy [3]. Therefore, differential diagnoses - such as psychogenic non-epileptic seizures, cardiovascular fainting, sleep behavior disorders, paroxysmal movement disorders or metabolic diseases have to be excluded. A differentiation from non-disease-relevant, paroxysmally occurring phenomena that do not require therapy (e.g. sleep myoclonus) is necessary before initiating therapy.

After a precise diagnosis, clarification of possible differential diagnoses and a positive therapy decision, drug treatment is usually the first choice in the treatment of epilepsy. Drug therapy is never curative, because the selected medication only

prevents or reduces seizures in the sense of symptom prophylaxis. The underlying cause of epilepsy is not cured with drug treatment. Most patients with epilepsy can be easily being treated with medication and, depending on the epilepsy syndrome, become seizure-free with monotherapy or combination therapy [4]. Meanwhile, many agents with different mechanisms have been approved for the treatment of epilepsy. In addition to the desired effect - successful seizure control or a significant reduction of seizure frequency - as with all medications, there are also undesirable effects with anticonvulsants that are only tolerable to a certain extent and then only with a significant improvement in the seizure situation. The tolerable extent of these interference effects differs individually and depends on the individual situation. In addition to "classic" physical disturbances such as dizziness, nausea, headache and double vision, negative effects on cognitive performance and mental health are the least tolerated effects. Since drug therapy ideally leads to seizure freedom but does not cure epilepsy, in most cases drug treatment is a long-term therapy.

2. Medical treatment

There is a large number of anticonvulsants for drug therapy of epilepsy, although those of more recent and of latest generations are not inferior to those of the older generation in their anticonvulsant effects. Therefore, a choice must be made on the basis of possible interference and interaction profiles and taking into account the individual situation of each patient.

Special attention in the treatment decision requires certain patient groups such as women of childbearing age because certain anticonvulsants have increased teratogenicity. For example, Valproic acid should be avoided due to an increased risk of malformation and an unfavorable effect on the later intellectual development of the unborn child, especially in higher doses during pregnancy. However, other patient groups also need specific consideration: Patients with intellectual disabilities may experience an increase in their existing limitations due to paradoxical disturbances or drug-related negative effects on cognitive performance. Older patients are particularly susceptible to drug interferences due to various co−/multi-morbidities, various concomitant medications and the resulting interactions that may not always be foreseeable, as well as pharmacodynamics that change due to age.

3. Cognitive side effects of antiepileptic drugs

At the onset of epilepsy and prior to treatment cognitive impairment can be already observed in a large number of patients. Frequently detectable deficits can be found early in the course of the disease in attention, memory and executive functions [5].

Basically, all anticonvulsants can have a negative impact on cognitive performance. If any cognitive deficits before treatment existed, these deficits may be exacerbated. The most common negative effect of anticonvulsants is a decrease in information processing speed, reaction speed and concentration. Most treatment related cognitive disorders are reversible and fade after dose reduction or completely disappear after a change in substance. Only visual field defects with vigabatrine are irreversible, which is why this substance has been used only in individual cases and under strict ophthalmological control.

Among the anticonvulsants of the older generation valproic acid, carbamazepine and phenytoin have the most favorable cognitive side effect profile with

comparatively little effects on concentration, memory, information processing speed or word fluency. The newer generation of anticonvulsants with a rather minor influence on cognitive performance are lamotrigine, levetiracetam, gabapentin, perampanel, lacosamide, oxcarbazepine, eslicarbazepine and pregabalin [6, 7]. For lamotrigine and lacosamide - in individual cases also for oxcarbazepine and perampanel - improvements in cognitive partial performance (e.g. information processing speed, concentration, vigilance) have been described [8–11]. In Contrast, topiramate and zonisamide are anticonvulsants with a relatively unfavorable cognitive disturbance profile. However, bromine, phenobarbital and primidone can also be associated with cognitive disturbances (e.g. cognitive slowing), whereby these substances are rarely used in everyday clinical practice. In combination therapies, a frequently condition in refractory epilepsy, undesirable interference effects can accumulate.

Topiramate relatively often and sometimes very impressively leads to deterioration in language skills such as verbal fluency and word finding, to a slowdown in the speed of reaction and to decline in working memory. In general, these interference effects occur even at relatively low doses and also if the dosage is very slow. In addition, there does not seem to be a habituation effect, so that the disturbance effects persist even with long-term therapy. Patients with intelligence impairment react to topiramate with the same cognitive disturbances as intellectually unaffected patients: Slow reactions, reduced language skills and reduced working memory can be found [12]. Even if these patients already have cognitive impairments, an additional drug-related deterioration should not be neglected, as this can have a fundamental impact on everyday competence and independence.

The following case study is intended to illustrate the possible scope of these cognitive effects caused by topiramate: A 20-year-old man introduced himself to the epilepsy centre. He developed epilepsy when he was 14 years old. At that time he attended the 8th grade of a secondary modern school (in German: Realschule). His former neuropediatric put him on topiramate, which he had tolerated subjectively well to this day (a current daily dose at admission 400 mg). He did not remember negative cognitive effects during school and did not complain about it when he was admitted. Soon after onset of epilepsy, the patient switched from secondary modern school to secondary school (in German: Hauptschule –a school with a lower level of graduation). In the end, he left school without graduating and subsequently found no apprenticeship training position, so at the time of admission to the epilepsy centre, he has been working in a supermarket as a temporary helper. While treatment optimization he was given an alternative anticonvulsant. Before changing his mediaction, he underwent neuropsycholgical examination (**Figure 1**).

With a dosage of 400 mg topiramate, the patient displayed significant performance deficits in speech fluency, working memory and reaction speed were striking. These cognitive functions are associated with a successful performance in school: Linguistic skills are required to express yourself concretely and correctly in class and exams, to understand learning content and tasks and to apply or implement them. Working memory functions include the short-term holding and simultaneous manipulation of information – fundamental achievements to understand spoken language. If these skills are impaired or even slowed down, a student will not be able to adequately follow the lessons, which can lead to an overall failure in school. Though epilepsy can be accompanied with cognitive impairments or even global impairments of intelligence regardless of the medication, it is likely that a slight intellectual disability has caused the failed educational/professional career of our patient. After several months he came back to the epilepsy centre for further medication changes. At this point topiramate was completely discontinued.

The patient did not report any cognitive changes. However, he has started to catch up on the secondary school graduation. He even planned the next higher school graduation as well, to start apprenticeship as a car mechanic. We examined our patient again (**Figure 2**).

In contrast to the first neuropsychological examination, cognitive performances that have previously been below range (verbal fluency, reaction speed and working memory), were now within normal range. So, there were significant improvements in cognitive performance after stopping topiramate, which suggests that the deficits

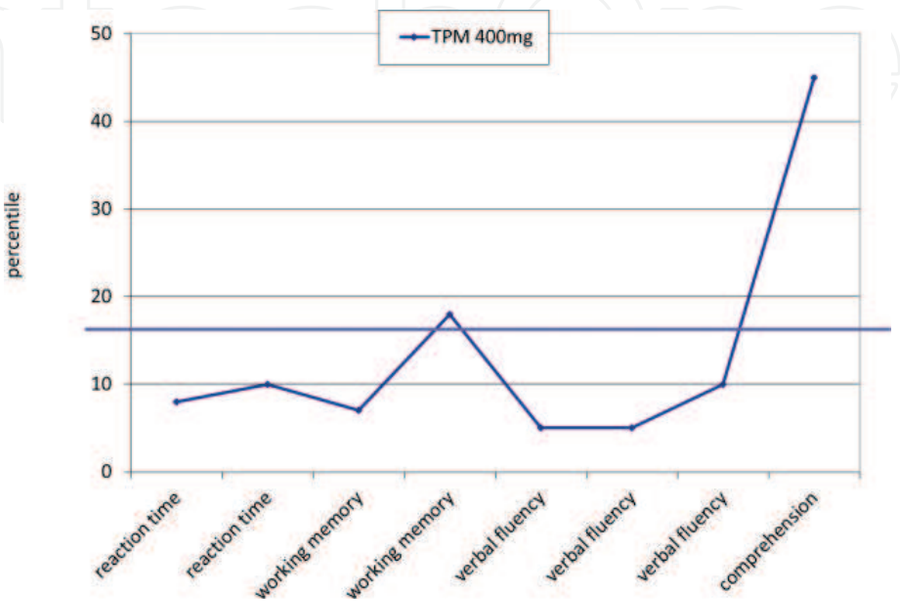

Figure 1.
Note: Percentile rank 16 = lower average limit compared to a healthy control group; reaction time = tasks on reaction speed, comprehension = task to understand language, TPM = topiramate; with 400 mg TPM, the patient's performance in almost all of the cognitive areas examined is below average compared to a healthy control group.

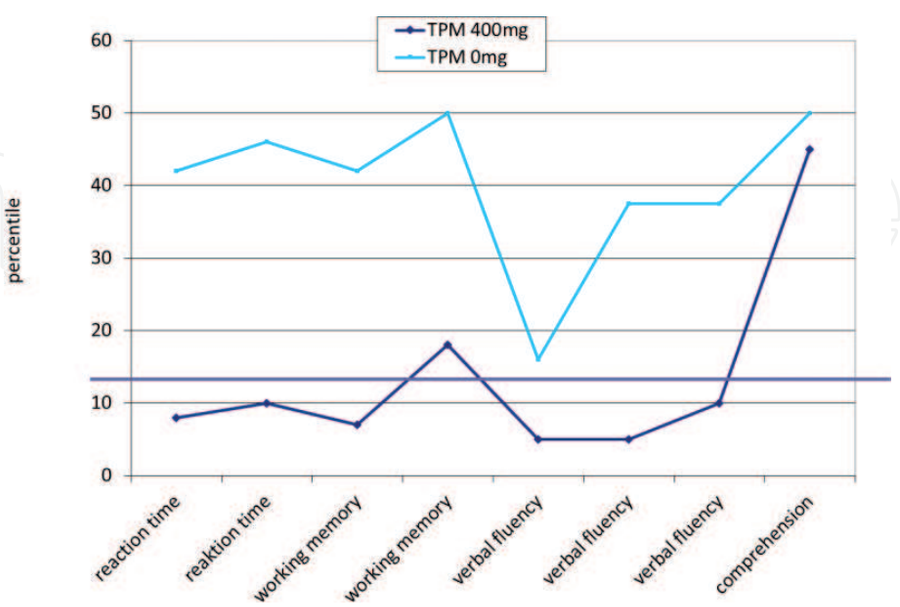

Figure 2.
Note: Percentile rank 16 = lower average limit compared to a healthy control group; reaction time = tasks on reaction speed, comprehension = task to understand language, TPM = topiramate; after discontinuing TPM (0 mg), all examined cognitive areas showed normal findings and thus shows a clear improvement compared to the previous examination (400 mg TPM).

found earlier (and thus probably also the failure in school) are related to the drug topiramate. Based on this case study, the possibly life-long social consequences due to the decision in favor of a certain drug at a certain point in patient patient's life, is very impressive.

Zonisamide - similar to topiramate - can lead to cognitive disturbances with memory disorders, cognitive slowdown and word finding disorders [13]. In contrast to topiramate, a dose effect can be observed here (the higher the dose, the more serious the impairment). It is supposed that the negative interference effects fade, but this is not reported in all studies [14], so that under certain circumstances a therapy attempt could be considered despite the initial interference effects (e.g. if other anticonvulsants have not led to the desired therapeutic success despite increasing them to the limit of interference).

Benzodiazepines (clobazam, clonazepam, diazepam, lorazepam) are a group of anticonvulsant drugs with well-known and sometimes clear cognitive side effects (sedation, fatigue, concentration disorders). Apart from this, additional problems such as development of tolerance and the risk of addiction rule out these drugs for long-term therapy in epilepsy treatment. Apart from individual cases, they are used only as a bridge drug in medication changes and as an emergency medicine with one-time dose.

4. Cognitive side effects in children

Most studies examining unwanted interference effects mainly focus on adults. For the treatment of children there are often no separate data available. Transferring the study results just to children and adolescents is not advisable. Naturally, a child's brain can, on the one hand, be restricted in its function by anticonvulsants, analogous to an adult brain. However, what is more is that unwanted interference effects can also adversely affect the further cognitive development. Disruptions in cognitive performances (e.g. working memory performance) can prevent or hinder the acquisition of new abilities and skills and may slow down the entire development. Especially child epilepsy syndromes can be associated with severe intellectual disabilities and developmental delays. Additional negative interference effects of the medication are detrimental, so that the child may not be able to exploit its entire and eventually already reduced development potential.

Not all available anticonvulsants are approved for the treatment of epilepsy in children Compared to adults, children are more sensitive to the undesirable effects of drugs. Lamotrigine, levetiracetam, rufinamide, and gabapentin appear to have a rather minor effect on cognitive performance - Lamotrigine is said to even improve concentration disorders in children [8, 15]. Topiramate and zonisamide, however, can also have a negative effect on cognitive performance in children. Both substances lead to the cognitive interference effects in children that have been observed in adults as well: word-finding disorders, cognitive slowdown, memory and working memory disorders [12]. In contrast to adults deteriorations in information processing speed, linguistic abilities, verbal learning and memory processes have also been described for valproic acid, oxcarbazepine and carbamazepine in children [16].

In contrast to adults, the drug-related cognitive deterioration is more serious in children, as further development and potential development in childhood and adolescence can be negatively influenced. Since school performance in particular plays an immense role in setting the course for later professional and social careers, the relevance of drug-related cognitive disruptive effects in childhood needs to be emphasized again, as the case study from the beginning illustrates very vividly.

As mentioned earlier, there is a connection between valproic acid during pregnancy and the intellectual abilities of the unborn child [17]. Compared to children who were exposed to carbamazepine during pregnancy, children after exposure to valproic acid (especially in higher doses) achieve an IQ value up to 10 points lower in the 6th year of life [18, 19]. Therefore this must be assessed as an irreversible, undesirable cognitive interference effect of valproic acid, even if this does not have a direct effect on the performance of the patient being treated, but rather on the unborn child who is been treated to. Since an association was also found between valproic acid during pregnancy and a later autism disorder in the child [20], therapy with valproic acid for women of childbearing age should be avoided.

5. Control of possible cognitive side effects

As the case study shows, the patient - and also the clinicians - are not always aware of the cognitive interference effects of anticonvulsants. In order to control possible influences on cognitive performance, it is therefore advisable - at least for certain substances (topiramate, zonisamide), to record the performance in a standardized manner before starting therapy, after reaching the target dose and if the patient reports any of new subjective cognitive complaints that occur during adjustment respectively. In specialized centres, this is carried out by experienced neuropsychologists as part of neuropsychological follow-up examinations with change-sensitive test procedures. In the outpatient neurological setting, however, a neuropsychological examination accompanying the drug setting is often not possible. Therefore, it is important to monitor potential changes by a detailed and repeated questioning of the patients or their caregivers about tolerability, including specific questions about possible changes/failures in school or work since the medication changeover, as well as test instruments specially designed for this question, such as EpiTrack and EpiTrack Junior (only available in German [21, 22]). Many different neuropsychological tests are available to control cognitive functions. The following cognitive performances should always be recorded: Attention (especially information processing speed), executive functions, language functions (especially verbal fluidity) and working memory. When selecting tests, care should be taken to ensure that the tests can be used repeatedly (e.g. parallel versions). In addition, possible mood changes should always be recorded.

In summary, because of their low negative impact on cognitive performance, certain anticonvulsants (e.g. lamotrigine, levetiracetam) are superior to others (topiramate, zonisamide, valproic acid). A monotherapy is always preferable to a combination therapy and a low dose to a high one, since most of the undesirable interfering effects described are both dose-dependent (lower dose - fewer or less interfering effects) and can tend to accumulate in combination therapies. In some cases, negative interfering effects can be counteracted by slowly increasing the medication (start low – go slow). However, this does not apply to all substances (see topiramate). In the case of drugs known to have undesirable cognitive interferences, the start of therapy should, if possible, be accompanied by neuropsychological follow-up examinations.

The best possible seizure control or seizure reduction is necessary for both the quality of life and the general performance of a patient. Therefore, substances with cognitive interference effects may sometimes be preferable to others (e.g. when other substances are not effective). In these cases, an individual assessment of the cost–benefit profile is necessary.

6. Psychological side effects of anticonvulsant medication

Like people with other chronic diseases, patients with epilepsy suffer significantly more often from psychological comorbidities such as depression or anxiety than healthy people. Treatment-refractory epilepsy and epilepsy with a seizure origin in temporal structures are affected with particular frequency [23]. Psychological complaints represent a significant impairment of the quality of life for those affected and require both precise diagnostics and consistent therapy. Treatment with mood-stabilizing, antidepressant drugs and accompanying psychological psychotherapy should therefore be considered for these patients. Concerns about possible proconvulsive effects of antidepressants are usually unfounded (with a single exception: amitriptyline) and should not prevent therapy.

However, before starting antidepressant therapy, it must be clarified whether the psychological complaints of the patient are possibly an undesirable interference of the anticonvulsant medication: Substances like topiramate, zonisamide, levetiracetam, and perampanel can have a negative impact on mood [13, 24]. Depressive and psychotic symptoms as well as increased aggressiveness were observed with topiramate. With levetiracetam, depressive symptoms can occur in individual cases as an undesirable drug interference effect as well. Much more common with this substance, however, are increased irritability and aggressiveness, which can unsettle both patients and relatives and in some cases lead to serious problems in the social environment. A dose reduction or a switch to another medication is advisable in both cases. For example, brivaracetam, which has been available since the beginning of 2016, promises to have a lower impact on psychological well-being with a similar mechanism of treatment [25–27].

With regard to psychological comorbidities, lamotrigine should be emphasized as an anticonvulsant with a probably additional antidepressant effect. Lamotrigine is therefore particularly recommended for patients with depression. However, lamotrigine can lead to unwanted sleep disorders, especially in the initial phase. This can be countered either by reducing the dose and then increasing it more slowly or by redistributing the individual doses during the day (higher dose in the morning, lower dose in the evening). In addition to lamotrigine, pregabalin also has a beneficial effect on psychological comorbidities, especially anxiety and sleep disorders. Topiramate, which is used in lower doses also for migraine prophylaxis and addiction therapy [28], can be used in patients with additional migraines - taking into account the above-mentioned factors relating to cognitive performance.

7. Psychological side effects in children

There is evidence that both topiramate and levetiracetam can lead to undesirable mood changes, particularly depression, irritability, personality changes, and hyperactivity in some children. Phenobarbital and primidone can lead to behavioral problems in children as well. Lamotrigine, on the other hand, has a mood-enhancing effect in children like in adults [29], and in children also has a positive effect on aggressiveness and impulsiveness [15]. Rufinamide appears to be unproblematic with regard to undesirable psychological disturbances [30].

In children and adolescents with intellectual disabilities, an increase in behavioral problems has occasionally been described with lamotrigine. Here, however, this might be due to the "lack of" sedation under lamotrigine compared to other anticonvulsants and the possible associated improved vigilance. If the medication switch to lamotrigine leads to behavioral problems, this might not be related to the medication

but to the possibly underlying disease and then of course it requires another handling than that of a re-sedation.

In summary, it is advisable to check a possible relationship between a newly dosed anticonvulsant and the psychological complaints of a patient and then to counteract this by switching to an alternative medication. Since correlations between emotional side effects of anticonvulsants, a rapid dose escalation, an already existing mental illness and a family predisposition for mental illness were found, it is advisable to consider these aspects in drug selection [31].

8. Control of possible psychological side effects

To control possible psychological side effects, questionnaires can be used in addition to exploration and behavioral observation. The Beck Depression Inventory (BDI-II), Beck Anxiety Inventory (BAI) and the Hospital Anxiety and Depression Scale (HADS) are well-known and well established methods [32–34]. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) was developed specifically for people with epilepsy to detect depressive symptoms [35]. For children, the Child Behavior Checklist (CBCL-4-18) is recommended [36].

9. Alternatives to drug therapy

Due to the diverse side effects of anticonvulsants, alternative treatment methods (e.g. epilepsy surgery) should be considered early if therapy refractivity is determined. Therapy-refractory epilepsy is present if two suitable anticonvulsants dosed up to the interference limit in monotherapy and a combination therapy has not led to seizure freedom. For a clearly defined group of patients, epilepsy surgery is a safe, well-established and very promising treatment option: For example, in the case of unifocal temporal lobe epilepsy due to proven hippocampal sclerosis, the chance of postoperative freedom from seizures is up to 80%. In comparison, the chances of success of a further drug change for these patients are significantly lower.

10. Conclusion for practice

Since drug-based epilepsy therapy is mostly a long-term – sometimes a lifelong – therapy, it is of particular importance to take undesirable interfering effects into account. In addition to the frequency of seizures, cognitive and psychological side effects are particularly serious for the quality of life of patients. Therefore, when treating epilepsy with drugs, the focus should not only be on the desired effects on the frequency and severity of seizures, but also on possible undesirable effects on cognitive performance and mental health. Both the individual living conditions of the individual patient (e.g. possible later desire for children, upcoming training/studies) as well as possible comorbidities (e.g. previous psychological comorbidity, intellectual impairment, cognitive partial performance disorders) must be taken into account when selecting drug therapy. Especially in children, patients with intellectual disabilities and elderly patients (due to the increased vulnerability to undesirable disturbances), it is recommended to start with a low dose and slowly increase the dose ("start low, go slow"). For certain substances, the monitoring of cognitive functions and mood before and during the change/adjustment is necessary, e.g. based on neuropsychological follow-up examinations, special screening procedures and a detailed and specific questioning of the patient and the caregivers (**Table 1**).

Abbreviations/anticonvulsants		Possible cognitive side effects	Possible emotional side effects
BR	Bromine	—	o
BRV	Brivaracetam	o	o
CBZ	Carbamazepine	(– In children)	+
CLB	Clobazam	—	Drug addiction problem
CLZ	Clonazepam	—	Drug addiction problem
DZP	Diazepam	—	Drug addiction problem
ESL	Eslicarbazepine	o	o
GBP	Gabapentine	o	(– In children)
LCM	Lacosamide	+	o
LEV	Levetiracetam	o	—
LTG	Lamotrigine	+	+
LZP	Lorazepam	—	Drug addiction problem
OXC	Oxcarbazepine	(+),(– In children)	o
PER	Perampanel	(+)	—
PB	Phenobarbital	—	(– In children)
PHT	Phenytoine	—	o
PGB	Pregabalin	—	+
PRM	Primidon	—	(– In children)
RFM	Rufinamide	o	o
TPM	Topiramate	—	—
VGB	Vigabatrin	Irreversible visual field defects	
VPA	Valproic acid	(– In children, – in the unborn child)	+
ZNS	Zonisamide	—	(–)

Legend: – negative interfering effect, + positive effect, o no known interfering effect.

Table 1.
Overview of possible cognitive and psychological side effects of anticonvulsants.

Author details

Katja Eva Brückner
Epilepsiezentrum Hamburg, Ev. Krankenhaus Alsterdorf, Hamburg, Germany

*Address all correspondence to: k.brueckner@eka.alsterdorf.de

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