Antiepileptic drugs in psychiatry

F Ovsiew

The potential risks of AEDs widely used in psychiatric patients are not fully understood

Antiepileptic drugs (AEDs) have been widely used by psychiatrists to treat disorders other than epilepsy for two decades. Here I survey those uses and selectively review the side effects of AEDs in the psychiatric context.

AEDs are now so widely used for non-epileptic indications that the appellation "anti-epileptic drug" may verge on mislabelling (to paraphrase David Healy's comment about serotonin-reuptake inhibitors and "antidepressants"). Nonetheless, no better designation is available, and I refer to these drugs as AEDs. Oddly, the newer AEDs may prove to be more useful in psychiatric illness than in epilepsy, where their greater efficacy than the older agents has not yet been conclusively demonstrated.¹

An assumption that the mechanisms of action of AEDs are the same in epilepsy and in psychiatric disorders would go beyond the evidence. Activity against kindling has been proposed to explain the psychotropic effect,² but this seems to account for neither the spectrum of psychiatric benefits nor the range of beneficial drugs. A division of psychotropic effects into "sedating" (mediated by GABAergic action) and "activating" (mediated by antiserotonergic action)³ likewise may fail to capture the diversity of psychotropic "principles" by which the diverse category of AEDs exerts psychotropic effects.⁴

Although I review scientific data regarding the use of AEDs in psychiatry, a non-scientific factor, of uncertain power, may partly account for the rise in prescription of AEDs. The interest of pharmaceutical firms in expanding the use of their products and their willingness, at least in some instances, to use improper means have recently been highlighted by the guilty plea of a major company in a case involving marketing an AED for off-label indications.⁵ Since the scientific evidence in the realm reviewed is far from complete, the clinician needs to be alert for non-scientific influences on practice.

AEDS IN MOOD AND ANXIETY DISORDERS

Lithium remains the agent for bipolar mood disorder with the best documentation of efficacy across the phases of the disorder, depressed and manic, acute and maintenance.⁶ However, AEDs are now commonly used in the treatment of bipolar mood disorder. Limited data suggest that over the course of the 1990s the use of AEDs approximately doubled, while the use of lithium fell below that of AEDs.⁷ At least three findings account for this development. First, certain syndromes of bipolar mood disorder respond poorly to lithium. Patients responding poorly to lithium include those with mixed bipolar states (states that include a mixture of manic and depressive features, often presenting in atypical fashion, for example as characterological irritability) and patients with rapid cycling (defined as having more than four episodes of mood disorder in a year). Second, bipolar mood disorder may be much more common than assumed: though conventional epidemiology has it that unipolar major depression is several times more common than bipolar mood disorder, recent studies suggest that half of patients presenting with major depression may have bipolarity.⁸ Third, patients with bipolar disorder often suffer from sub-syndromal depressive symptoms during much of their lives, but the use of antidepressants in these patients risks evoking mania or exacerbating cycling.⁹

Thus agents with efficacy for bipolar depressive or mixed states or for lithium refractory patients are particularly welcome, and considerable high quality evidence—and much more anecdotal or uncontrolled evidence—supports the use of AEDs for these indications. Reports of psychotropic effects of valproic acid (an amide derivative of valproic acid available in Europe but not in the United States) and carbamazepine emerged soon after their introduction.⁴ Divalproex (an enteric-coated formulation of valproic acid and sodium valproate, the most widely used preparation of

valproic acid in the United States because it has fewer gastrointestinal side effects than valproic acid) and carbamazepine have now been shown to be effective in the treatment of acute mania, with a spectrum of action that includes the "non-classical" manic states of dysphoric mania and rapid cycling.^{3, 10} Efficacy for prophylaxis is less securely supported by clinical trial evidence, although many clinicians employ these agents as well as the newer AEDs in this fashion. Evidence for antidepressant efficacy is modest. Oxcarbazepine appears, on limited evidence, to have similar efficacy to carbamazepine but better tolerability.^{11, 12}

Of the newer AEDs, lamotrigine has occasioned particular interest. Its efficacy for bipolar depression was foreshadowed by reports of efficacy against depressive symptoms in epileptic patients.¹³ Evidence of its acute and prophylactic effects against bipolar depression is now available, with efficacy against manic relapse in maintenance treatment also finding support.¹⁴ Whether it is effective as acute treatment for mania is a less pressing clinical matter, because the required slow titration precludes reliance on its use in many such circumstances. Topiramate is less well studied, but open trials indicate good tolerability as well as efficacy for non-classical mania.¹⁵ Levetiracetam is of considerable interest for bipolar disorder, with reports of benefit for mania, depression, and rapid cycling, but adequate data are not available.^{16, 17} Limited uncontrolled data suggest utility of zonisamide and tiagabine for bipolar disorder.^{18, 19} On present evidence, gabapentin does not appear effective for bipolar disorder.^{20, 21}

However, gabapentin—an attractive compound because of a favourable side effect profile and a lack of drug interactions—appears on limited evidence to be of considerable use in anxiety states, including social phobia, post-traumatic stress disorder, panic disorder, and opiate withdrawal.^{22–24} The role of other AEDs in the treatment of anxiety is less well studied.

Fortunately, electroconvulsive therapy can safely be undertaken in patients treated with AEDs (and indeed in patients with epilepsy).^{25, 26} Often it will be necessary to reduce the dose or hold a dose prior to the treatment so as not to elevate the seizure threshold, especially later in a course of ECT when the seizure threshold has risen.

AEDS IN OTHER MENTAL DISORDERS

The potential use of AEDs in schizophrenia, the subject of many open trials, was highlighted by a blinded, placebo

controlled study in which lamotrigine was shown to be effective (in combination with clozapine) in treatment refractory schizophrenic patients.^{27 28} The anti-glutamatergic action of lamotrigine is of particular interest because of a current focus on glutamatergic mechanisms in schizophrenia; lamotrigine via inhibition of glutamate release may be synergistic with clozapine, which is a glutamate antagonist.

The overlap of mood disorder, especially sub-syndromal bipolar mood disorder with rapid cycling and dysphoria or irritability, and borderline personality disorder (BPD) is a matter of active investigation.²⁹ The problem of BPD is a major one, because of the morbidity associated with the disorder—a 10% lifetime suicide risk is estimated—and because of the patients' intense utilisation of mental health resources. An empirically validated pharmacological approach to these patients is desirable; study data and clinical experience show roles for antipsychotics and antidepressants. Carbamazepine reduced impulsivity in early trials.³⁰ In recent studies, divalproex and lamotrigine showed benefit for aggression, mood stability, and impulsivity even in the absence of a diagnosable mood disorder.^{31 32}

AEDS FOR AGITATION AND IN THOSE WITH LEARNING DISABILITY

AEDs have come to be widely used for agitation and aggression in the demented elderly and in children and adults with learning disability. A neuroprotective role for divalproex has even been suggested.³³ In general, the data supporting the practice of treating agitation with AEDs are not of high quality; a recent Cochrane review found major methodological flaws in existing studies and could not support the use of divalproex in dementia.³⁴ Further, clinicians need to be aware of the special risks of adverse behavioural effects of AEDs in the developmental disability population.³⁵ Nonetheless, open trial data and clinical anecdotes continue to encourage clinicians to use AEDs as less toxic alternatives to antipsychotics in these populations.^{33 36}

AEDS AND WEIGHT

Weight gain produced by psychiatric drugs and the related "metabolic syndrome" of insulin resistance, dyslipidaemia, abdominal obesity, and elevated blood pressure emerged as a focus of psychiatric concern with the advent of the newer antipsychotic agents. However, weight gain is an important consideration with antidepressants, lithium, carbamazepine, and divalproex.³⁷ The potential of divalproex to

cause fatty liver (by virtue of its association with the metabolic syndrome, not by idiosyncratic hepatotoxicity) is an additional concern.³⁸ Perhaps this latter risk extends to other agents that promote weight gain. The advent of AEDs that are weight neutral, such as lamotrigine and levetiracetam, or produce weight loss, such as topiramate and zonisamide, is thus an important development.³⁹ Topiramate may find a specific use in the treatment of bulimia.^{40 41} Zonisamide has been the subject of an impressively favourable trial in which it was prescribed solely for weight loss.⁴² Especially in psychiatric patients who are on other psychotropic drugs that promote weight gain, these considerations are of substantial importance to patients' general health and to their compliance with psychiatric regimens.

AEDS AND HORMONAL SIDE EFFECTS

Reproductive endocrine disorders are common in epileptic women, but the role of AEDs in the dysfunction remains controversial.^{43 44} Evidence from several centres demonstrates that valproate produces elevated androgen levels,^{45–48} although the elevations may not correlate with symptomatic measures of androgen excess (the polycystic ovary syndrome).^{45 47} This effect appears not to depend solely on valproate induced weight gain. Of particular interest is whether women with epilepsy and women with bipolar mood disorder are equally affected when valproate is administered. In one of the few direct tests of this question, valproate produced elevated androgens (compared with lithium treated bipolar patients) in both epileptic and bipolar women, but produced more clinical symptoms of hyperandrogenism in the epileptics than in the bipolars.⁴⁹ A differential effect is biologically plausible because of the known effects of epilepsy itself on reproductive endocrine function, so research on epileptic patients cannot easily be extrapolated to psychiatric populations. In view of the wide use of valproate in women with psychiatric disorders—not to mention female adolescents and children—such focused research is urgently required.

Reproductive endocrine disorders associated with AEDs are not confined to women. In epileptic men, AEDs including carbamazepine, oxcarbazepine, and valproate were found to produce alterations of sex hormones and of sperm morphology and function.^{50 51} This issue is entirely unstudied in male patients with psychiatric disorders.

COGNITIVE AND BEHAVIOURAL SIDE EFFECTS OF AEDS

The literature on the cognitive, emotional, and behavioural impact of AEDs on epileptic patients has been held up as a warning to psychiatrists about the potential for adverse effects in psychiatric patients.⁵² This potential was recognised early in the psychiatric literature when carbamazepine used in borderline personality disorder was reported to cause depression.⁵³ Such effects might be particularly likely because of vulnerability indicated by psychiatric history,^{54–56} and might be hard to recognise because of concurrent primary psychiatric symptoms.

However, adverse behavioural effects in epileptic patients might be a consequence of interaction between the epileptic brain and the AED, so such effects might be less likely in psychiatric populations. As an example, topiramate has salient adverse cognitive effects in epileptics, including executive cognitive dysfunction and a distinctive anomia, but these effects do not seem to be as prominently mentioned in the limited literature on the psychiatric use of topiramate.^{15 57 58} This might be because of their subtle nature, or it might be because of psychiatrists' inadequate sensitivity. On the other hand, since the occurrence of the anomia appears to be related to a left temporal seizure focus and that of depression and adverse cognitive effects to the presence of hippocampal sclerosis,^{56 59} and the occurrence of adverse behavioural effects may be critically related to abolition of seizures,⁶⁰ such phenomena may simply be less common in patients without organic disease.⁶¹ While certainly the warning provided by the epilepsy literature must be taken seriously in psychiatry, only systematic observations of AED use in psychiatric patients will resolve the issue.

Similarly, reports of parkinsonism and cognitive impairment due to valproic acid, which have repeatedly appeared in the neurological literature, are almost completely absent from the psychiatric literature.^{62–64} Either psychiatrists have been oblivious to this important phenomenon, or the drug has different effects in epileptics and patients with mood disorder.

AEDS AND BONE LOSS

AEDs cause bone loss and an increased risk of fracture by multiple mechanisms, notably by reducing serum vitamin D and increasing bone turnover. Enzyme inducers and enzyme inhibitors share this side effect, but evidence on its occurrence with the newer AEDs is limited. For example, lamotrigine may not produce bone loss.⁶⁵ The compelling

evidence of risk has led experts to propose that epileptic patients on AEDs should be screened at least with a baseline bone density scan and annual measurements of serum vitamin D, calcium, and alkaline phosphatase and should be treated with supplemental calcium and vitamin D.⁶⁵⁻⁶⁶ The elevated risk of fractures is not related solely to trauma during convulsions; the risk of fracture not related to a seizure is also elevated several-fold in patients on AEDs. Thus the risk could reasonably be expected to be present in patients treated with the same agents for psychiatric indications, especially in the elderly or developmentally disabled patient with limited mobility and exposure to sunlight. However, to my knowledge evidence on this point is not available. The issue is virtually unmentioned in the psychiatric literature, and recommendations for screening and prophylaxis for bone loss in psychiatric patients have not been provided.⁶⁷

CO-MORBIDITY OF EPILEPSY AND PSYCHIATRIC ILLNESS

A crucial aspect of the use of AEDs in psychiatric patients is their use when the psychiatric patient also has epilepsy. The prevalence of psychiatric illness in epilepsy is high, particularly depression, which is under-recognised but has a substantial impact on quality of life.⁶⁸⁻⁶⁹ As a first step in assessing such situations, consideration of adverse effects of the AEDs being used to treat epilepsy is appropriate.⁵² This caution applies particularly to the learning disability population, in which such side effects may be both more common and more difficult to recognise.³⁵ The potential psychotropic effects of AEDs can, in part, guide the choice of agent for epilepsy; for example, the benefit of lamotrigine for depression has already been mentioned.¹³

When other psychotropic drugs are to be used in patients with epilepsy, consideration of drug interactions is necessary and complex. Certain antidepressants produce marked changes in AED levels, while others (such as citalopram, escitalopram, and sertraline) do not. De Leon⁷⁰ recently provided a useful summary of the literature on dosage adjustment of antipsychotic drugs necessitated by concurrent administration of AEDs.

SUMMARY AND CONCLUSIONS

This review has surveyed the utility and selected aspects of the adverse effects of AEDs for psychiatric indications. Without doubt these agents are a welcome advance. That their use has, in some respects, gone beyond the systematic evidence for efficacy testifies to the

difficulty and urgency of providing effective treatment to many psychiatric patients. (The use of AEDs in epilepsy routinely goes beyond the evidence, when drugs approved on the basis of add on trials are used as first line treatment or monotherapy.) That the potential risks of AEDs in psychiatric patients are not fully understood signals a need for research and for caution on the part of clinicians, for caution does not have to mean undertreatment.

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Emotion

Clear indications of emotion depend on vivid stimuli

J Zihl

Implications for style of communication with depressed patients

In this issue, recognition of emotion in depressed subjects is the focus of a paper by Kan *et al* (pp 1667–71).¹ In contrast to others, these authors report that recognition of positive and negative visual and prosodic emotions is not impaired in depressed patients. Differences in methodological approaches most likely explain the discrepancy. Whereas earlier authors relied on presentation of static visual images, Kan and colleagues used moving facial stimuli, and it appears that the nature (clarity) of the latter stimulus helped depressed subjects to correctly assess facial emotions.

Since the literature is abundant with reports on facial emotion recognition deficits in a variety of neurological conditions (e.g. stroke, temporal lobe epilepsy, Parkinson's disease, Huntington's disease), neuropsychiatric disorders

(e.g. schizophrenia, frontotemporal dementia, dementia of the Alzheimer type, autism) and other disorders (e.g. adolescent mood and anxiety disorders, body dysmorphic disorder, social phobia), the results of the study by Kan *et al* has broad implications. It is, however, necessary to replicate their protocol and findings before drawing any firm conclusions on this issue. At the same time, it would also be important to seek possible differences in emotion recognition within the category "depression". For example, impaired emotion recognition may not be a common finding in all depressed patients. Further, as has been shown for schizophrenic patients,² the possibility that cognitive deficits may also contribute to difficulties in facial recognition should be considered, especially in depressives that have cognitive dysfunction.

It is worthwhile noting that brain imaging studies on facial recognition in normal subjects also (mostly) depend on presentation of static faces. In studies where moving faces have been used, greater responses to dynamic versus static emotional expressions were found.³ Given that dynamic properties of an image increase attention to faces moving in the context of emotional expressions,⁴ it is not at all surprising that transmission of high quality facial emotion improves emotion recognition, thereby also enhancing face-to-face teleconferencing in virtual space.⁵ It is highly likely that similar principles hold true for all types of facial confrontation.

The observations made by Kan and colleagues also have very practical implications. The main difficulty in discerning facial and, of course, prosodic emotion correctly may be as much due to the disposition of the "actor" (e.g. psychiatrist, neurologist, psychologist, family, friends) as to patients' emotional perceptual difficulties. This interpretation takes on greater importance when one considers that facial and vocal expressions represent the main source of information in social perception and thus, social interaction. In this context, the work by Kan *et al* has far reaching implications for style of communication with depressed patients, as well as for the diagnostics and therapeutics of patients with neurological or psychiatric disorders.

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Stroke

Using PET to identify carotid occlusion patients at high risk of subsequent stroke: further insights

J-C Baron

Identifying carotid occlusion patients at risk of stroke

Although atherothrombotic occlusion of the internal carotid artery (ICA) can cause a devastating stroke, in many instances it is a benign event, causing only transient ischaemic attacks (TIAs), a minor stroke, or even no symptom at all. Despite optimal medical treatment, however, the subsequent risk of stroke in patients with symptomatic ICA occlusion is around 7% per year, with 6% ipsilateral. It would be important to be able to identify patients at high risk of subsequent stroke to implement appropriate prevention. Studies performed over the last two decades have provided strong evidence that haemodynamic factors play a major role in such risk. The association of focally decreased cerebral blood flow (CBF) and increased oxygen extraction fraction (OEF)—coined “misery perfusion”—was first described in a patient with medically intractable TIAs distal to a previously documented ICA occlusion with poor collateralisation.¹ This abnormal physiology pointed to reduction in perfusion pressure beyond the lower limit of autoregulation, so quite logically an extracranial-intracranial bypass was performed, after which both the TIAs and the misery perfusion resolved.¹ Prospective studies have since documented that in patients with symptomatic ICA occlusion the presence of misery perfusion (or severely impaired vasodilatory reserve as a surrogate) considerably increases the risk of subsequent ipsilateral stroke, with an odds ratio of 7 to 8.^{2–5} This in turn led to challenge of the negative results of the international EC-IC bypass

study, of which haemodynamic assessment was not part. Accordingly, two trials this time focusing only on patients with documented misery perfusion or inadequate vasodilation reserve are currently underway in the US and Japan. However, whether knowledge of the pattern of collaterals predicts the presence of misery perfusion and therefore avoids complicated physiological investigations would be important to know.

In view of the contradictory findings from earlier studies, Yamauchi *et al*⁶ have revisited the issue and their results are published in this issue (pp 1697–701).

Their hypothesis was that cortical metabolic depression secondary to diaschisis or to selective neuronal damage might confound the occurrence of high OEF. By reducing synaptic activity, cortical diaschisis—a frequent occurrence in striato-capsular infarction, probably secondary to disruption of the thalamo-cortical fibres,⁷—might reset the perfusion-metabolism imbalance and thus “mask” misery perfusion (fig 1). Selective neuronal damage secondary to episodes of ischaemia is another putative cause of cortical metabolic depression.⁸ Supporting their hypothesis, Yamauchi *et al* found that the presence of ophthalmic or leptomeningeal collateralisation (assessed by conventional four vessel angiography) predicted the occurrence of misery perfusion, but only in the absence of striatocapsular infarction.

Figure 1 Idealised graph illustrating the expected increase in oxygen extraction fraction (OEF) from its physiological value of around 40% in the face of a primary reduction in cerebral blood flow (CBF) below its physiological value of around 50 ml.100 g⁻¹ min⁻¹, and the resetting of this relationship towards normal levels of OEF in the presence of primary metabolic depression such as induced by superimposed diaschisis.

The clinical implications from this work are potentially important—the presence of ophthalmic or leptomeningeal collaterals in a patient with no striatocapsular infarct accurately predicts increased OEF, and in turn a high risk of subsequent ipsilateral stroke. It remains to be seen if some patients without misery perfusion as a result of subcortical infarct are still at a high risk of subsequent ipsilateral stroke, and whether other indicators of impaired haemodynamic reserve would identify them. Also, whether the clinical presentation—especially continuing haemodynamic type TIAs—helps in identifying ICA occlusion patients at high risk of stroke would be worth investigating.

This study has pathophysiological implications in cerebrovascular disease

beyond chronic ICA occlusion. For instance, does diaschisis afford neuroprotection to the penumbral cortex in the acute stage of stroke in the presence of an early striato-capsular core?

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Stroke

Variations in care and outcome in the first year after stroke: a Western and Central European perspective

H S Markus

Large differences in outcome and resource utilisation

Stroke is a major health burden throughout Europe. Despite a reducing incidence in Western Europe,¹ the rise in the elderly population and increasing incidence rates in Eastern Europe will result in it becoming a mounting population burden. It consumes a large amount of healthcare resources; in the UK about 5% of the National Health Services' budget is spent on stroke care. Therefore optimal models for delivery of stroke care, which result in good outcome at reasonable cost, are of great importance. Although robust data has shown that care in a stroke unit (with most trials looking at rehabilitation units) is associated with improved outcome,² we have limited understanding of which components of this organised care are responsible for this benefit. Comparing practice and outcome across different European countries may give clues that can help us to develop new hypotheses and interventions, which should then be ideally tested in controlled studies.

In this issue (pp 1702–6) the BIOMED European Study of Stroke Care Group present data from 11 centres in several Central and West European countries.³ The group have previously shown wide variation in early (3 month) mortality and dependency, even after adjustment for case mix and other confounding factors. Three month mortality ranged from 42% in one UK centre to 19% in France.⁴ Centres involved in this study may not be typical of stroke care within their countries; their involvement in a research project of this type suggests they are already particularly interested in stroke care. Indeed a UK audit suggests wide variations in stroke care provision within a single country.⁵ However, the national differences noted by the BIOMED group are consistent with data from other sources. For example, in the International Stroke Trial there were wide national differences in outcome, not fully explained by case mixed variables, and the UK again had poor outcome.⁶

What explains these differences? One needs to be cautious that they are not, at least partly, explained by differences in case mix including hospital referral practice, ethnic and other differences in stroke subtype, and socio-economic differences. The latter was not controlled for in the BIOMED project, while some residual confounding by stroke severity is likely despite attempts to control for it. However, such confounding is unlikely to fully account for these differences, and the wide variations in patterns of stroke care seen throughout Europe appear to be important. Many of these have been described previously by the European BIOMED Group.⁷ One feature that varies widely across Europe is the intensity with which the acute episode of stroke is managed. In many units (e.g. Dijon, France and Kuopio and Turku, Finland), almost all patients are admitted directly to a neurology unit, while in others admission is to a dedicated acute stroke unit (e.g. Florence, Italy and Copenhagen, Denmark). In contrast many patients in the UK are admitted to a general medical ward. Fifty percent in Dijon are admitted to an intensive care unit while in other countries the figure is zero. There are wide variations in the use of physiological monitoring, and attempted control of cerebral blood flow, fever, blood glucose, and hydration, and in the treatment of severe cerebral oedema with drugs, craniectomy, or hypothermia. There are also wide variations in availability and use of early brain imaging and other investigational facilities, as well as total medical, nursing, and therapist time utilised per patient. Importantly total cost is not directly related to outcome.

For example, in one UK centre overall cost was one of the highest, but outcome was one of the worst.⁷ The great majority of stroke care cost is due to bed occupancy, including nursing and therapy costs. Therefore improved acute care—if it results in reduced length of stay—is likely to be very cost effective.

This paper extends the previous findings to focus on longer term (12 month) survival and outcome, and again demonstrates large differences in both outcome and resource utilisation. For example, availability and support from family and friends differed widely between countries. A number of variables were identified as being associated with death and dependency, and these included male gender, pre-stroke handicap, and at presentation the presence of coma, incontinence, swallowing problems, or weakness.

How can we use this and other data to improve stroke care? A number of messages are emerging from different studies. Stroke care should be in specialised units and should be delivered by appropriately trained teams. Increasing evidence suggests early admission to a specialised unit, early brain imaging and diagnosis, and attention to early physiological care is associated with improved outcome,^{8–10} although the evidence for benefit of most specific acute

interventions is not well founded.¹¹ However, many questions remain. We understand little about which components of rehabilitation therapy are beneficial and what the dose–response relationship is for these. There are also many uncertainties in acute care. For example, how aggressive should we be with blood pressure lowering and other physiological interventions in the immediate post stroke period? What is the role of interventions such as craniectomy, hypothermia, and extending the time window for thrombolysis? Many of these issues are being addressed in randomised controlled trials, but others are difficult to test in this way, and answering them all in sufficiently powered trials is a major challenge. Until then comparative data provided by this and other studies will provide useful clues to best management. It will also act as a useful reminder to those countries with poor outcome, such as the UK, of the need for an improvement in stroke services.

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