Out of the pipeline

Extended-release carbamazepine

Targeting acute bipolar mania

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Over 2 decades, carbamazepine has become a well-established, off-label alternative to lithium for treating acute mania. In December, the FDA approved an extended-release form of the anticonvulsant to treat type I bipolar disorder (*Table 1*).

This article addresses clinical use of extended-release capsules of carbamazepine (ERC-CBZ) and their safety, tolerability, and potential to interact with other medications.

PHARMACOKINETICS

Because ERC-CBZ and carbamazepine yield similar molecules, the extended- and immediate-release forms have similar pharmacodynamic properties. There are notable pharmacokinetic differences, however.

With chronic use, carbamazepine autoinduces cytochrome P-450 (CYP) 3A4 hepatic enzymes. These enzymes rapidly break down carbamazepine to its active 10, 11-epoxide metabolite and the epoxide to the inactive diol. Because this sequence shortens carbamazepine's half-life con-

Table 1

Extended-release capsules of carbamazepine: Fast facts

Brand name: Equetro

Class: Anticonvulsant

FDA-approved indication:
Bipolar mania

Manufacturer:
Shire Pharmaceuticals Group

Dosing form:
100-, 200-, and 300-mg capsules

Recommended dosage:
Manufacturer recommends starting at 400 mg/d in two divided doses.* Adjust dosage in 200-mg increments to achieve optimal response. Dosages >1,600 mg/d have not been studied.

*The author recommends starting at 200 mg/d using once-daily, nighttime dosing and titrating slowly based on tolerability and efficacy, continuing with nighttime dosing only.

siderably—from 35 to 40 hours to 12 to 17 hours after 2 to 3 weeks of use—multiple daily dosing and minor dosage increases often are needed to maintain carbamazepine blood levels. Also, with immediate-release carbamazepine's peak/trough variations, transient side effects such as ataxia, dizziness, or diplopia may emerge 2 to 3 hours after dosing once steady state is reached.

By contrast, ERC-CBZ should be more tolerable and easier to use because it smooths out these variations. Although studies of ERC-CBZ in mania have examined twice-daily dosing, using once-nightly dosing instead (starting at 200 mg) will harness carbamazepine's sedative and other side effects to promote sleep onset, and lower levels throughout the day will further increase its tolerability.[1] Patients who experience breakthrough afternoon or evening manic symptoms with once-nightly dosing can be returned to twice-daily dosing.

Table 2

Carbamazepine's common to rare side effects

Common	Infrequent
Ataxia	Hyponatremia (asymptomatic to symptomatic, reversed by demeclocycline or lithium)
Benign rash	Liver enzyme elevations
Benign white blood cell count suppression (reversed by lithium)	Tremor
Decreased thyroid hormones	Weight gain
Diplopia	**Rare/serious**
Dizziness	Agranulocytosis
Fatigue, sedation	Aplastic anemia
Increased cholesterol	Hyponatremia (symptomatic)
Nausea	Severe rash - Stevens-Johnson syndrome - Lyell's syndrome (toxic epidermal necrolysis)
	Spina bifida (following in utero exposure)

EFFICACY IN BIPOLAR DISORDER

ERC-CBZ has shown efficacy for treating bipolar disorder in three studies,[2,3,4] including two large double-blind, placebo-controlled, multi-center trials that followed patients with type I bipolar disorder with current manic or mixed episodes.

In the first trial,[2] 204 patients received ERC-CBZ, 400 to 1,600 mg/d (mean±SD daily dosage 756.4±413.4 mg/d, mean plasma level 8.9 μg/mL), or placebo for 3 weeks. Young Mania Rating Scale (YMRS) scores decreased ≥ 50% in 41.5% of the treatment group and in 22.4% of the placebo group. Hamilton Rating Scale for Depression (HAM-D) scores decreased more in the ERC-CBZ group, but the difference was not clinically significant.

In a second trial of 239 patients,[3] YMRS scores fell ≥ 50% across 3 weeks in 60.8% of those taking ERC-CBZ, 400 to 1,600 mg/d (mean±SD dosage 642±369.2 mg/d), compared with 28.7% of placebo-treated patients. HAM-D total scores also improved significantly in ERC-CBZ-treated patients compared with the placebo group in a subanalysis of 188 intent-to-treat patients with a manic episode.

In a 6-month extension following 92 patients from two double-blind trials,[4] mean total YMRS scores decreased among former placebo group patients switched to open-label ERC-CBZ, 200 to 1,600 mg/d (mean dosage 938 mg, mean serum level 6.6 μg/mL). Patients who had taken ERC-CBZ during the acute trial saw little change in YMRS scores during continued ERC-CBZ treatment, except in the second month. At end point, however, YMRS scores fell further for both treat-

Table 3

Carbamazepine decreases serum concentrations of these drugs

Analgesics
Buprenorphine
Methadone

Antimicrobials
Caspofungin
Doxycycline

Anticoagulants
Warfarin*†

Anticonvulsants
Carbamazepine*†
Lamotrigine*†
Oxcarbazepine
Phenobarbital
Phenytoin
Topiramate
Valproate*‡
Zonisamide

Antidepressants
Bupropion*
Citalopram*
Mirtazapine
Tricyclics

Antipsychotics
Aripiprazole*
Clozapine
Haloperidol*
Olanzapine*
Risperidone*
Thiothixene
Ziprasidone*

Antivirals
Delavirdine
Protease inhibitors†

Anxiolytics/sedatives
Alprazolam*

Steroids
Estrogen in hormonal contraceptives*†
Mifepristone
Prednisolone*

Stimulants
Methylphenidate*
Modafinil*

Others
Cisplatin
Doxorubicin
Theophylline

* Carbamazepine is often given with this medication.
† Potentially serious interaction.
‡ Less-serious interaction likely with carbamazepine.

ment groups. HAM-D total scores differed little across 6 months, but 54 patients with mixed states maintained significant reductions.

Maintenance therapy. In many studies, carbamazepine has compared favorably with lithium for long-term bipolar maintenance in some patients. Consider patients who respond well to acute carbamazepine therapy for continuation treatment with ERC-CBZ. Patients who may be most likely to respond to carbamazepine therapy include those with:

- type II bipolar disorder
- substance abuse comorbidity
- mood-incongruent delusions
- no family history of bipolar illness among first-degree relatives.[5]

Contraindications (such as use during pregnancy or breast-feeding) are the same for extended- and immediate-release carbamazepine.

TOLERABILITY

Carbamazepine in any form can cause a range of common to rare side effects (*Table 2, page 73*), which have been reviewed elsewhere.[4-6]

Side effects of ERC-CBZ most commonly reported during the double-blind, placebo-controlled studies include dizziness, nausea, somnolence, headache, vomiting, dyspepsia, dry mouth, pruritus, and benign rash. Slower upward titration of single nighttime doses—instead of the twice-daily dosing used in these studies—could prevent most of these effects.

Only one patient in either study developed a serious side effect possibly related to ERC-CBZ (fever with rash); the rash resolved 6 days after the drug was stopped.

Total cholesterol in patients taking ERC-CBZ also rose 12% to 13% in the double-blind studies.[2,3] Consider dietary and/or cholesterol-lowering medications in patients taking ERC-CBZ who are at high risk for cardiovascular events.

In the 6-month open-label study, headache, dizziness, and benign rash were most frequently reported. No serious adverse events related to the study drug were reported.

INTERACTIONS WITH OTHER MEDICATIONS

Because of its potent induction of CYP 3A4 enzymes,[6] carbamazepine in any form may substantially lower blood levels of several compounds metabolized principally by CYP 3A4 isoenzymes (*Table 3*), including typical antipsychotics such as haloperidol and the atypical antipsychotic arip-

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iprazole. Even so, patients often improve with combination carbamazepine/haloperidol therapy despite lower haloperidol blood levels.

If a patient is taking oral contraceptives, inform her primary care physician or OB/GYN when prescribing carbamazepine. Because the anticonvulsant lowers circulating estrogen, a higher contraceptive dosage or alternate birth-control method should be considered to prevent unwanted pregnancy.

Most other drug-drug interactions have been well-delineated and can be avoided. Inform the patient and his or her primary care physician when giving carbamazepine concomitantly with any drug.

Numerous medications can also increase serum carbamazepine levels, causing problems in a patient already near his or her side-effect threshold (*Table 4*). Reduce the carbamazepine dosage to avoid these adverse effects.

Table 4

These drugs increase serum carbamazepine and may cause toxicity

Anticonvulsants
Valproate (increases carbamazepine 10, 11-epoxide levels)*†

Antidepressants
Fluoxetine*‡
Fluvoxamine*‡
Nefazodone*‡

Antimicrobials
Isoniazid†
Quinupristin/dalfopristin

Calcium channel blockers
Diltiazem*†
Verapamil*†

Hypolipidemics
Gemfibrozil
Nicotinamide

Macrolide antibiotics
Clarithromycin*†
Erythromycin*†
Flurithromycin*†
Josamycin*†
Ponsinomycin*†
Triacetyloleandromycin*†

Others
Acetazolamide
Cimetidine§
Danazol
d-Propoxyphene‡
Ketoconazole†
Niacinamide
Omeprazole
Ritonavir†
Ticlopidine

* Carbamazepine is often given with this medication.
† Potentially serious interaction.
‡ Less-serious interaction likely with carbamazepine.
§ Data on interactions with carbamazepine unclear.

CLINICAL IMPLICATIONS

Long-acting carbamazepine suitable for single nighttime dosing should facilitate adherence and reduce daytime side effects. Consider ERC-CBZ for patients not responding adequately to lithium or valproate, as individual response to any of these three drugs can vary greatly. Side-effect tolerability (such as less weight gain with carbamazepine than with valproate) also could help guide drug choice. In patients with rapid cycling, carbamazepine plus lithium may be more effective than either drug alone.

New data suggest that carbamazepine offers acute antidepressant effects in some individuals and in long-term depression treatment.[5] More research is needed to identify depressed patients most likely to respond to this agent.

For now, when using ERC-CBZ, we can draw from the larger experience with immediate-release carbamazepine to treat epilepsy, bipolar disorder, and related mood disorders. Once you master carbamazepine's pharmacokinetic interactions with other commonly used agents, ERC-CBZ in slowly titrated, single nighttime dosages should simplify the compound's administration and tolerability.

References

1. Miller AD, Krauss GL, Hamzeh FM. Improved CNS tolerability following conversion from immediate- to extended-release carbamazepine. *Acta Neurol Scand* 2004;109:374-7.

Bottom Line

Extended-release carbamazepine has shown efficacy for treating acute mania in double-blind, placebo-controlled trials. Once-nightly dosing can promote sleep onset while improving tolerability during the day.

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Related resources

- Carbamazepine (extended-release) Web site. www.equetro.com.
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DRUG BRAND NAMES

Aripiprazole • Abilify
Carbamazepine (extended-release) • Equetro
Carbamazepine (immediate-release) • Tegretol, others
Haloperidol • Haldol
Lithium • Eskalith, others
Valproate • Depakote

DISCLOSURE

Dr. Post reports no current financial relationship with any company whose products are mentioned in this article, or with manufacturers of competing products.