

Anxiety Disorders Program Bests Usual Care

BY MARY ANN MOON
FROM JAMA

A program aimed at treating the most common anxiety disorders in primary care clinics proved more effective than usual care, according to the findings of a randomized controlled trial reported in JAMA.

The Coordinated Anxiety Learning and Management (CALM) program in-

volves evidence-based treatment of panic disorder, generalized anxiety disorder, social anxiety disorder, and posttraumatic stress disorder, with or without the presence of comorbid depression, said Dr. Peter Roy-Byrne of the University of Washington, Seattle, and his associates.

The CALM model uses an Internet-based system to monitor the delivery of care by “anxiety clinical specialists”

such as nurses, social workers, or psychologists who are trained to deliver the program’s treatment. These specialists keep in close touch with a primary care physician throughout the 10-12 weeks of treatment. They use a computer program to help them administer cognitive-behavioral therapy and/or pharmacotherapy with selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake in-

hibitors, other types of antidepressants, or benzodiazepines.

Outcomes among 503 patients randomized to the CALM program were compared with 501 patients assigned to usual care. Patients were enrolled from 17 primary care clinics in Arkansas, California, and Washington. Usual care involved in-clinic mental health resources – which often involved “a single clinician with limited familiarity with evidence-based psychotherapy” – or referral to a mental health specialist. Treatment duration lasted 3-12 months (JAMA 2010;303:1921-8).

The study participants were diagnosed as having one or more of the four anxiety disorders, with or without comorbid depression, and were referred by 120 internists and 28 family physicians. The patient population was ethnically diverse and had a broad age range (18-75 years). Patients underwent a battery of assessments at baseline and at 6-month intervals for 18 months to track their outcomes.

Patients in the intervention group were significantly more likely than those in the usual-care group to receive psychotherapy that included elements of cognitive-behavioral therapy and to receive the appropriate type, dose, and duration of medication. In addition, their scores on the Brief Symptom Inventory measuring psychic and somatic anxiety were significantly lower than those of the usual-care group at all follow-up assessments, Dr. Roy-Byrne and his associates said.

Accordingly, a significantly higher proportion of patients in the CALM program responded at 6 months (57%), 12 months (64%), and 18 months (65%) than patients who received usual care (37%, 45%, and 51% response rates, respectively).

Similarly, a significantly higher proportion of patients in the CALM program were in remission at these intervals (43%, 51%, and 51%, respectively) than were usual-care patients (27%, 33%, and 37%).

At 1 year, the number needed to treat was 5.3 for response and 5.5 for remission. This “was well within the range for treatments in medicine that are generally considered to be efficacious, and beneficial effects of the intervention persisted for at least 1 year after clinical visits had ceased, suggesting a long-term effect,” the investigators noted.

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Dr. Roy-Byrne reported receiving support from the National Institutes of Health. The researchers reported receiving support or have relationships with Jazz Pharmaceuticals, Solvay Pharmaceuticals, the American Psychiatric Association, the Anxiety Disorders Association of America, CMP Media, Current Medical Directions, Immedex, Massachusetts General Hospital Academy, and PRIMEDIA Healthcare, as well as serving as expert witnesses on multiple legal cases related to anxiety. ■

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hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, stupor, and suicidal ideation. *Rare:* Chorea/athetosis, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, and peripheral neuritis. **Respiratory System:** *Infrequent:* Yawn. *Rare:* Hiccup and hyperventilation. **Special Senses:** *Frequent:* Amblyopia. *Infrequent:* Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. *Rare:* Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field defect. **Urogenital System:** *Infrequent:* Abnormal ejaculation, hematuria, impotence, menorrhagia, polyuria, and urinary incontinence. *Rare:* Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, and urinary urgency.

6.3 Postmarketing Experience: The following adverse events (not listed above in clinical trials or other sections of the prescribing information) have been identified during postapproval use of LAMICTAL. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Blood and Lymphatic:** Agranulocytosis, hemolytic anemia. **Gastrointestinal:** Esophagitis. **Hepatobiliary Tract and Pancreas:** Pancreatitis. **Immunologic:** Lupus like reaction, vasculitis. **Lower Respiratory:** Apnea. **Musculoskeletal:** Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions. **Neurology:** Exacerbation of Parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics. **Non-site Specific:** Progressive immunosuppression.

7 DRUG INTERACTIONS

Significant drug interactions with lamotrigine are summarized in Table 2. Additional details of these drug interaction studies are provided in the Clinical Pharmacology subsection [see *Clinical Pharmacology* (12.3) of full prescribing information].

Table 2. Established and Other Potentially Significant Drug Interactions

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ lamotrigine	Decreased lamotrigine levels approximately 50%.
Carbamazepine (CBZ) and CBZ epoxide	↓ lamotrigine ? CBZ epoxide	Decrease in levonorgestrel component by 19%. Addition of carbamazepine decreases lamotrigine concentration approximately 40%. May increase CBZ epoxide levels.
Phenobarbital/Primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin (PHT)	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. Decreased valproate concentrations an average of 25% over a 3-week period then stabilized in healthy volunteers; no change in controlled clinical trials in epilepsy patients.

↓ = Decreased (induces lamotrigine glucuronidation).
↑ = Increased (inhibits lamotrigine glucuronidation).
? = Conflicting data.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Teratogenic Effects: Pregnancy Category C. No evidence of teratogenicity was found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m² basis, the highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose, the incidence of intrauterine death without signs of teratogenicity was increased. A behavioral teratology study was conducted in rats dosed during the period of organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg/day or higher displayed a significantly longer latent period for open field exploration and a lower frequency of rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion was increased in offspring of dams receiving 25 mg/kg/day. These doses represent 0.1 and 0.5 times the clinical dose on a mg/m² basis, respectively. Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to 0.4 times the highest usual human maintenance dose on a mg/m² basis. When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human maintenance dose (on a mg/m² basis) during the latter part of gestation (days 15 to 20), maternal toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced, and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group). Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between days 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal toxicity. A no-observed-effect level (NOEL) could not be determined for this study. Although lamotrigine was not found to be teratogenic in the above studies, lamotrigine decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.


Non-Teratogenic Effects: As with other AEDs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response.

Pregnancy Exposure Registry: To provide information regarding the effects of in utero exposure to LAMICTAL, physicians are advised to recommend that pregnant patients taking LAMICTAL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>. Physicians are also encouraged to register patients in the Lamotrigine Pregnancy Registry; enrollment in this registry must be done prior to any prenatal diagnostic tests and **before fetal outcome is known.** Physicians can obtain information by calling the Lamotrigine Pregnancy Registry at 1-800-336-2176 (toll-free).

8.2 Labor and Delivery: The effect of LAMICTAL on labor and delivery in humans is unknown.

8.3 Nursing Mothers: Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking LAMICTAL is not recommended.

8.4 Pediatric Use: LAMICTAL is indicated for adjunctive therapy in patients ≥2 years of age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures. Safety and efficacy of LAMICTAL, used as adjunctive treatment for partial seizures, were not demonstrated in a small randomized, double-blind, placebo-controlled, withdrawal study in very young pediatric patients (1 to 24 months). LAMICTAL was associated with an increased risk for infectious adverse reactions (LAMICTAL 37%, Placebo 5%), and respiratory adverse reactions (LAMICTAL 26%, Placebo 5%). Infectious adverse reactions included: bronchiolitis, bronchitis, ear infection, eye infection, otitis externa,

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