

# Amino Acid May Be Effective for Trichotillomania

BY MARY ANN MOON

The glutamate modulator *N*-acetylcysteine significantly reduces trichotillomania symptoms, according to a study of 50 patients.

In what the investigators described as the first clinical trial assessing a glutamatergic agent for this disorder, *N*-acetylcysteine was judged effective by both patients and physicians, to a degree

comparable with other medications plus cognitive-behavioral therapy.

"*N*-acetylcysteine is an amino acid, is available in health-food stores, is cheaper than most insurance copayments, and seems to be well tolerated. [It] could be an effective treatment option for people with trichotillomania," said Dr. Jon E. Grant and his associates at the University of Minnesota, Minneapolis (Arch. Gen. Psychiatry 2009;66:756-63).

Moreover, the study results indicate that "pharmacologic manipulation of the glutamate system (in the nucleus accumbens) may target core symptoms of compulsive behaviors," they added.

Trichotillomania is the recurrent pulling out of hair—head hair, eyebrows, eyelashes, pubic hair, or other body hair—to obtain relief of tension, which leads to noticeable hair loss. There is no Food and Drug Administration–approved

treatment for trichotillomania at present, but glutamatergic dysfunction has been implicated in the pathogenesis of disorders that have a compulsive component, and glutamate modulators like *N*-acetylcysteine have been used to treat cocaine urges and gambling behavior.

Dr. Grant and his colleagues assessed the agent in 45 women and 5 men (mean age, 34 years) who reported spending a mean of 65 minutes every day pulling out hair, usually from multiple sites. Most of these patients had never sought mental health treatment for hair pulling.

Thirty of the study subjects (60%) reported having at least one clinically important comorbid disorder, such as major depressive disorder; an anxiety disorder; another impulse-control disorder, such

## Levulan® Kerastick®

(aminolevulinic acid HCl) for Topical Solution, 20%

For Topical Use Only • Not for Ophthalmic Use

Brief Summary (For full prescribing information, see physician's insert)

### INDICATIONS AND USAGE

The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses (Grade 1: slightly palpable, better felt than seen or Grade 2: moderately thick, easily seen and felt) of the face or scalp.

### CONTRAINDICATIONS

The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the LEVULAN KERASTICK for Topical Solution.

### WARNINGS

The LEVULAN KERASTICK for Topical Solution contains alcohol and is intended for topical use only. Do not apply to the eyes or to mucous membranes. Excessive irritation may be experienced if this product is applied under occlusion.

### PRECAUTIONS

General: During the time period between the application of LEVULAN KERASTICK Topical Solution and exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, the treatment site will become photosensitive. After LEVULAN KERASTICK Topical Solution application, patients should avoid exposure of the photosensitized treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. Exposure may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Before exposure to sunlight, patients should, therefore, protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the LEVULAN KERASTICK Topical Solution outside the treatment site to eye or surrounding skin.

Application of LEVULAN KERASTICK Topical Solution to perilesional areas of photodamaged skin of the face or scalp may result in photosensitization. Upon exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, such photosensitized skin may produce a stinging and/or burning sensation and may become erythematous and/or edematous in a manner similar to that of actinic keratoses treated with LEVULAN PDT. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK for Topical Solution should be used by a qualified health professional to apply drug only to actinic keratoses and not perilesional skin.

The LEVULAN KERASTICK for Topical Solution has not been tested on patients with inherited or acquired coagulation defects.

### Information for Patients:

LEVULAN Photodynamic Therapy for Actinic Keratoses. The first step in LEVULAN KERASTICK photodynamic therapy (PDT) for actinic keratoses is application of the LEVULAN KERASTICK for Topical Solution to actinic keratoses located on the patient's face or scalp. After LEVULAN KERASTICK for Topical Solution is applied to the actinic keratoses in the doctor's office, the patient will be told to return the next day. During this time the actinic keratoses will become sensitive to light (photosensitive). Care should be taken to keep the treated actinic keratoses dry and out of bright light. After LEVULAN KERASTICK Topical Solution is applied, it is important for the patient to wear light-protective clothing, such as a wide-brimmed hat, when exposed to sunlight or sources of light. Fourteen to eighteen hours after application of LEVULAN KERASTICK Topical Solution the patient will return to the doctor's office to receive blue light treatment, which is the second and final step in the treatment. Prior to blue light treatment, the actinic keratoses will be rinsed with tap water. The patient will be given goggles to wear as eye protection during the blue light treatment. The blue light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, the patient will experience sensations of tingling, stinging, pricking or burning of the treated lesions. These feelings of discomfort should improve at the end of the light treatment. Following treatment, the actinic keratoses and, to some degree, the surrounding skin, will redden, and swelling and scaling may also occur. However, these lesion changes are temporary and should completely resolve by 4 weeks after treatment.

### Photosensitivity

After LEVULAN KERASTICK Topical Solution is applied to the actinic keratoses in the doctor's office, the patient should avoid exposure of the photosensitized actinic keratoses to sunlight or bright indoor light (e.g., from examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. If the patient feels stinging and/or burning on the actinic keratoses, exposure to light should be reduced. Before going into sunlight, the patient should protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect the patient against photosensitivity reactions.

If for any reason the patient cannot return for blue light treatment during the prescribed period after application of LEVULAN KERASTICK Topical Solution (14 to 18 hours), the patient should call the doctor. The patient should also continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. If stinging and/or burning is noted, exposure to light should be reduced.

**Drug Interactions:** There have been no formal studies of the interaction of LEVULAN KERASTICK for Topical Solution with any other drugs, and no drug-specific interactions were noted during any of the controlled clinical trials. It is, however, possible that concomitant use of other known photosensitizing agents such as griseofulvin, thiazide diuretics, sulfonyleureas, phenothiazines, sulfonamides and tetracyclines might increase the photosensitivity reaction of actinic keratoses treated with the LEVULAN KERASTICK for Topical Solution.

**Carcinogenesis, Mutagenesis, Impairment to Fertility:** No carcinogenicity testing has been carried out using ALA. No evidence of mutagenic effects was seen in four studies conducted with ALA to evaluate this potential. In the Salmonella-Escherichia coli/mammalian microsome reverse mutation assay (Ames mutagenicity assay), no increases in the number of revertants were observed with any of the tester strains. In the Salmonella-Escherichia coli/mammalian microsome reverse mutation assay in the presence of solar light radiation (Ames mutagenicity assay with light), ALA did not cause an increase in the number of revertants per plate of any of the tester strains in the presence or absence of simulated solar light. In the L5178Y TK<sub>+</sub> mouse lymphoma forward mutation assay, ALA was evaluated as negative with and without metabolic activation under the study conditions. PpIX formation was not demonstrated in any of these *in vivo* studies. In the *in vivo* mouse micronucleus assay, ALA was considered negative under the study exposure conditions. In contrast, at least one report in the literature has noted genotoxic effects in cultured rat hepatocytes after ALA exposure with PpIX formation. Other studies have documented oxidative DNA damage *in vivo* and *in vitro* as a result of ALA exposure.

No assessment of effects of ALA HCl on fertility has been performed in laboratory animals. It is unknown what effects systemic exposure to ALA HCl might have on fertility or reproductive function.

**Pregnancy Category C:** Animal reproduction studies have not been conducted with ALA HCl. It is also not known whether LEVULAN KERASTICK Topical Solution can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. LEVULAN KERASTICK Topical Solution should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** The levels of ALA or its metabolites in the milk of subjects treated with LEVULAN KERASTICK Topical Solution have not been measured. Because many drugs are excreted in human milk, caution should be exercised when LEVULAN KERASTICK Topical Solution is administered to a nursing woman.

### ADVERSE REACTIONS

In Phase 3 studies, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK Topical Solution application followed by blue light exposure.

**Photodynamic Therapy Response:** The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK Topical Solution plus BLU-U treatment was observed in all clinical studies of LEVULAN KERASTICK for Topical Solution Photodynamic Therapy for actinic keratoses treatment. Stinging and/or burning subsided between 1 minute and 24 hours after the BLU-U Blue Light Photodynamic Therapy Illuminator was turned off, and appeared qualitatively similar to that perceived by patients with erythropoietic protoporphyria upon exposure to sunlight. There was no clear drug dose or light dose dependent change in the incidence or severity of stinging and/or burning.

In two Phase 3 trials, the sensation of stinging and/or burning appeared to reach a plateau at 6 minutes into the treatment. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of the patients at some time during treatment. The majority of patients reported that all lesions treated exhibited at least slight stinging and/or burning. Less than 3% of patients discontinued light treatment due to stinging and/or burning.

The most common changes in lesion appearance after LEVULAN KERASTICK for Topical Solution Photodynamic Therapy were erythema and edema. In 99% of active treatment patients, some or all lesions were erythematous shortly after treatment, while in 79% of vehicle treatment patients, some or all lesions were erythematous. In 35% of active treatment patients, some or all lesions were edematous, while no vehicle-treated patients had edematous lesions. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy. LEVULAN KERASTICK Topical Solution application to photodamaged perilesional skin resulted in photosensitization of photodamaged skin and in a photodynamic response. (see Precautions).

**Other Localized Cutaneous Adverse Experiences:** Table 1 depicts the incidence and severity of cutaneous adverse events, stratified by anatomic site treated.

**Adverse Experiences Reported by Body System:** In the Phase 3 studies, 7 patients experienced a serious adverse event. All were deemed remotely or not related to treatment. No clinically significant patterns of clinical laboratory changes were observed for standard serum chemical or hematologic parameters in any of the controlled clinical trials.

TABLE 1 Post-PDT Cutaneous Adverse Events - ALA-018/ALA-019

	FACE				SCALP			
	LEVULAN (n=139)		Vehicle (n=41)		LEVULAN (n=42)		Vehicle (n=21)	
Degree of Severity	Mild/Moderate	Severe	Mild/Moderate	Severe	Mild/Moderate	Severe	Mild/Moderate	Severe
Scaling/Crusting	71%	1%	12%	0%	64%	2%	19%	0%
Pain	1%	0%	0%	0%	0%	0%	0%	0%
Tenderness	1%	0%	0%	0%	2%	0%	0%	0%
Itching	25%	1%	7%	0%	14%	7%	19%	0%
Edema	1%	0%	0%	0%	0%	0%	0%	0%
Ulceration	4%	0%	0%	0%	2%	0%	0%	0%
Bleeding/Hemorrhage	4%	0%	0%	0%	2%	0%	0%	0%
Hypo/hyper-pigmentation	22%		20%		36%		33%	
Vesiculation	4%	0%	0%	0%	5%	0%	0%	0%
Pustules	4%	0%	0%	0%	0%	0%	0%	0%
Oozing	1%	0%	0%	0%	0%	0%	0%	0%
Dysesthesia	2%	0%	0%	0%	0%	0%	0%	0%
Scabbing	2%	1%	0%	0%	0%	0%	0%	0%
Erosion	14%	1%	0%	0%	2%	0%	0%	0%
Excoriation	1%	0%	0%	0%	0%	0%	0%	0%
Wheal/Flare	7%	1%	0%	0%	2%	0%	0%	0%
Skin disorder NOS	5%	0%	0%	0%	12%	0%	5%	0

### OVERDOSAGE

**LEVULAN KERASTICK Topical Solution Overdose:** LEVULAN KERASTICK Topical Solution overdose have not been reported. In the unlikely event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 40 hours. The consequences of exceeding the recommended topical dosage are unknown.

**BLU-U® Light Overdose:** There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK Topical Solution application.

### HOW SUPPLIED

The LEVULAN KERASTICK for Topical Solution, 20%, is a single-unit dosage form, supplied in packs of 6. Each LEVULAN KERASTICK for Topical Solution applicator consists of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of solution vehicle. The other ampule contains 354 mg of aminolevulinic acid HCl. The applicator is covered with a protective cardboard sleeve and cap.

### Product Package

Individual LEVULAN KERASTICK for Topical Solution, 20% 67308-101-01  
Carton of 6 LEVULAN KERASTICKS for Topical Solution, 20% 67308-101-06

### NDC number

**Storage Conditions:** Store between 20°–25°C (68°–77°F); excursions permitted to 15°–30°C (59°–86°F) [See USP Controlled Room Temperature]. The LEVULAN KERASTICK for Topical Solution should be used immediately following preparation (dissolution). Solution application must be completed within 2 hours of preparation. An applicator that has been prepared must be discarded 2 hours after mixing (dissolving) and a new LEVULAN KERASTICK for Topical Solution used, if needed.

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This patient extracted most of the hair from a wide area of the scalp.

as skin picking or nail biting; or an eating disorder. Four patients were receiving psychotherapy, and 28 were taking a psychotropic medication or a stimulant.

Subjects were randomly assigned to receive 12 weeks of *N*-acetylcysteine or a matching placebo. A significant treatment effect was evident at 9 weeks and persisted for the duration of the study.

At the conclusion of treatment, those who had taken *N*-acetylcysteine showed significant improvement on both the severity subscale and the "resistance and control" subscale of the Massachusetts General Hospital Hairpulling Scale, as well as on the Psychiatric Institute Trichotillomania Scale.

A total of 56% of those in the active-treatment group said they were "much" or "very much" improved on the Clinical Global Impression (CGI) scale, compared with 16% of the placebo group.

Patients who received *N*-acetylcysteine did not show a greater improvement in psychosocial functioning than those who received placebo. However, this sample may have been too small to detect a meaningful difference between the two groups, given that at baseline, most of the subjects had only mild psychosocial dysfunction and reported a quality of life in the "average" range, Dr. Grant and his associates said.

Dr. Grant has received research grants from Forest Pharmaceuticals, Glaxo-SmithKline, and Somaxon Pharmaceuticals and has served as a consultant to Pfizer Pharmaceuticals and Somaxon. In addition, Dr. Grant, who also is a lawyer, has consulted for law offices as an expert regarding impulse control disorders. ■

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