RESEARCH LETTER

## Accuracy of Labeling of Galantamine Generic Drugs and Dietary Supplements

Studies have reported mislabeling of both generic drugs and dietary supplements.[1,2] While the regulatory framework for prescription drugs and dietary supplements are distinct in the US, labels in both categories are required to accurately represent the products' contents. To our knowledge, whether label accuracy differs between generic drugs and dietary supplements containing the same active pharmaceutical ingredient has not been studied.

Supplemental content

Galantamine, a plant alkaloid with anticholinergic effects, is available in the US as either a dietary supplement or as a prescription medication. As a prescription medication, galantamine is approved by the US Food and Drug Administration (FDA) for the treatment of mild to moderate Alzheimer dementia. However, galantamine is ineffective in treating mild cognitive impairment or preventing Alzheimer dementia,[3,4] but, when sold as a dietary supplement, the drug is marketed for a variety of cognitive conditions including memory enhancement.[5]

We investigated the label accuracy of galantamine products formulated both as generic drugs and dietary supplements. We also quantified microorganisms in the products because contamination may occur when products are manufactured without following appropriate control measures.

**Methods** | In June 2023, all dietary supplements available for sale on Amazon.com labeled with both galantamine as an ingredient and a Supplement Facts panel were purchased online in the US. A Supplement Facts panel was required to ensure the product was marketed as a dietary supplement. In September 2023, all generic immediate-release formulations of galantamine available in the US were purchased.

The content of the products was reconstituted in water then analyzed for the presence of galantamine using ultrahigh-performance liquid chromatography–mass spectrometry and quantified using liquid chromatography–diode array detection. Contamination with microorganisms was determined by membrane filtration, and retrieved microorganisms were quantified and identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry and whole-genome sequencing (see eMethods in the Supplement for additional details).

**Results** | Ten brands of galantamine supplements and 11 brands of generic galantamine medications were included. Generic drugs were labeled as containing 4, 8, and 12 mg of galantamine per tablet or capsule. The actual content of galantamine in the generic drugs ranged from 97.5% to 104.2% of the labeled content (**Table 1**). No generic drugs were contaminated with microorganisms.

Table 1. Labeled and Measured Galantamine and Microbial Contamination in Galantamine Supplements and Generic Drugs

| Supplement brand code | Claim | Description of galantamine on the label[a] | Labeled galantamine, mg[b] | Measured galantamine, mean (SD), mg | Measured vs labeled galantamine, %[c] | Microbial contaminant[d] |
|---|---|---|---|---|---|---|
| Dietary supplements | | | | | | |
| A | Supports dream recall | Galantamine HBr | 4 | 1.45 (0.06) | 36.3 | ND |
| B | Supports and maintains cognitive function | Galantamine HBr (*Lycoris radiata*) extract (root) | 4 | 2.90 (0.03) | 72.5 | ND |
| C | Supports cognitive acuity, increases memory and recall, and supports lucid dream induction | Galantamine HBr (*Lycoris radiata*) extract (root) | 4 | 2.47 (0.03) | 61.8 | *Bacillus cereus sensu stricto* |
| D | Memory optimizer | Galantamine HBr (botanical extract) | 4 | 4.38 (0.03) | 109.5 | ND |
| E | Memory recall optimizer | Galantamine HBr | 4 | 2.93 (0.08) | 73.3 | ND |
| F | Cognitive support and support with lucid dream induction | Galantamine | 6 | <0.1 mg[e] | <1.6 | ND |
| G | None | Galantamine HBr | 8 | 3.92 (0.2) | 49.0 | ND |
| H | None | Galantamine HBr | 8 | 4.76 (0.08) | 59.5 | *B cereus ss* |
| I | Memory optimizer | Galantamine HBr | 8 | 6.03 (0.1) | 75.4 | *B cereus ss* |
| J | Nootropic brain support | Galantamine HBr (*Lycoris radiata* extract) | 8 | 0.56 (0.03) | 7.0 | ND |

(continued)

Table 1. Labeled and Measured Galantamine and Microbial Contamination in Galantamine Supplements and Generic Drugs (continued)

| Supplement brand code | Claim | Description of galantamine on the label[a] | Labeled galantamine, mg[b] | Measured galantamine, mean (SD), mg | Measured vs labeled galantamine, %[c] | Microbial contaminant[d] |
|---|---|---|---|---|---|---|
| Generic drugs | | | | | | |
| K | | Galantamine HBr, USP | 4 | 3.94 (0.02) | 98.4 | ND |
| L | | Galantamine HBr, USP | 4 | 3.95 (0.05) | 98.8 | ND |
| M | | Galantamine HBr, USP | 4 | 4.10 (0.04) | 102.5 | ND |
| N | | Galantamine HBr, USP | 4 | 4.09 (0.05) | 102.3 | ND |
| O | | Galantamine HBr, USP | 4 | 4.14 (0.07) | 103.6 | ND |
| P | | Galantamine HBr, USP | 8 | 7.84 (0.05) | 97.9 | ND |
| Q | | Galantamine HBr, USP | 8 | 8.15 (0.1) | 101.9 | ND |
| R | | Galantamine HBr, USP | 8 | 7.80 (0.2) | 97.5 | ND |
| S | | Galantamine HBr, USP | 12 | 12.50 (0.1) | 104.2 | ND |
| T | | Galantamine HBr, USP | 12 | 11.93 (0.06) | 99.4 | ND |
| U | | Galantamine HBr, USP | 12 | 12.36 (0.2) | 103 | ND |

Abbreviations: HBr, hydrobromide; ND, not detected; USP, US Pharmacopeia.

[a] Four brands of dietary supplements also labeled the presence of other ingredients as follows: for D, vitamin C, vitamin E, vitamin $B_6$, folic acid, green tea leaf extract, turmeric root, hesperidin and quercetin, vitamin $B_{12}$, and lithium; for E, vitamin $B_6$, Na-R-lipoic acid, and benfotiamine; for F, α-glycerylphosphorylcholine, choline bitartrate, and L-theanine; and for I, vitamin $B_5$ and choline. Except for the presence of vitamin $B_{12}$ in D, all other ingredients were detected.

[b] The amount of galantamine is reported per capsule or tablet, except for J, which is in liquid form and reported per serving size.

[c] For the purpose of this calculation, the labeled amount of galantamine was assumed to represent the actual amount of active product.

[d] Contamination was defined as the presence of bacterial species with a bioburden exceeding $10^3$ colony-forming units per gram product and not associated with the manufacturing process (eg, the presence of *Bacillus amyloliquefaciens* in D and *Bacillus velezensis* in E, because these strains might have been used for vitamin production).

[e] Amount found in the sample was less than the limit of quantification and for this sample corresponds to a quantity of galantamine less than 0.1 mg per capsule.

Table 2. Toxin-Producing and Antibiotic Resistance Genes in the *Bacillus cereus sensu stricto* Strains in Galantamine Supplements

| Supplement brand code | Toxin encoding genes | | Antibiotic resistance genes[c] |
|---|---|---|---|
| | Cytotoxin/enterotoxins associated with diarrheal syndrome[a] | Toxin associated with emetic syndrome[b] | |
| C | *hbl*, *nhe*, and *cytK-2* | ND | *tet(45)*, *vanR-A*, and *vanS-Pt* |
| H | *hbl*, *nhe*, and *cytK-2* | ND | *tet(45)* |
| I | *nhe* | ND | *mphL* |

Abbreviation: ND, not detected.

[a] The gene *Hbl* encodes for hemolysin BL, *Nhe* encodes for nonhemolytic enterotoxin, and *cytK2* encodes for cytotoxin K2.

[b] The bacterial genome was interrogated for the *ces* gene cluster, which is responsible for the biosynthesis of the heat-stable emetic toxin cereulide.

[c] Only the antimicrobial resistance genes not already known to be associated with resistance to β-lactam antibiotics, fosfomycin, and streptothricin resistance are reported in the table because resistance genes against these antibiotics have been shown to be frequently present in *B cereus* species. The 2 strains present in the samples from C and H are predicted to be resistant to tetracycline as *tet(45)* was encountered. The strain present in samples from C also contained the *vanR-A* and *vanS-Pt* genes, indicating a possible resistance to vancomycin. The strain encountered in I was quite different from the 2 abovementioned strains as the *mphL* gene was found. This gene encodes for a macrolide phosphotransferase that inactivates macrolides.

Dietary supplements were labeled as containing 4, 6, 8, and 12 mg of galantamine per serving. The actual quantity of galantamine in the dietary supplements ranged from less than 2% to 110% of the labeled quantity. Three supplements (30%) were contaminated with *Bacillus cereus sensu stricto*–encoding enterotoxin genes associated with diarrheal illness (**Table 2**). The contaminated supplements contained 60%, 62%, and 75% of the labeled quantity of galantamine. All 11 generic drugs (100%) and 1 supplement (10%) contained a quantity of galantamine that was within 10% of the quantity declared on the label.

**Discussion** | Galantamine sold as generic drugs was accurately labeled and free of contamination, in contrast to galantamine sold as dietary supplements. The detected quantities of *B cereus ss* may suggest lack of appropriate quality control during manufacturing. However, adverse health effects would not be expected with these quantities of bacteria. For patients with Alzheimer disease, use of galantamine supplements instead of generic galantamine may adversely affect their care. Furthermore, the sale of inaccurately labeled galantamine supplements promoted for nonspecific memory and other cognitive

problems is concerning given the lack of proven efficacy, potential drug-drug interactions, and adverse effects, including nausea, vomiting, dizziness, bradycardia, and syncope.[6]

The study has limitations. First, products were purchased at only 1 time point and the results may not be generalizable to galantamine supplements currently available given that manufacturers can introduce, reformulate, or withdraw supplement products without notifying the FDA. Second, whether the results are generalizable to other supplement ingredients, such as niacin, potassium, and iron, which are also available as either dietary supplements or generic drugs, is unknown.

The laws regulating dietary supplements should be reformed such that the FDA has enforcement mechanisms to ensure that dietary supplement labels accurately reflect their contents. Meanwhile, clinicians should query patients with memory concerns about the use of dietary supplements and advise patients not to use galantamine supplements.

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