RESEARCH
Commentary

Addressing Barriers for Patients with Celiac Disease When Assessing for Gluten in Medications

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CELIAC DISEASE IS AN AUTOIMMUNE AND INFLAMmatory disorder that causes a reaction to gluten, a protein found in wheat, barley, and rye.[1] The small intestine is the main site of injury, but celiac disease is a multisystem disorder, and comorbidities or other autoimmune disorders may develop if it is not treated with a strict gluten-free diet. Celiac disease can present with a wide variety of symptoms including diarrhea, weight loss, failure to thrive, migraines, iron deficiency anemia, osteoporosis, and infertility.[2] Long-term consequences of untreated celiac disease include an increased risk for cancers of the mouth, pharynx, or esophagus and non-Hodgkin's lymphoma.[1,3,4] It is estimated that celiac disease affects approximately 1% of the population; however, with increased screening and awareness, the incidence in the United States is increasing.[5]

Very small amounts of gluten can cause intestinal damage along with a myriad of other ailments for individuals with celiac disease. Although in the past decade, there has been standardization of safe thresholds for what food items can be labeled with the term *gluten-free*, this does not apply to medications. A few articles in the literature describe resources available for use in investigation of the gluten content of medications, yet there is no concise mechanism or standard manner with which pharmacists can approach this problem or registered dietitian nutritionists (RDNs) can provide clear guidance to patients. We set out to summarize the importance of determining the gluten content in medications and developed a flowchart (Figure 1) that summarizes the current recommendations in the literature to aid in making this determination.

EVOLUTION OF CELIAC DISEASE

The recognition and diagnosis of celiac disease has been an evolving process over the past 60 years. Although it was recognized as early as 1888 that dietary treatment may benefit those with what is thought to have been celiac disease at the time, it was not until the 1950s that the exclusion of gluten was found to lead to improvement.[6] The first biopsy to be reliably used to diagnose celiac disease was documented in 1955. Small bowel biopsies remain the gold standard for diagnosis. However, serology tests were more recently developed to aid in screening.[7] Current research is exploring the use of whole blood tests to diagnose celiac disease. A review article by Bruins[8] demonstrates that patients should consume gluten for a minimum of 3 months for blood test and biopsy results to be accurate. This often poses issues when patients have stopped consuming gluten before the diagnosis is made. With the development of the whole blood tests, the intention is for patients to be diagnosed without having to re-introduce gluten to their diets for weeks. Whole blood testing, which is estimated to become available in the next 2 years, may also eliminate the need for a small bowel biopsy for diagnosis. The initial study showed that whole blood testing was 85% to 94% sensitive for celiac disease and 100% specific.[9] More recently, researchers in Spain have developed a less invasive finger prick test to detect auto-antibodies in capillary blood samples obtained from children.[10] Positive outcomes require confirmation with serology testing, but progress toward simplified screening and diagnosis continues to be made.

The gluten-free diet itself has evolved greatly from the 1920s when Haas discovered that a strict diet of ripe bananas and milk seemed to resolve symptoms.[11] The option of labeling foods as "gluten-free" has also become readily available since then.

Development of drugs for treating celiac disease, or for use as an adjunct to the diet, is growing. A review of drugs for celiac disease currently in development shows that eight companies are developing medications that are between Phase 1 and Phase 3 trials.[12] Potential therapies in development include orally administered gluten-specific proteases to degrade gluten; a vaccine in which peptides that cause an immune response to gluten are combined, which is designed to reprogram gluten-specific T cells triggered by the autoimmune response; and orally administered antibodies.

Despite the increased recognition of celiac disease, advances in diagnosis, expansion of gluten-free food options, and ongoing research for medications to be used as adjunct therapy, few advances have been made in the ability to identify gluten in medications. A review of the literature shows that the concern about being able to identify gluten in medications for patients with celiac disease was first

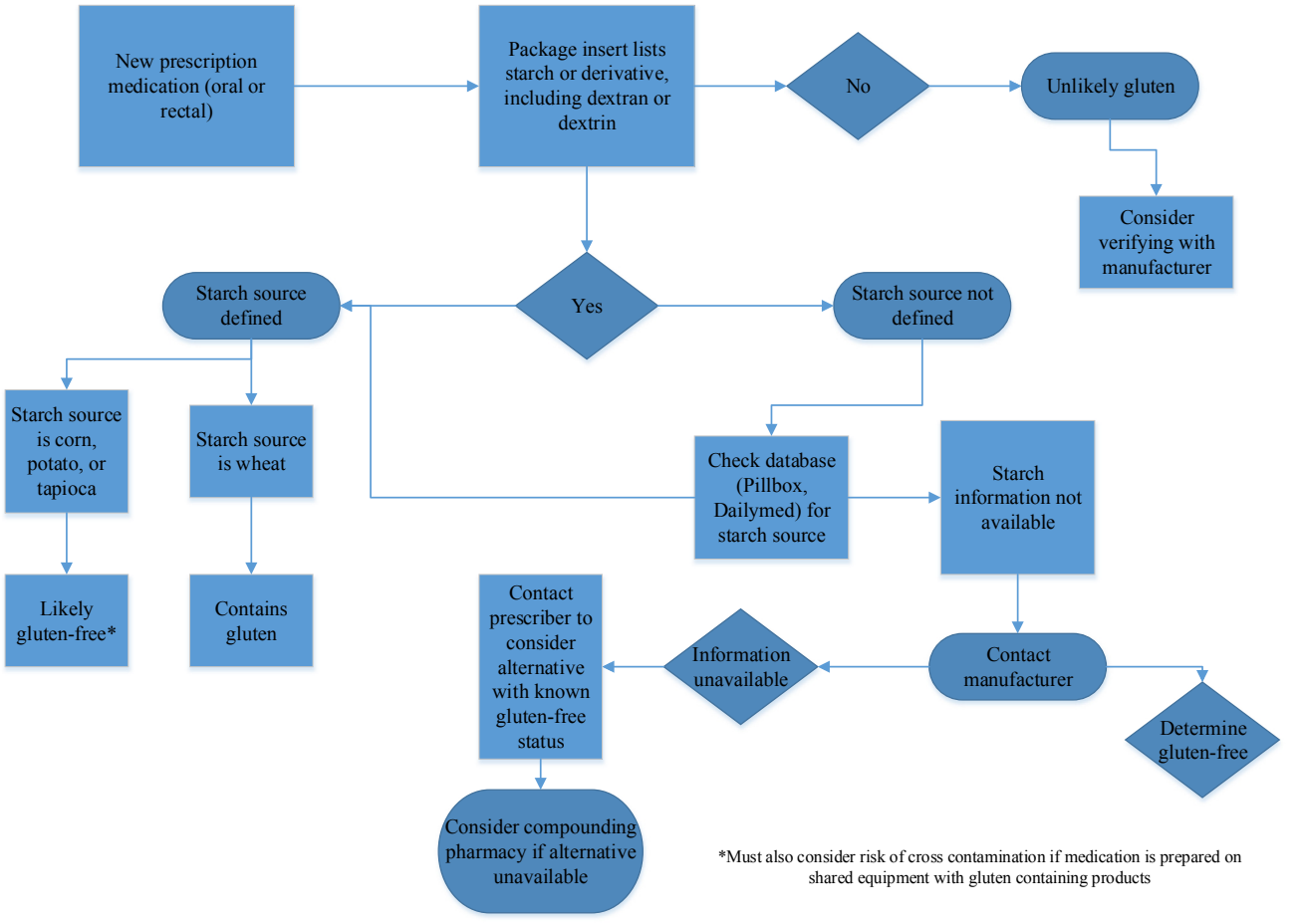

Figure 1. Process for pharmacists to verify gluten-free status of medications.

recognized in 1985.[13] More than 30 years later, a standardized resolution has not been determined.

QUANTIFYING GLUTEN

The Food and Drug Administration (FDA) has defined the term *gluten-free* as less than 20 ppm.[14] Recent food labeling laws (as of August 2014) require gluten-free food labels to meet this definition, which only applies to food and dietary supplements. The threshold of 20 ppm being deemed the maximum amount of gluten permitted to be detectable in gluten-free food has been established in the United States, since a goal of 0 ppm would not be easily attained.[15]

In addition, studies have demonstrated that the maximum amount of gluten tolerated by patients with celiac disease per day is below 50 mg.[16] When patients eat gluten-free products with less than 20 ppm gluten, this provides a safety margin for not reaching the threshold of 50 mg/day even when as much as 500 g (approximately 2,000 kcal of food a day) is consumed.[17] This would roughly equate to keeping any gluten exposure to 1% or less in a 2,000-kilocalorie diet.

CONSEQUENCES OF INABILITY TO READILY DETERMINE GLUTEN CONTENT OF MEDICATIONS

There is no FDA-regulated term for gluten-free labeling of medications, and few medications are actually labeled as being gluten-free. However, no medications containing gluten should be consumed by patients with celiac disease.[18,19] Many medication side effects can mimic gluten-like reactions in patients with celiac disease. A patient may be more likely to discontinue a medication because of fear that the reaction is due to gluten if the medication has not been confirmed to be gluten-free.

According to a case report, a 52-year-old woman with celiac disease was being treated with pain medications.[20] This patient was taking a high dose of oxycodone—up to 360 mg daily. When she was switched to methadone, she experienced viral infection–like side effects after 3 weeks of treatment. The methadone was replaced with oxycodone, and the dose was increased to 480 mg/day, which led to resolution of the viral infection-like symptoms. After some time, methadone was prescribed again, and the patient had severe diarrhea. Because the patient was concerned that the methadone contained gluten, she suddenly stopped taking it. Laboratory testing confirmed that gluten was not detectable in the methadone. The authors conclude that a patient with celiac disease may be hypervigilant about the presence of gluten in medications and may discontinue treatment inappropriately because of a belief that gluten is causing the adverse effect. This lack of compliance may lead to adverse outcomes. With better labeling and clearer information, instances such as this could be avoided.