EXECUTIVE SUMMARY

Since 2007, the National Foundation for Celiac Awareness (NFCA) has been engaged in advocating for the elimination of gluten in medication or, alternatively, labeling of gluten as an ingredient in over-the-counter (OTC) and prescription medications.

In November 2011, the National Foundation for Celiac Awareness (NFCA) received a grant from the Food and Drug Administration (FDA) as part of its Safe Use Initiative to study the impact of Gluten in Medication. A Research Team led by Loretta Jay, MA, consultant to NFCA, Parasol LLC and Robert A. Mangione, RPh, EdD, Provost and Professor, St. John's University and member of NFCA's Scientific/Medical Advisory Council addressed the issues surrounding gluten in medication to determine if gluten is, in fact, present in prescription and over-the-counter medications.

The team collected information from 5,623 people with celiac disease and gluten sensitivity through an online survey. 1,399 of these respondents reported that they suspected an adverse reaction caused by gluten in their medication.

The Research Team analyzed results from testing 39 drugs reported by these respondents, including the seven most frequently reported over-the-counter and eight most frequently reported prescription drugs and 24 additional drugs. It is important to note that this is a small sample of the total number of medications available to consumers in the US.

Key findings are:

- *Patients and healthcare providers find it difficult to ascertain whether a medication is gluten-free causing anxiety, lack of confidence, medication substitutions and noncompliance.*

- *Patients reported a wide range of symptoms associated with their suspected gluten exposure, including: constipation, nausea, diarrhea, abdominal pain, bloating, headache, fatigue, irritability, muscle tremors/cramps, failure to thrive and skin rash. Some of the reactions reported by survey respondents are also known side effects of these mediations, others are not.*

- *Some of the drugs tested based on criteria created by the Research Team tested over the level of quantification, while a substantial number of the drugs tested below this level of quantification. It is important to note that this is a small sample of the total number of medications available to consumers in the US. Additional drugs could test above that limit when dosage is considered, a clear indicator for the need for additional research.*

The following are excerpts taken from "Gluten in Medication: Qualifying the extent of exposure to people with celiac disease and identifying a hidden and preventable cause of an adverse drug event"

by

Loretta Jay, MA;, Robert A. Mangione, RPh, EdD; Somnath Pal, Ph.D, MBA, MS; S. William Zito, Ph.D.; Carmela Avena-Woods, PharmD, CGP; Gregory G. Sarris, MS; Dharam V. Ajmera, MS; Steven Pak

Introduction

An estimated two to three million Americans have celiac disease, a genetically based autoimmune digestive disease. The only treatment is a lifelong gluten-free diet. Millions more Americans have Non-Celiac Gluten Sensitivity (NCGS) and also refrain from ingesting gluten. Gluten, a protein in wheat, barley and rye, is deleterious to these populations. Manifestations of ingested gluten are varied and may impact every system of the body: Gastrointestinal problems, neurological disorders, reproductive system problems and malignancies are among the myriad signs and symptoms of this disease.

Since gluten-derived ingredients may be used as excipients in the formulation of medication, understanding and identifying the preventable harm from gluten in medication is imperative for the drugs' safe use by this large patient population. The number of people with celiac disease has increased 400% in the past 50 years, dramatically raising the public health risk.

Prior to embarking on this study, the National Foundation for Celiac Awareness (NFCA) was alerted to numerous anecdotal reports of patients experiencing adverse effects from medication in which gluten was suspected as the cause. Healthcare providers and pharmacists also expressed frustration at their inability to consistently and readily ascertain if a needed medicine contained gluten. NFCA received one report of a pharmacy refusing to serve a patient because it feared legal liability if a dispensed drug did contain gluten.

Background

In this study we use the term *adverse drug event* as defined by the FDA: "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

The FDA also defines a *suspected adverse reaction* as: "any adverse event for which there is a reasonable possibility that the drug caused the adverse event. … Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug."

As we consider the various reports, it is worth noting that the preventable harm may be a direct effect of the gluten in the drug (physical harm), or a result of additional diagnostic procedures, changes in the therapeutic regimen and other modifications of therapy that may not have been needed (physical harm). The patient's confidence in the medication therapy and their healthcare provider may also be compromised (psychological harm).

The Problem: Labeling

In the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA), Congress recognized celiac disease as a multi-system disease affecting one percent of the US population that must be treated with a gluten-free diet, and it ordered the FDA to define gluten-free. In response, on August 2, 2013, the FDA announced to the public its Final Rule defining gluten-free for food products. In its most basic sense, a packaged food product regulated by the FDA that is labeled gluten-free must contain less than 20 ppm gluten, and it must also comply with additional criteria beyond this

specific threshold.

There are no US regulations requiring or guiding manufacturers on how to specify if gluten is present in medication.

Through the FALCPA process, the FDA received some comments about gluten in drugs. To better understand this area, the FDA published an invitation on December 21, 2011 for public comment about drug ingredients that are derived from wheat, barley or rye, and for information about ways to help people with celiac disease avoid gluten in medicine, if it was contained in the oral dosage form. The notice also sought information from manufacturers about medicines that have ingredients that are derived from wheat, barley, or rye. The comment period closed on March 20, 2012, and FDA's Center for Drug Evaluation and Research is reviewing those comments.

Red-Flag Ingredients

Wheat, barley or rye may be the source of a limited number of excipients. Examining a medication's inactive ingredient list for a red-flag ingredient is the only way that people following a medically necessary gluten-free diet and their healthcare providers have to assess for gluten in a drug. The following inactive ingredients may be sourced from wheat, barley or rye:

- Wheat
- Modified starch (source not specified)
- Pregelatinized starch (source not specified)
- Pregelatinized modified starch (source not specified)
- Dextrates (source not specified)
- Dextrin (source not specified but usually corn or potato)
- Dextrimaltose (when barley malt is used)
- Caramel coloring (when barley malt is used)

Method

Through this research study we sought to identify and characterize the problem, qualify the extent of harm, and conduct a root cause analysis. We did this by applying the findings of the patient reported adverse reactions to gluten in medication to existing scientific research: safe threshold of gluten, manifestations of celiac disease, and the ELISA assay.

Since there was little pre-existing research exploring the area of gluten in medicine, we aimed to gain new insights and better understanding of how the celiac disease and NCGS populations are impacted by unlabeled gluten in medicine with the hope of both awakening the industry and other stakeholders to the potential harm for patients and informing future research. We first collected data through a survey of the celiac disease and NCGS populations. Information gathered included demographic characteristics of the respondents, why they are on a gluten-free diet and how they manage that diet. Only subjects who indicated that they always follow a gluten-free diet or usually follow a gluten-free diet had their responses included.

Subjects who reported that they believe that they experienced an adverse drug event due to gluten were asked additional information about the medication, the reaction, and what actions the respondent took as a result of the reaction. Subjects were given the option to share identifying information and to report additional information in narrative form.

Those findings were analyzed and a short list of drugs suspected of causing adverse effects was established. Finally, the drugs were tested to determine gluten content, and the findings were compared to the information available to pharmacists, prescribers and patients through both labeling and manufacturer disclosure.

Medications have not been tested for gluten in clinical research prior to this study. The lessons learned here will guide funders, future researchers, manufacturers and regulatory bodies when considering next steps.

Changing Concepts

Research conducted in 2007 and 2008 indicates that people with celiac disease cannot tolerate as little as 10-50 mg gluten/day. These studies explored the immune response to gluten in people affected with celiac disease as observed through villous atrophy, serology, and reports of clinical symptoms. Some of the studies did not consider the subjects' symptoms, only histological response.

In 2011, the FDA conducted an evaluation of existing research to determine what are tolerable amounts of gluten for people with celiac disease. It found that the tolerable daily intake level of gluten for people with celiac disease was determined to be 0.4 mg gluten/day for adverse morphological effects and 0.015 mg gluten/day for adverse clinical effects.

Results

This study shows that the celiac disease and NCGS populations experienced what *they believe* to be gluten exposure from medication. Virtually all respondents said that when they stopped taking the medication their symptoms went away. While this relationship will be consistent with the active ingredient of the drug product causing the side effect, it also confirms the consumers' *perception* that gluten in inactive ingredients of the medication caused the reaction.

Emotional Harm

Patients experienced anxiety and they did not adhere to prescribed medication regimens. This was not an isolated case of patients going it alone. Sometimes ending a treatment regimen was against medical advice. Answers are not available after regular business hours, and sometimes manufacturers are not prepared with the responses when contacted during the day. Further, the formulations may change after investigation, rendering each inquiry valid only for that specific timeframe. Attempts have been made to develop consumer-driven lists of gluten-free medication, but these require constant updating and oftentimes contain errors.

When an individual or healthcare provider is unsure of the gluten status of a medicine, then additional harm may occur. The first choice medication may not be prescribed and this may prolong the illness that is being treated. If patients lack trust with the prescribed drug then there are adherence concerns as well.

Financial Cost

As a result of incomplete information, patients are experiencing unnecessary referrals to other medical specialists, unnecessary medical procedures, and missed time from work. This results in avoidable healthcare costs and loss of income.

Survey

An electronic and print survey was distributed to people with celiac disease and NCGS in the US in order to better understand their experiences securing and taking drugs. The total number of survey respondents was 5,623. The total number of respondents who reported they had an adverse reaction caused by gluten was 1,399 (25%).

Subjects named 242 different drugs suspected of causing a gluten-related reaction. Of the 242 drugs, 39 drugs were tested: the seven most frequently reported OTC and eight prescription (Rx) drugs were tested, along with 24 other

medications. Herbal supplements, topical formulations and injections were excluded from the study.

Criteria for selecting drugs for testing included the number of reported reactions; the severity of the reported reactions; how often the drug is used; and the ability to exclude common drug (non-gluten related) side-effects.

Two assays were used to quantify gluten in the medicines: R-Biopharm's Competitive ELISA tests for hydrolyzed product and measures a level of quantification (LOQ) of 10 parts per million (ppm) while its Sandwich ELISA measures gluten at a LOQ of 5 ppm. None of the medications tested above the LOQ on the Sandwich ELISA and three medications tested over the LOQ on the Competitive ELISA.

Clinical Significance

The Office of Food Safety at the FDA concluded in its May 2011 Health Hazard Assessment for Gluten Exposure in Individuals with Celiac Disease that those affected with the disorder should consume no more than 0.4mg gluten per day to prevent adverse morphological effects and 0.015 mg gluten per day to prevent adverse clinical effects.

Throughout the analysis and reporting process, we considered how the patient and prescriber populations would use our findings. We concluded that it is important to report the quantification of gluten per dosage form, rather than in their raw, or testing form.

In addition to testing above the LOQ, the three drugs that tested positive using the Competitive assay contained gluten at a level above 0.015 mg per dosage form:

- Sertraline tablets were tested two times. When the amount of gluten per dosage form was calculated, we determined that there was 0.077 mg gluten during the first test, and 0.054 mg gluten in the second test.
- Acetaminophen/dextromethorphan HBr/doxylamine liquid capsules were tested one time and they contained 0.022 mg gluten per dosage form.
- Omeprazole capsules were tested two times. The first time they contained 0.023 mg gluten per dosage form. The second time they were tested they contained 0.025 mg gluten per dosage form.

When we calculated the gluten content of all of the drugs, several of the drugs tested (using the Competitive assay, which tests for hydrolyzed gluten) contained gluten in quantities that would result in adverse clinical effects if two or more dosage forms were given in one day.

Most of the drugs that tested above the LOQ in the Competitive ELISA did not contain any red-flag ingredients. In addition, there were positive test results for the Competitive ELISA, which tests for gluten in hydrolyzed products, and there were no hydrolyzed products among the ingredients listed by the manufacturer. Reasons for these test results might include:

- Manufacturer's cross-contamination (cross contact)
- Manufacturer's outdated information about ingredient's source
- Contamination in the lab
- A false-positive with the assay

Survey Limitations

The survey did not reach a representative sampling of the celiac disease and NCGS patient populations, nor were respondents randomized. Despite efforts to reach populations without access to a computer or the Internet, less than one percent of the completed surveys were non-electronic.

Furthermore, by virtue of their connection to celiac disease organizations or media sources, it is likely that the population that did receive the survey is more attentive to the gluten-free aspects of their lifestyle than the general celiac disease and NCGS populations.

Conclusion

Respondents to the *Gluten in medication: Qualifying the extent of exposure to people with celiac disease and identifying a hidden and preventable cause of an adverse drug event* survey indicated that they experienced adverse drug events, and they believe that gluten was the cause.

When we proposed this project, we knew that the study design would not allow us to show a cause and effect relationship between potential gluten in a medication and a survey respondent's reported adverse events that they attribute to gluten. Rather, we expected to demonstrate that because the gluten content of medicine was unknown, the celiac disease and NCGS patient populations would attribute any adverse drug events to gluten, even if caused by the drug itself. When manufacturers use clear, unambiguous language about the inactive ingredients in their products, the end users and their healthcare professionals will have greater trust in the message and the product.

Collaboration between the FDA, drug manufacturers, manufacturers of testing kits, healthcare providers and the celiac disease and NCGS community is needed.

The qualified findings of the survey, coupled with the test results of the identified medications, provide the preliminary basis for further study in this area. It is expected that findings from this research study will drive future studies toward human clinical research to support additional root cause analysis. We recommend pursuing the development of optimum testing protocols, and determining if there is clinical significance to the identified amounts of gluten that is present in medicine.

1. Labeling: The FDA Safe Use Initiative has repeatedly requested scientific data to support the need for labeling of gluten in medication. Although preliminary, this research began the process of advancing knowledge in this area from anecdotal patient reports to a scientifically valid and trusted body of data. With this information, we hope that the FDA's Safe Use Team will be able to move forward to address this area of preventable harm.

2. Research: The findings of this preliminary study identified the need for additional research in the area of gluten in medication: human clinical research on the effects of gluten in medication when ingested by people with celiac disease. Subsequent research projects may involve controlled studies that include pre and post-test biopsies of human subjects exposed to the medications that are identified in this study.

The research team had some testing difficulties due to the small size of each dosage form. This suggests that future research of various testing methods for the presence of gluten in drugs is needed. The study was not intended to show a cause and effect of the alleged gluten reactions; this may be another area for further exploration.

In addition … we recommend that guidance should be given to drug manufacturers on appropriate labeling of inactive ingredients. It is expected that by providing prescribers, pharmacists and patients with needed information to make informed decisions, the incidence of adverse drug events can be reduced.

By characterizing the factors that lead to adverse drug events, and the elements that are needed to identify risk, we established a foundation of knowledge to be built upon. Our hope is that action will be taken so individuals following a

medically required gluten-free diet will have access to the full spectrum of available medications and also can avoid preventable harm.