

1.2.3: What can go Wrong in Research - Two Stories

The first story is about a drug that was thought to be effective in research, but was pulled from the market when it was found to be ineffective in practice.

FDA Orders Trimethobenzamide Suppositories Off the market⁶

FDA today ordered makers of unapproved suppositories containing trimethobenzamide hydrochloride to stop manufacturing and distributing those products.

Companies that market the suppositories, according to FDA, are Bio Pharm, Dispensing Solutions, G&W Laboratories, Paddock Laboratories, and Perrigo New York. Bio Pharm also distributes the products, along with Major Pharmaceuticals, PDRX Pharmaceuticals, Physicians Total Care, Qualitest Pharmaceuticals, RedPharm, and Shire U.S. Manufacturing.

FDA had determined in January 1979 that trimethobenzamide suppositories lacked "substantial evidence of effectiveness" and proposed withdrawing approval of any NDA for the products.

"There's a variety of reasons" why it has taken FDA nearly 30 years to finally get the suppositories off the market, Levy said.

At least 21 infant deaths have been associated with unapproved carbinoxamine-containing products, Levy noted.

Many products with unapproved labeling may be included in widely used pharmaceutical reference materials, such as the *Physicians' Desk Reference*, and are sometimes advertised in medical journals, he said.

Regulators urged consumers using suppositories containing trimethobenzamide to contact their health care providers about the products.

The second story is about promising research that was abandoned because the test data showed no significant improvement for patients taking the drug.

Drug Found Ineffective Against Lung Disease⁷

Treatment with interferon gamma-1b (Ifn-g1b) does not improve survival in people with a fatal lung disease called idiopathic pulmonary fibrosis, according to a study that was halted early after no benefit to participants was found.

Previous research had suggested that Ifn-g1b might benefit people with idiopathic pulmonary fibrosis, particularly those with mild to moderate disease.

The new study included 826 people, ages 40 to 79, who lived in Europe and North America. They were given injections of either 200 micrograms of Ifn-g1b (551 people) or a placebo (275) three times a week.

After a median of 64 weeks, 15 percent of those in the Ifn-g1b group and 13 percent in the placebo group had died. Symptoms such as flu-like illness, fatigue, fever and chills were more common among those in the Ifn-g1b group than in the placebo group. The two groups had similar rates of serious side effects, the researchers found.

"We cannot recommend treatment with interferon gamma-1b since the drug did not improve survival for patients with idiopathic pulmonary fibrosis, which refutes previous findings from subgroup analyses of survival in studies of patients with mild-to-moderate physiological impairment of pulmonary function," Dr. Talmadge E. King Jr., of the University of California, San Francisco, and colleagues wrote in the study published online and in an upcoming print issue of *The Lancet*.

The negative findings of this study "should be regarded as definite, [but] they should not discourage patients to participate in one of the several clinical trials currently underway to find effective treatments for this devastating disease," Dr. Demosthenes Bouros, of the Democritus University of Thrace in Greece, wrote in an accompanying editorial.

Bouros added that people deemed suitable "should be enrolled early in the transplantation list, which is today the only mode of treatment that prolongs survival."

Although these are both stories of failures in using drugs to treat diseases, they represent two different aspects of hypothesis testing. In the first story, the suppositories were thought to be effective in treatment from the initial trials, but were later shown to be ineffective in the general population. This is an example of what statisticians call **Type I Error**: supporting a hypothesis (the suppositories are effective) that later turns out to be false.

In the second story, researchers chose to abandon research when the interferon was found to be ineffective in treating lung disease during clinical trials. Now this may have been the correct decision, but what if this treatment was truly effective and the researchers

just had an unusual group of test subjects? This would be an example of what statisticians call **Type II Error**: failing to support a hypothesis (the interferon is effective) that later turns out to be true. Unlike the first story, the second story will never result in answer to this question since the treatment will not be released to the general public.

In a traditional Introductory Statistics course, very little time is spent analyzing the potential error shown in the second story. However, both types of error are important and will be explored in this course material.

Preliminary Results – bringing the holistic approach to the entire statistics curriculum.

After writing what are now chapters 8, 9 and 10, I decided to use this holistic approach in several of my courses. I found students were more engaged in the course, were able to understand the logic of hypothesis testing, and would state the appropriate conclusion. I wanted to bring this approach to the entire statistics course and this book is the result.

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