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Oral Fluoroquinolones, Retinal Detachments and Claims Database Studies

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In this issue, Raguideau and colleagues¹ add to the literature supporting an association between oral fluoroquinolone use and an increased risk of retinal detachment (RD). Understanding the potential adverse events associated with fluoroquinolone use is of great public health importance due to their widespread clinical utility. In performing this study, the authors use two French national administrative medical claims databases to generate their data. Although databases similar to the ones used within this study have been commonly employed in observational research across most other medical specialties for the past 25 years, their application to ophthalmic research has only recently become more commonplace. Because of this, it is important to remember both the inherent strengths and weaknesses these types of databases offer before the reported association is applied to clinical decision making.

The Raguideau *et al.*¹ study exemplifies many of the strengths these databases provide. First and foremost is the ability to collect a tremendously large number of either exposures or outcomes. In this instance, the authors were able to collect over 27,000 RDs, by far the largest collection of outcomes used to study this question to date. In addition, the richness of the data often contained within an administrative claims database gives researchers wide latitude to perform all types of observational studies. The authors were interested in addressing some of the limitations of previous fluoroquinolone-RD studies and did so by conducting a case-crossover study. This design allowed the authors to contrast rates of fluoroquinolone exposure between different time periods of interest within the same person.

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This permitted patients to serve as their own controls and limited potential confounding due to factors that should be stable over a short observation period (i.e. severity of myopia, presence/absence of systemic diseases). This type of study is ideal for exposures that are brief, well defined and anticipated to cause an effect shortly after exposure, all of which accurately describe oral fluoroquinolone use and its anticipated effects.

A last strength as it pertains to the Raguideau study is the ability to precisely time the exposure. Often retrospective studies rely on patient recall or potentially out-of-date medication lists from a patient chart. Knowing the exact date a prescription was filled by using pharmacy claim data without recall bias, especially for short-term, acute illness medications such as antibiotics, is integral in assessing the exposure/outcome association of interest.

To date, the literature on a possible association between oral fluoroquinolones and retinal detachments has been mixed.²⁻⁶ One possible explanation for the discrepancy in the findings can also be tied to the potential weaknesses of administrative database research. In contrast to the relative reliability of the pharmaceutical claim data to define an exposure in these studies, numerous issues can plague the outcome variable if it is not appropriately defined with strict inclusion and exclusion criteria.

First, due to the vastness of the available data within an administrative medical claims database, it is easy to include patients who may not be directly relevant to the question being asked. Many of fluoroquinolone/RD studies have included multiple kinds of retinal detachments.^{1,4-6} This lumping is difficult to justify on a pathophysiologic basis, as each type of RD (rhegmatogenous, exudative and tractional) has a unique root cause unrelated to the other types. Although possible, it is unlikely a single class of antibiotics would adversely affect the eye in three distinct manners necessary to increase the risk of each unique type of RD. Raguideau *et al.* did distinguish between exudative and rhegmatogenous detachments, but did not exclude tractional detachments. Nor is it clear that the authors excluded cases where trauma likely played a significant role as not all traumas require hospitalization prior to causing an RD. Additionally, the authors do not disclose how patients diagnosed with more than one type of RD were used within the study.¹

It is also important to understand the data available to researchers within each claims database used for a particular study. In the current study, an RD was defined as happening on the date a hospitalization with a claim for which RD surgery occurred. This is a potential concern because RDs are commonly repaired up to a week after the initial date of diagnosis and are not necessarily hospitalized that same day. Unlike other studies²⁻⁵ that used a combination of outpatient diagnosis and surgical procedure codes to define the outcome, this ambiguity of diagnosis date allows for a possible surveillance bias. The decision for surgery, particularly when it is delayed for a day or more, often induces a pre-operative primary care exam on which concern for an unrelated infection could induce an antibiotic prescription to be written. Although filled after the diagnosis date, this would not be evident in the data used in the current study. The reported concurrent antibiotic use (both oral, >2%, and topical, >12%) at the time of surgery, which is much higher than would be expected in a general population, points to this possibility.

An additional concern of many pharmacoepidemiology studies performed in claims databases is indication bias, where an association between a drug and an adverse event is attributed to the drug itself, instead of the true cause of the association, the underlying disease for which the medication was given. Sandhu *et al.*⁷ demonstrated this in a recent JAMA Ophthalmology article where fluoroquinolone exposure was associated with an increased risk of being diagnosed with a systemic disease associated with uveitis within a year of taking the prescription, possibly explaining a previous study's positive finding of a fluoroquinolone/uveitis association. This together with the current study not excluding uveitis patients offers one possible explanation as to why the risk of exudative RD was so elevated in their study.

The last thing to remember when considering findings from a claims database study is that due to their size, it is very common to find a statistically significant result. This, however, is not the same as a clinically significant result. According to Raguideau *et al.*, 5,000,000 prescriptions of fluoroquinolones were dispensed in France in 2013.¹ Despite this high number of prescriptions, only 80 of the 27,540 included RD patients had a fluoroquinolone exposure concurrent with their RD repair. Due to the design of the study, an absolute risk (number of RDs specifically attributable to fluoroquinolone use) cannot be calculated. However, in the unlikely case fluoroquinolone use truly causes rhegmatogenous RDs, the increase in absolute risk is at most very minimal. This idea was also supported by an earlier study that found a non-significant increase of only 1.5 RDs per 1,000,000 treatment episodes.⁶ It is one thing to ask the question what are the risks of taking a specific class of medications? It is quite another however, to ask, if we should limit the use of such a widely beneficial and typically safe medication over a debatably increased risk for RD? Hopefully with further insights into this proposed association, answers will be forth coming.

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