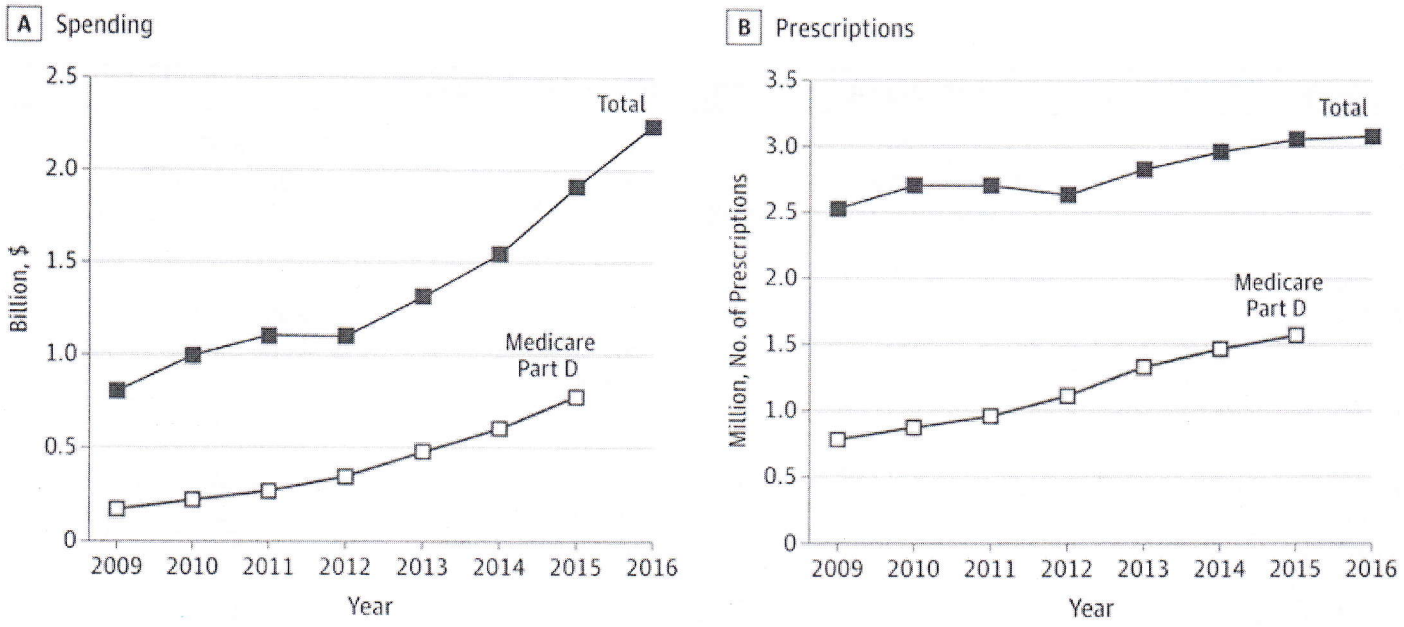
A Clear-Eyed View of Restasis and Chronic Dry Eye Disease

In a legal maneuver that has left many rubbing their eyes, Allergan recently transferred the 6 patents on its blockbuster "dry eyes" drug Restasis (cyclosporine ophthalmic emulsion, 0.05%) to the Saint Regis Mohawk Tribe, which will exclusively license the patents back to the company. The deal, which may delay the marketing of generic alternatives to Restasis, is under legal challenge, amid calls for Congress to ban the strategy Allergan has sought to exploit.

But the more fundamental question has received little attention: does Restasis work? Restasis is not approved in the European Union, Australia, or New Zealand, where in 2001 registration applications were "withdrawn prior to approval due to insufficient evidence of efficacy."[1] Although Canada approved Restasis,[2] its national health technology assessment unit, unconvinced of meaningful benefit, recommended Canada not pay for it.[3] Our research found no Canadian provincial or federal drug plan that currently does.

But Americans pay for Restasis—a lot: $8.8 billion in US sales between 2009 and 2015, including over $2.9 billion in public monies through Medicare Part D (Figure).



Total US and Medicare Part D Sales and Dispensed Prescriptions of Restasis (Allergan Inc) From 2009 to the Most Recent Available Data[a]

Annual US spending increased by 342% from 2009 to 2016, and Part D spending increased by 135% from 2009 to 2015. Spending increased more rapidly than the number of prescriptions, reflecting price increases. Spending was adjusted to 2016 dollars using the Consumer Price Index.

[a]Data sources are Symphony Health Data through Bloomberg Professional Services (https://www.bloomberg.com/professional/solution/bloomberg-terminal/) (including Restasis MultiDose formulation in 2016) and the 40% Medicare Part D file.

In 1999, Allergan sought approval from the US Food and Drug Administration (FDA) for Restasis to treat moderate to severe dry eye (keratoconjunctivitis sicca). Cyclosporine is thought to act as an immunomodulator, which reduces ocular inflammation that suppresses tear production.[4] The application failed when FDA reviewers and a unanimous FDA advisory committee concluded that it did not meet protocol-defined efficacy criteria: improvement on both a sign (ocular surface damage) and symptoms (Ocular Surface Disease Index symptom score). The findings of the 2 identical, placebo-controlled pivotal trials were inconsistent: one showed no improvement in either criterion,[4] and the other found statistically significant—but not clearly meaningful—improvements at some time points but not others.[4] Subsequently, Allergan amended the application 4 times, reanalyzing the same data.

In 2003, the FDA approved Restasis to increase tear production based on a surrogate sign, the Schirmer response.[4] The response was defined as at least 10 mm of moisture on a filter-paper strip 5 minutes after placed in the eyelid. In a pooled analysis of 4 trials, at 6 months, 15% of patients had a response with Restasis compared with 5% with vehicle (placebo).[4] The FDA required Allergan to establish the clinical relevance of the Schirmer response. Even though Restasis did not improve symptom scores (compared with placebo) when tested directly in the pivotal trials, FDA accepted

weaker indirect evidence from the validation study: Schirmer test responders had better symptom scores than nonresponders.[4]

By contrast, in the only other regulatory review of the drug that is publicly available, Australia's Therapeutic Goods Administration evaluator found "minimal or no benefit over and above placebo at most time points" and that the trials—the same ones submitted to the FDA—showed no "convincing or sustained benefit of 0.05% [or] (0.1%) cyclosporine eye drops vs. vehicle in patients with moderate to severe keratoconjunctivitis sicca treated up to 6 months, using a range of objective and subjective efficacy criteria."[1]

In 2010, Canada approved Restasis for a narrower population: patients with moderate to moderately severe (but not severe) dry eye disease.[2] Approval was based on another reanalysis of the trials submitted to FDA using severity subgroups defined post hoc by the International Dry Eye Workshop, which was funded by Allergan and other drug companies. In 2011, Allergan reapplied for marketing approval in Australia, using the subgroup approach that succeeded in Canada.[1] Allergan withdrew the application after the Australian review committee recommended rejection because of concerns about "data dredging" (efficacy was only seen in post hoc subgroups) and the lack of a prospective trial in patients with moderate to moderately-severe disease.

Clinicians typically do not learn about new drugs from regulatory documents; many learn from company-sponsored promotional efforts, such as detailing visits and events where food and beverages are provided.

In the case of Restasis, even evidence-based clinical resources may be misleading. For example, the "Dry Eyes" chapter in UpToDate,[5] a point-of-care resource, summarized a systematic review[6] as follows: "All nine [Restasis] trials that evaluated symptoms ... found improvement." But 4 of these 9 trials only demonstrated within-group—not between-group—improvements. The other 5 trials found that only 1 or 2 of the 4 to 8 symptoms tested improved.[6] For the symptom score (a primary outcome in drug approval trials), Restasis was superior to artificial tears or placebo in just 1 of the 9 trials of initial treatment. Although the UpToDate authors note that they "have not seen such a degree of beneficial results in their practice,"[5] the chapter does not mention that, as disclosed in the systematic review,[6] the senior author was an Allergan consultant. Moreover, neither the UpToDate chapter nor the systematic review discusses the tenuous evidence of efficacy found in the treasure trove of regulatory documents.

Given the scant evidence of efficacy, why does Restasis have more than $2 billion in annual sales in the United States? An important reason may be the extensive marketing campaign to sell a disease —chronic dry eyes—and its treatment. From 2007 to 2016, Allergan spent $645 million on television, magazine, and electronic ads, according to data provided by Kantar Media (https://www.kantarmedia.com/us), including its mydryeyes.com website.[7] The website recasts ordinary unpleasant life experiences as disease: "those who experience stinging, burning, and watering eyes might attribute these symptoms to the weather, allergies, contacts or even their eye makeup, when in fact they may be suffering from Chronic Dry Eye (CDE) disease." Mydryeyes.com invites people to take a quiz. The results come with a warning: "Don't wait; over time, CDE disease

may get worse and may have potential health consequences for your eyes, including damage to the front surface of the eye, an increased risk of eye infection, and effects on your vision." Another Allergan website, Restasis.com,[8] calls CDE "a chronic condition with no permanent cure ... which reduces your natural tear production." The results of its Dry Eye quiz warn that over-the-counter artificial tears provide temporary relief but "do not increase your eyes' ability to make their own tears. Restasis ... is the only prescription treatment proven to help you make more of your own real tears."[9]

Both websites suggest sharing quiz results with a doctor, and offer online help locating one, though neither website discloses that participating eye doctors may have company ties. Allergan paid $9.1 million to 24 152 physicians in the United States from 2013 to 2015.[9] The Find-a-doctor feature includes 7 of the top 10 payees.

People learning about dry eye disease or taking a company-sponsored quiz may mistakenly assume that Restasis is FDA approved to reduce symptoms and artificial tear use.[4] Research conducted by FDA scientists shows why this may be the case: merely listing symptoms of a disease can promote the misconception that the drug treats the symptoms, even if it is not approved to do so.[10]

Based on the evidence, why should consumers, private insurers, and the federal government spend billions of dollars on a marginally effective drug for a condition that many would not consider to be a disease? Restasis might never have reached blockbuster status if payers, clinicians, and consumers had easy access to independent drug information. Regulatory documents from the United States and other countries are valuable but underused sources of this information. Although reviews for older drugs, such as Restasis, are often poorly organized, regulators now produce more readable documents. Unfortunately, missing information remains a problem: reviews may be heavily redacted, and some are never released. The FDA, for example, does not—but should—release reviews for drugs not approved (even when marketing applications are withdrawn prior to final regulatory action), as is currently done by drug regulators in the European Union and Australia.

Think about all the good that could have been done with the billions spent in the United States on Restasis. It should bring tears to your eyes. Which is what Restasis is supposed to do—just not like this.

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