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Entrepreneurship in Off-Label Drug Prescription: Just What the Doctor Ordered!

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Abstract
This paper finds that physicians and pharmaceutical companies working as entrepreneurial actors were able to better serve patients by finding effective alternative uses of three drugs. I examine off-label drug prescription within an entrepreneurial framework by examining the development processes of aspirin, Viagra, and minoxidil. In each case, the medical community reached research and treatment conclusions quicker than the FDA did. These examples provide counterevidence to the view that off-label prescription is reckless and requires additional governmental oversight due to a lack of sufficient testing.

JEL Codes: I18, I12, K23
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I. Introduction

Any legally prescribed drug in the United States must undergo a lengthy, costly, and uncertain process enforced by the Food and Drug Administration (FDA). The time between drug discovery and approval averages sixteen years, and the probability of approval for human use is approximately 10 percent (Stossel 2015). Completing this approval process requires an average investment of $403 million (Demasi, Hansen, and Grabowoski 2003).[1] The high cost of FDA drug approval creates significant barriers to entry and reduces the number of pharmaceuticals available to consumers (Tabarrok 2000, 2009). Physicians are left with few options to serve patients (Benson 2004).

Despite these high barriers to entry, physicians can exercise an entrepreneurial role in their practices by prescribing and recommending pharmaceuticals off-label. As noted by Salbu (1999),

[1] The authors provide this estimate in 2000 dollars. In 2016 dollars, $403 million is approximately $560 million.

the FDA's authority to regulate the pharmaceutical market only extends to *approval* for human use for a specific condition. The FDA does not have the authority to tell doctors what an approved drug can be prescribed or used for. Off-label prescription, by some estimates, accounts for 25 percent of all prescriptions, (Leibman 2003) but can be significantly higher for certain conditions.

Although off-label prescribing is common, many consumers, physicians, and other medical professionals believe that unregulated off-label prescription is reckless and requires additional FDA oversight (Stafford 2008; Dresser and Frader 2009; Buppert 2012; Howard and Copland 2013). A common assumption in proregulation literature is that prescribing pharmaceuticals outside of the FDA's scope of approved uses is unsafe and, because the evidence is insufficient to demonstrate safe use, prescribing for off-label uses is negligent. Despite a circuit court decision that promoting off-label uses of pharmaceuticals by manufacturers is protected under the First Amendment,[2] the FDA has recently engaged in efforts to more narrowly construe the definition of "promotion." This effort results in less information available for physicians to find effective ways to treat patients.

Physician Randall Stafford believes off-label prescription needs greater FDA oversight. He writes, "Evidence regarding the efficacy and safety of off-label use is nearly always inferior to that required by the FDA in approving a product for its intended calculation" (2012, p. 291). Stafford concludes that the FDA may need to increase its mandate to monitor off-label drug prescription better. Radley, Finkelstien, and Stafford (2006) call for policy makers to "consider strategies for mandatory post-approval surveillance that focus on curtailing off-label practices" (p. 1026). Public opinion has demonized off-label prescription to an extent where, according to the Consumers Union, "Most of those [off-label uses] are for a use that *lacks any evidence or rigorous study to back it up*" (emphasis original) (2007, p. 1).

The critical question is, Who is better suited to find effective and safe alternative uses for existing drugs and who can find them promptly: the bureaucratic FDA or the entrepreneurial physicians and pharmaceutical companies? This paper holds that the entrepreneurial actions taken by physicians and pharmaceutical companies through the market in a comparatively less-regulated area

[2] See *United States v. Alfred Caronia.*

of healthcare serve patients better, expand medical knowledge, and increase treatment options in a more effective manner than the FDA approval method does. To bolster this claim, this paper uses three case studies: the use of aspirin for cardiovascular health, the development of sexual pharmacology and Viagra, and the use of minoxidil to treat hair loss. In these case studies, physicians and pharmaceutical companies attained new medical knowledge and effectively treated patients by acting entrepreneurially through the market process. This entrepreneurship developed research and effective treatment more efficiently than the FDA's approval process did.

The next section examines the entrepreneurial framework for the off-label drug prescription market. The paper then uses this framework to examine each case study mentioned above. I conclude by examining the implications of the potential for entrepreneurial activity in the pharmaceutical market and by providing directions for future research.

II. Off-Label Prescriptions, Entrepreneurship, and the Market Process

The entrepreneur serves as a unique economic actor who determines "what resources should be used, and/or what goods should be produced" (Kirzner 1963, p. 13). For an entrepreneur's product or service to remain on the market, it must provide a benefit that consumers consider greater than the price (Lewin 2015). The entrepreneur's ability to perform this role depends on the number of restrictions placed on using their means to create products and services to exchange with consumers (Kirzner 1978). When consumers and entrepreneurs engage in buying and selling, a market process develops where inefficient or ineffective uses of resources to produce products create losses, and those products that add value to customers' lives produce profits for the entrepreneur. Entrepreneurs seek profits through competition to provide the best product possible.

The profit-and-loss system plays an informational role, guiding entrepreneurs to distribute scarce resources to their highest desired uses (Hayek 1945; Mises 1952). Profits provide information that the consumer values the product, and losses provide information that the consumer values the product less than other products whose sales earned profits. Reducing the uncertainty of what consumers are willing to purchase requires constant discovery and innovation from

entrepreneurs, with consumers determining which products are valued and should continue being produced (Mises 1949). Those entrepreneurs who earn profits do so by effectively competing against other entrepreneurs (Kirzner 1974).

Competition among physicians, according to Phelps (2010), can be categorized as competition for correctly diagnosing patients and providing effective treatments. When common treatment methods fail, or no common and consistent treatments exist, a physician must be alert to treatment options that other doctors may not be aware of to compete on the treatment margin. Physicians who are better able to accurately assess alternative uses of pharmaceuticals and effectively evaluate the risk of less-common treatment options are better able to serve patients.[3]

Despite operating in a highly regulated market, there is evidence that physicians act entrepreneurially. By empirically assessing the relationship between physician concentration and economic growth at the state level, Reilly and Santerre (2013) find evidence that physicians in general act in a profit-seeking manner (in contrast to a rent-seeking manner). Other evidence suggests that physicians are responsive to their patients' desires. Schaumans (2015) reports that general practitioners facing more competition prescribed more medication in order to satisfy patients' expectations. Austin and Baker (2015) find that higher concentrations of physician practices are associated with lower prices paid by their patients for various common procedures. McCarthy (1985) finds that the market for primary care physicians is "reasonably characterized by market competition" (p. 93). Similarly, Dunn and Shapiro (2015) find that a one-standard-deviation increase in cardiologist concentration is associated with a 5 percent increase in cardiologist service provision and fewer overall remissions.

A competitive environment in conjunction with limited restrictions on off-label prescribing allows physicians to allocate means to desired ends through finding alternative uses for resources (pharmaceuticals) that are most valued by consumers (patients). In short, when commonly used pharmaceuticals fail to treat the patients or when a commonly used pharmaceutical treatment is unavailable, the physician is performing the entrepreneurial act of determining what resources should be used to treat the patient.

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[3] This adjustment process pushes the market for treatment toward an equilibrium where existing pharmaceuticals are prescribed for their highest desired use. For a more detailed account of this process, see Boettke and D'Amico (2010).

Although the transaction costs of switching physicians can be significant, physicians' services are subject to the wishes of patients, who may decide to switch when they feel a physician's service was inadequate (Harris 2003; Tai-Seale and Pescosolido 2003; Fiscella et al. 2004). Patients may also review their physician online. These reviews, according to Segal (2012), can either "create significant reputational damage" or "help promote one's practice" (p. 341). As of 2012, over eighty websites exist where patients can review their physicians (Segal 2012), and an estimated 21 percent of patients read online reviews of physicians (Gay and Pho 2013). Given patients' heterogeneous expectations when obtaining medical services (Feldstein 1986), a physician's willingness to prescribe drugs off-label to provide treatment where typical treatment methods have failed could positively affect reputation and allow that physician to outcompete other physicians who are less willing to prescribe off-label.

Pharmaceutical companies also serve an entrepreneurial role in the prescription drug market through researching and developing alternative uses of currently manufactured drugs. This process (often called drug repurposing or drug repositioning) allows pharmaceutical companies to economize on previous testing (Pollack 2014; Tobinick 2009) and tailor existing drugs to serve patients' needs better (Ashburn and Thor 2004). Expanding the serviceability of an already approved pharmaceutical allows companies to obtain more profits by extending their market to include additional customers (patients) with additional conditions or ailments. As noted by Ashburn and Thor (2004), the idea to repurpose pharmaceuticals can originate from fortuitous observation, keen insight, or technology platforms developed to determine available opportunities.

In the medical field, information generated by the market process is distributed in medical journals. According to Wittich, Burkle, and Lanier, (2012) "Reports on OLDU [off-label drug usage], particularly original observations, are not only tolerated by indexed medical journals but also may actually be encouraged" (p. 987). The information collected in these journals is so critical for physicians that "articles may not only become accepted for publication but may also get journal promotion (editorials and media promotion) reserved for the highest-priority articles" (p. 987). Although the complex payment system faced by physicians can lead to market distortions in the allocation of medical goods (Goodman 2012; McGuff and Murphy 2015), medical journals still provide

physicians and pharmaceutical companies with information regarding how pharmaceuticals are effectively treating patients.[4]

III. Aspirin and Cardiovascular Well-Being

Although historians believe that acetylsalicylic acid (aspirin in herbal form) was first used to alleviate pain as early as 1453 BC (Fuster and Sweeney 2011), the use of aspirin for other purposes is comparatively recent. As early as 1966, aspirin was called "the wonder drug that nobody understands" in the *New York Times* (Boehm 1966, p. 1). In the 1940s, physicians began theorizing that aspirin might be serviceable in cardiology when it was observed that children given aspirin-laced chewing gum after a tonsillectomy bled more than those who did not receive the gum. If aspirin caused bleeding, it could also prevent clotting, a common cause of heart attacks.

This hypothesis was originally put forth by physician Laurence Craven, who published two papers testing aspirin's ability to reduce heart attack risk. These papers contained the results of experiments conducted with overweight men ages 45 through 65 who elected to take a daily dose of aspirin to mitigate heart attack risk. In both experiments, no participants experienced a heart attack. Craven's work promoted the off-label use of aspirin by other physicians who "enjoyed similar successful results in the administration of aspirin for prevention of coronary thrombosis in their own practices" (Craven 1950, p. 48).

Despite evidence supporting Craven's hypothesis, aspirin's use to promote cardiovascular health was met with skepticism from some in the medical profession. As noted by Miner and Hoffhines, "Most of Craven's writing is speculative and descriptive, lacking any statistics or formal presentation of data" (2007, p. 182). Much of this

[4] Payment arrangements between pharmaceutical companies, health insurance companies, and physicians can complicate which pharmaceuticals are prescribed. FDA approval may also affect a physician's comfort with prescribing a pharmaceutical for a particular use. However, payment systems may also work to promote newly found uses for pharmaceuticals. For example, as part of its promotion strategy, Pfizer issued payments to physicians to act as consultants and deliver public lectures to promote the newly found treatment (Lexchin 2006). Although this type of interaction between physicians and pharmaceutical companies would likely concern those who believe that more regulation of off-label drug prescription is desirable, it is unlikely that these interactions would occur for pharmaceuticals with harmful side effects or spurious treatment results. These promotional efforts are costly and would likely lead to reputational damage or legal penalties for the manufacturer.

skepticism and criticism was put to rest in the mid-1970s. In 1974, the Canadian Cooperative Study Group found that "aspirin reduced the risk of continuing ischemic attacks, stroke or death by 19 percent" and "also reduced risk for the 'harder,' more important events of stroke or death by 31 percent" (1978, p. 53). Further studies confirming aspirin's effectiveness in reducing blood clotting soon followed (Passamani 1980; Candelise et al. 1982).

The use of aspirin to prevent heart attacks and promote cardiovascular well-being would remain off-label until the FDA officially approved aspirin for a suspected myocardial infarction in 1996. This was approximately forty-six years after physicians began prescribing it for cardiovascular health. Despite physicians commonly recommending taking aspirin daily to prevent heart attacks or combat cardiovascular conditions, the FDA has still not approved aspirin for this use.

The absence of FDA approval has not deterred physicians from recommending aspirin's off-label use to prevent critical cardiovascular issues. Although taking aspirin daily could potentially have harmful side effects (Kormos 2013; Bundhun et al. 2016) and cardiovascular medication has improved since Craven's entrepreneurship, aspirin remains a commonly accepted treatment for a variety of cardiovascular conditions today. Dr. Carl Pepine, codirector of cardiovascular medicine at the University of Florida, estimated that approximately 10,000 deaths could be prevented a year by taking a daily dose of aspirin (Ross 1996). Dr. Deepak Bhatt, professor of medicine at Harvard University, espoused the views of many physicians when he said that barring special circumstances, "if somebody already has evidence of cardiovascular disease, there's no question they should be on an aspirin" (2012, p. 5).

Craven's work demonstrates the discovery process, which emerged as a result of experimenting based on knowledge developed from previous treatment. Other physicians were able to capitalize on this knowledge and offer effective treatment for their patients. The entrepreneurial actions of Craven and other physicians have helped countless individuals avoid or reduce the risk of a heart attack and combat other serious heart conditions.

IV. Sexual Pharmacology and Viagra

According to the School of Public Health at the University of Wisconsin-Madison, nearly 60 percent of men in their sixties suffer from impotence (2016). Despite the frequency of impotence,

treatment was historically overlooked by the medical community. The development of sexual pharmacology and the resulting creation of Viagra emerged from a market process in which physicians fundamentally changed the way impotence was medically understood and how to treat it.

The medical community began viewing sexual dysfunction as a condition requiring research in the late 1950s and early 1960s. At this time, sexual dysfunction, including impotence, was considered a psychological (in contrast to a physiological) issue. As a result, those suffering from sexual dysfunction were limited to psychoeducation and behavioral therapy for treatment (Tiefer 2006; Maggi et al. 2000). Unfortunately, little innovation or discovery was attempted to better serve patients with impotence. These treatments were the only ones available until the late 1970s (Tiefer 2006).[5]

In 1978, entrepreneurial urologists met in New York City to discuss the physiology of an erection. The innovation and discovery that emerged from that meeting "became the turning point, changing forever the old, erroneous way of thinking of impotence as being exclusively a psychogenic [psychological] problem" (Wagner and Kaplan 1993, p. 22). Physicians accepted the challenge to change the understanding and treatment of impotence on a global scale. In 1982, the Society for Impotence Research formed to distribute information and research findings related to advancing this new theory. The organization quickly developed regional chapters in Europe, Asia, and Latin America and began publishing half a dozen specialized medical journals (Tiefer 2006).

Advances in medical research bolstered innovations in impotence treatment. By the mid-1980s, a small group of entrepreneurial urologists discovered drugs that produced erections. Wagner and Kaplan (1993) note that some of these injections "were well known, older compounds that had been registered and marketed for other purposes [making them off-label]" (p. 49). Wagner and Kaplan continue, "There appeared to be no hurry as the patents for these drugs were old and the size of the market was not known with any precision" (p. 49). The entrepreneurial alertness of these urologists created the nascent field of sexual pharmacology.

Tests for the injectable treatment primarily consisted of volunteers. However, physicians self-testing these serums were not unheard of (Tiefer 2006). In some cases, volunteers in clinical trials

[5] The rare exception at this time was patients receiving penile prosthetics.

gave injections to themselves over the course of months with few complications (Zorgniotti and Lefleur 1985). By the mid-1980s, ample evidence supported the effectiveness of solution injections to treat impotence (Virag et al. 1984; Virag 1985; Sidi et al. 1986). Soon, injection became a preferred method of treatment for patients with impotence. Despite its accepted effectiveness and commonality of usage, the FDA would not approve any injection serum for the treatment of impotence until 1995. Approval came approximately fifteen years after evidence from the medical community indicated that injectable treatment options were reliable and effective.

Although unintentional, in 1989, another key discovery drastically changed the market for impotence treatment. During the late 1980s, scientists Peter Dunn and Albert Wood began clinical trials for a hypertension drug called sildenafil citrate (what would become Viagra). During a testing phase involving older volunteers, the volunteers reported few beneficial effects on their blood pressure but noticeable increases in the duration and firmness of their erections. Pfizer, the producer of Viagra, "did not immediately realize they had a blockbuster on their hands, but when a member of the team read a report that identified PDE5 [an enzyme that can help procure erections] . . . a trial in impotent men was quickly set up" (Ashburn and Thor 2004, p. 676). Dunn and Wood's discovery would eventually introduce a new oral medication option to the market for impotence treatment. The FDA's approval of Viagra for impotence treatment would not occur for nearly ten years despite Viagra's standing as the most common method to treat impotence during this period.

The emergence of sexual pharmacology and the development of Viagra to treat impotence is another example of off-label prescription as a way entrepreneurial physicians (mostly urologists) and pharmaceutical companies discovered more effective ways to treat patients. This example began with physicians experimenting with an entirely different method of treatment. The discovery process of research developed within a network of entrepreneurial urologists led to experimenting by using off-label serums to treat impotence. The success of these experiments would help develop the market for impotence treatment and replace treatment options of lesser quality. Oral medication would eventually become the most common method for treating impotence with the development of Viagra by Pfizer, which acted entrepreneurially on the unintended findings of early clinical trials. The transformation from the medical community

condoning impotence to treating over 23 million Americans with Viagra is the result of a competitive market process.

V. Minoxidil's "Harmless Side Effect"

The pharmaceutical company Upjohn first produced minoxidil in the late 1960s. Although Upjohn executives originally planned for minoxidil to treat respiratory issues, researchers quickly realized the drug's ability to combat hypertension during its animal testing phase. Additional evidence of minoxidil's ability to reduce blood pressure was procured from further animal testing in the late 1960s. By 1971, testing on humans began (Zins 1988). Another inadvertent discovery was made during these clinical trials.

To the surprise of volunteers and researchers, minoxidil both reduced blood pressure and stimulated hair growth in areas where a topical solution was applied. Upjohn executives dismissed the unexpected and unintended hair growth as "a harmless side effect" (Bryan 2011, p. 1), and additional studies were conducted to demonstrate minoxidil's ability to combat hypertension (Nawar et al. 1977; Watkins et al. 1979). The FDA approved minoxidil under the name Loniten in 1979.

While minoxidil provided effective treatment for hypertension, news and excitement of its "harmless side effect" quickly spread. An article featured in the prestigious *New England Journal of Medicine* (Zappacosta 1980) highlighted minoxidil's ability to stimulate hair growth. This discovery led to further and more rigorous tests to determine how effectively minoxidil could combat the effects of hair loss and male pattern baldness.

At this time, the market for the treatment of hair loss (specifically male pattern baldness) was largely unexplored. Anthony Chu, professor of dermatology at Buckingham University in the United Kingdom, described the market for the treatment for male pattern baldness as "a wasteland, with predatory clinics [offering] spurious remedies to vulnerable men at considerable costs" (Bryan 2011, p. 3). As a result, men afflicted with male pattern baldness "were prepared to try anything to make their hair grow back," including "standing on their heads to stimulate blood flow to the scalp" (Bryan 2011). The market for hair restoration was a grand opportunity for physicians and pharmaceutical companies to fill the needs of balding consumers. Upjohn understood that "if it did not develop minoxidil as a hair-restorer, someone else would" (Bryan 2011).

Scientific studies of minoxidil's effectiveness in the treatment of hair growth swiftly became part of the medical literature. In the 1980s, topical minoxidil was shown to increase terminal hair growth in early male pattern baldness in 1 percent (Fenton and Wilkinson 1983), 2 percent, and 3 percent solutions (Olsen et al. 1985). Minoxidil was also shown to be effective in treating the difficult case of hereditary male pattern baldness (De Villez 1985; Savin 1987) and maintained signs of effective treatment nearly five years after a clinical trial (Olsen et al. 1990). These studies were conducted with willing volunteers who "inundated" Upjohn's headquarters hoping to participate in a hair loss trail (Bryan 2011). By 1986, British dermatologist Rodney Dawber noted, "Owing to the proliferation of articles and programmes on the subject by the media, many patients have attended their general practitioners and dermatology clinics asking for information, and often demanding topical minoxidil whatever the potential adverse consequences" (1986, p. 201).

Patients were serviced by entrepreneurial physicians much more swiftly than they were by the FDA, which would finally approve minoxidil oral tablets for the treatment of male pattern baldness in 1987. The topical 2 percent solution of minoxidil, known by its more familiar name Rogaine, was approved in 1988, eight years after its ability to effectively treat hair loss was highlighted in the *New England Journal of Medicine*. Currently, minoxidil is one of only two drugs approved by the FDA to treat male pattern baldness. Minoxidil has also been effective in treating female pattern hair loss (Hoedemaker, van Egmond, and Sinclair 2007; Blume-Peytavi et al. 2007).

Physicians and drug manufacturers exercising an entrepreneurial role in using minoxidil to combat hair loss serviced a market in which reliable treatment was previously unavailable. The testing and repositioning of minoxidil illustrates pharmaceutical companies acting to fill the needs of patients. Minoxidil is also an example of knowledge and medical discovery obtained through the market process outpacing FDA approval. Zins (1988, p. 132) summarizes the story of minoxidil:

> This, together with a more stringent surveillance by government regulatory agencies, has increased the time required to develop a newly discovered entity from a few years in the 1950s and early 1960s to as much as 10–12 years at the present time [Zins was writing in 1988]. In cases where serendipitous discovery of new opportunities results in added dimensions for pursuit, the time required is even greater. The

> development of minoxidil as an agent to reverse androgenetic alopecia [pattern baldness], now being concluded *after 27 years*, characterizes this more elaborate process. (emphasis added)

A condition as common as male pattern baldness provides a large market for treatment options. The chemists of Upjohn and the entrepreneurial dermatologists of the '70s and '80s provided this treatment option while, as history would predict, the FDA was a distant second to the medical community in recognizing beneficial alternative uses of pharmaceuticals.

VI. Conclusion

Although the pharmaceutical market faces steep barriers to entry, physicians can exercise an entrepreneurial role in the medical field through prescribing and recommending approved medications for uses that are not approved. The freedom of physicians to prescribe medication off-label allows for an economic environment where physicians compete to offer the best treatment available to the patients they serve. Similarly, pharmaceutical companies act entrepreneurially when they compete to find effective alternative uses for approved pharmaceuticals. This competition in creating or offering the best product for the consumer is the embodiment of the discovery that occurs in the market process.

Aspirin's impact on cardiovascular well-being, Viagra's ability to provide a simpler treatment option for impotence, and minoxidil's unexpected capacity to treat hair loss are three cases where physicians' and pharmaceutical companies' alertness to patient need provided more effective and desirable treatments than those previously available. The knowledge generated through this market process also provided products and information in a timelier manner than the FDA approval process could. It is critical to note that these case studies are not unique. Additional examples of commonly accepted off-label uses of pharmaceuticals are provided in table 1.

Those who hold that drugs are prescribed off-label without sufficient evidence or that they require additional governmental oversight may not recognize the ability of the market process to guide physicians and pharmaceutical companies to find effective and safe alternative uses of pharmaceuticals. With the quality and duration of life dependent on physicians' ability to treat ailments, conditions, and disorders, it is critically important to gain a more thorough understanding of the merits of off-label drug use.

Table 1. Common Off-Label Uses of Drugs*

Drug	Original approved use	Off-label uses
Abilify	schizophrenia	dementia, Alzheimer's disease
Albuterol	asthma	bad coughs
Singulair	asthma	COPD
Lamictal	epilepsy	depression, bipolar disorder mood stabilization
Gabitril	antiseizure	depression, mood stabilization
Neurontin	antiseizure	depression, nerve pain, migraines
Topamax	antiseizure	migraines, bipolar disorder, depression, nerve pain
Lidoderm	shingles	lower back pain, sore muscles, tennis elbow
Desyrel	antidepressant	insomnia
Cymbalta	depression	generalized anxiety disorder
Botox	wrinkles	stroke-induced muscle spasms, headaches, juvenile cerebral palsy
Avastin	metastatic cancers	macular degeneration
Topamax	antiseizure	migraine prevention, weight loss, pain management, alcoholism
Clonazepam	antiseizure	restless leg syndrome, post-traumatic stress disorder
Latisse	glaucoma	lengthening eyelashes
Sertraline	antidepressant	premature ejaculation
Celebrex	joint sprain/strain	fibromatosis
Desyrel	depression	sleep disturbance, panic attacks, cocaine withdrawal
Procrit	chronic renal failure	anemia of chronic kidney disease
Plaquenil	malaria	rheumatoid arthritis
Prozac	depression	premenstrual dysmorphic disorder

*Some of these drugs' off-label uses have been approved by the FDA. Cymbalta was approved to treat generalized anxiety disorder in 2007. Botox was approved to treat chronic migraine and stroke-induced muscle spasms in 2010. Latisse was approved to lengthen eyelashes in 2008. Topamax was first approved for the preventive treatment of migraines in adolescents in 2014.

Although any treatment recommended by physicians contains some risk, these risks may be better minimized when competition and the market process are allowed guide physicians into making the most of available resources to treat patients. Off-label prescription has historically provided for this environment and will continue to better the lives of patients if its unregulated practice is preserved.

While this paper has examined evidence of the market process's ability to guide physicians and pharmaceutical companies to generate information and provide effective treatment, it has not examined external factors that may influence the decisions made by physicians or pharmaceutical companies—for example, payments from pharmaceutical companies might significantly influence prescribing habits. It also has not examined some of the more controversial off-label drug prescriptions and uses including uses to treat children (Dörks et al. 2013; Kimland and Odlind 2014) and patients with mental illnesses (Haw and Stubbs 2005; Radley, Finkelstien, and Stafford 2006). Further research conducted on these issues is recommended to expand the knowledge of how off-label prescription and use benefits patients.

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