

The Law and Practice of Off-Label Prescribing and Physician Promotion

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Prescription of medications for off-label indications is an increasingly common practice; recent events highlight such prescribing as one of the cornerstones of evolving clinical treatment. Clinicians are afforded substantial deference in prescribing practices and other treatments falling within the realm of the actual practice of medicine, including prescribing for off-label indications. Yet clinicians are not necessarily free to promote a medication for the same off-label indication they may have just prescribed for a patient. While trends in jurisprudence appear to be favoring clinicians' freedom to promote prescription medication for any use, in a majority of jurisdictions, the U.S. government can still bring considerable weight to bear on clinicians promoting off-label uses of prescription medications. We review the relevant laws and regulations pertaining to off-label prescription and promotion, as well as the possible legal consequences. The regulations pertaining to physician and pharmaceutical manufacturers regarding off-label drug use are complex. Suggestions are provided to help physicians better navigate the medical-legal landscape when prescribing or promoting medications for off-label use. Physician mindfulness to pertinent legal precedents will allow them to prescribe and promote medications with a higher level of critical reasoning to optimize care and reduce risk.

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Off-label use of medications approved by the U.S. Food and Drug Administration (FDA) for other indications has been at the forefront of the news in the early months of 2020 due to the COVID-19 outbreak. With any off-label use, physicians look to evidence-based studies or guidelines that validate the use of a medication for an off-label use as beneficial for treating a specific illness. Medications can have a variety of side effects, some potentially significant enough to worsen an individual's health. With COVID-19, both chloroquine and its close relative

hydroxychloroquine offered initial signs that they may ease some of the symptoms of coronavirus infection in patients who were hospitalized. Many health care providers began promoting their use, particularly in severe cases of the virus. To date the drugs have largely failed to deliver significant improvements either in practice or in rigorous research studies.¹ In fact, there is no evidence from randomized clinical trials that any potential therapy improves outcomes in patients with either suspected or confirmed COVID-19, and both agents can cause rare and serious adverse effects, including QTc prolongation, hypoglycemia, neuropsychiatric effects, and retinopathy.¹ This highlights the risks and benefits of prescribing and promoting off-label use of medications. This article primarily focuses on the promotion of off-label use by physicians and provides some guidance on off-label prescribing in general.

Recent years have seen a significant increase in off-label prescribing by clinicians in all medical specialties. A review of commonly used medications in general office-based practice showed that 21 percent of prescriptions were prescribed for an off-label

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indication.² Clinicians treating select patient populations have even higher rates of off-label prescription.³ This is especially true for those prescribing for psychiatric disorders, many of which have a limited number of treatments approved by the FDA. As a result, the highest rates of off-label prescription are for psychotropic medications.⁴ A survey of office-based physicians reported that 31 percent of all antidepressants, anticonvulsants, and antipsychotic medications prescribed were for off-label indications.⁵ In recent studies in community clinical practices, 40 to 80 percent of recipients of commonly prescribed psychotropic medications (including antidepressants, antipsychotics, and anticonvulsants) were receiving these medications for off-label indications.⁶ Furthermore, off-label prescribing with limited proof of efficacy was common. In the primary care setting, a survey in the use of antidepressant medications showed that 84.2 percent of off-label prescriptions had no strong evidence of efficacy for the indication.⁶ In different patient populations, off-label prescription has been consistently shown to present a significant increased risk of adverse drug events.⁷

While the practice of off-label prescription of FDA-approved medications is common and often medically beneficial to patients, the promotion of such uses places physicians at heightened risk. The case of psychiatrist Peter Gleason is illustrative of such a scenario. For several years, Dr. Gleason prescribed the narcolepsy drug Xyrem (sodium oxybate) for off-label treatment of major depression and fibromyalgia. In 2003, he was asked by the drug's manufacturer to speak about his experiences to other physicians both in promotional talks and continuing medical education conferences. Three years later, he was arrested and charged with conspiracy to illegally market the prescription drug. He eventually pleaded guilty to a federal misdemeanor of engaging in interstate commerce of a misbranded drug and surrendered his license to practice medicine.⁸ A sound understanding of the laws pertaining to off-label promotion could be helpful to physicians in their prescribing practices, allowing them to optimize care to patients while reducing potential risk.

Applicable Laws and Regulation

The basis for the statutory and regulatory framework affecting off-label prescription is the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA).⁹

As the name implies, this set of laws authorizes the FDA to monitor the safety of foods, drugs, cosmetics, and medical devices.⁹ Both prescription and non-prescription medications are covered under the FDCA.⁹ Section 321 of the FDCA makes it illegal to distribute directly or indirectly a covered product in interstate commerce that is misbranded.¹⁰ Section 352 provides that a drug "shall be deemed to be misbranded . . . if its labeling is false or misleading in any particular."¹¹ Labeling is further defined in the FDCA as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."⁹ Notably, "labeling is defined very broadly to cover a wide variety of statements or claims made by or on behalf of the manufacturer, in a wide variety of contexts" (Ref. 12, p 128).

The FDA enforces the FDCA through administrative mechanisms, including premarket authority to ensure that prescription drugs meet standards related to their intended use¹³; postmarket authority to monitor prescription drugs to ensure that they continue to adhere to the FDCA¹⁴; the ability to conduct examinations and investigations¹⁵; the ability to disseminate information about products, including prescription drugs, that involve "imminent danger to health" or "gross deception to the consumer"¹⁶; the ability to publicize information on all formal enforcement actions resolved in court¹⁵; and the ability to issue warning or information letters to regulated entities believed to be violating the act.¹⁸ The FDA also coordinates with the U.S. Department of Justice to further effectuate enforcement through "product seizures, injunctions, civil penalty proceedings, or criminal prosecution" (Ref. 19, p 717).

These mechanisms of enforcement give the FDA strong authority over pharmaceutical companies' practices and, by extension, physicians believed to be improperly engaging in promotional activities toward off-label uses of specific medications. Physician-oriented promotional activities include science symposia and teleconferences given on behalf of a pharmaceutical company, but they also extend to consumer-oriented communications, such as press conferences and interviews.²⁰ Despite this potential power over off-label prescribing, the FDA has consistently maintained that "it does not regulate the practice of medicine between physicians and patients" (Ref. 21, p 307). Although FDA clearance of a medication ensures physicians that a drug effectively produces certain

physiological actions that are proven to treat an illness, “[i]t is the physician, not the FDA, that determines whether these specific physiological effects would be useful or beneficial with respect to particular patients” (Ref. 22, p 1998). Physicians then continue to retain the autonomy to prescribe drugs for any reason they believe, in their clinical judgment, will benefit their patients. Because FDA approval can be extremely costly, a pharmaceutical manufacturer will typically lose incentive to put one of its drugs already approved for one indication back through the same FDA approval process to be approved for another indication. These pharmaceutical manufacturers are instead incentivized to market their FDA-approved drugs and rely on practicing physicians utilizing their judgment to find new, non-FDA-approved uses for which they are free to prescribe the drug. This off-label prescribing often occurs if there is no effective alternative for a patient population (e.g., in children), when a patient has not responded to other on-label medication use, or when a patient has residual symptoms that may be treated with medication the FDA has approved for a different disorder.²³ In effect, off-label prescribing by physicians is legal and common, but it is often done in the absence of adequate supporting data.

Important amendments to the FDCA, known as the Kefauver-Harris amendments, were enacted in 1962 after the widespread crisis related to thalidomide, a common treatment for morning sickness in pregnant women that was eventually linked to pervasive occurrences of birth defects throughout Europe and Canada.²⁴ The 1962 amendments established “scientific safeguards used today by the FDA to ensure that consumers will not be the victims of unsafe and ineffective medications” (Ref. 24, p 1). Focused on pharmaceutical manufacturers, the 1962 amendments required these companies to prove their products’ effectiveness before the product is allowed on the market and to report serious side effects after their release.²⁴ In proving the effectiveness of their products, the manufacturers had to rely upon clinical studies for evidence and use only subjects who gave their informed consent.²⁴ Most important for the purposes of this article, the 1962 amendments gave the FDA control of prescription drug advertising.²⁴

While off-label prescribing remains a common and necessary practice, it is the advertising or

promoting of various off-label uses on behalf of the manufacturer that carries with it a risk that “such conduct may be deemed ‘misbranding’” in violation of the FDCA.²⁵ The FDA notes that “[p]romoting an approved drug for off-label uses is not itself a prohibited act under the FDCA” (Ref. 12, p 126), nor is it an element of any prohibited act. Instead, the FDA argues, off-label promotion “plays an evidentiary role in determining whether a drug is ‘misbranded’” (Ref. 12, p 126). Promotion may include pharmaceutical sales representatives visiting health care providers directly to discuss products or, more commonly, courses for continuing medical education credits where physicians themselves are doing the promoting of off-label uses.²⁶ The broad definition of labeling is critical to the FDA’s argument that off-label promotion violates the FDCA.¹² The result is that the FDA may now consider even simple oral statements by physicians regarding off-label medication use as off-label promotion that is subject to prosecution.

To prosecute oral statements by pharmaceutical-sponsored physicians as off-label promotion, the federal government primarily uses the premise that the FDA may consider that implicated physicians have misbranded a drug by “failing to provide adequate . . . information for prescribers” (Ref. 27, p 477). Underlying the FDA’s ability to take action in this regard is the “intended use doctrine.”¹² The FDA defines intended use as “the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons’ expressions or may be shown by the circumstances surrounding the distribution of the article.”²⁸ “[T]he intended use doctrine allows the FDA to take action against marketers based on the content of their communications, without necessarily asserting jurisdiction over the communications themselves” (Ref. 12, p 135). By relying on Supreme Court precedent establishing that “[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent” (Ref. 29, p 489), federal courts addressing the intended use doctrine have found no First Amendment concerns with the government utilizing speech as evidence of intended use.³⁰ “[T]he FDA rule that defines ‘adequate direction’ makes clear that intended uses include uses suggested orally” (Ref. 10, p 135). As a result, the FDA has taken official action against communications made “in physicians’ offices, at exhibit booths, [and] before formulary boards”

(Ref. 12, p 135) because the promotional statements can serve as proof of a drug's intended use and thus could be evaluated as misbranding.

Until 1997, promotion of any off-label uses of prescription drugs was clearly prohibited. That partially changed, for a time, with the passage of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), which further amended the FDCA. Section 401 of the FDAMA permitted pharmaceutical "manufacturers to distribute copies of peer-reviewed articles and book chapters and to sponsor independent continuing medical education programs describing uses of products beyond approved indications" (Ref. 31, p 1047). The FDA did not permit this off-label promotion without conditions. First, any such materials related to the off-label uses had to be provided to the FDA. Second, the promoting manufacturer had to "verify its plans to seek approval for the new indications" (Ref. 32, p 220). "If a drug manufacturer was in compliance with all of the[se] requirements, the FDA could not use this activity as proof of a company's intent to inappropriately promote off-label drug use" (Ref. 32, p 220). This was known as Section 401's "safe harbor" for manufacturers' promotion of off-label drug uses.³³ In 1999, the federal district court for the District of Columbia held, in *Washington Legal Foundation v. Friedman*,³⁴ that the section of the FDAMA designed to prevent off-label promotion was overly prohibitive and in violation of the First Amendment right to commercial free speech. Given that the FDAMA contained a sunset provision, such that it would cease to be in effect after September 30, 2006, the FDAMA expired and was not reauthorized by Congress.³⁵ In its place, the FDA issued a "guidance document" on February 5, 2008 (finalized in January 2009) which was an attempt at implementing a practical approach to regulating the distribution of off-label information without violating the First Amendment. This document did away with burdens such as preclearance from FDA for companies to distribute off-label articles as well as the need to inform health care providers that alternative FDA-approved therapies are available for the condition discussed in the distributed article.³² The FDA stated that they recognized "the public health can be better served when health care providers receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical

products" (Ref. 32, p 221). These FDA guidelines are very specific on the type of reprints and the manner of distribution. Over the ensuing years since the expiration of the FDAMA, there have been other legal developments reinforcing First Amendment doctrine.

In the case involving Dr. Gleason, a federal district court also convicted Alfred Caronia, the pharmaceutical sales representative involved in the presentations for Xyrem. In *United States v. Caronia*, tape recordings of Mr. Caronia's marketing interaction with doctors led to his conviction of misbranding Xyrem's use for an off-label indication.⁸ In 2012, he appealed this decision, which was overturned on First Amendment grounds.³⁶ This same premise was utilized in *Amarin Pharma, Inc. v. FDA* in 2015 in response to the FDA's claim of a misbranding violation by the pharmaceutical company.³⁷ The U.S. District Court for the Southern District of New York sided with Amarin Pharma, citing the Second Circuit Court of Appeals in *U.S. v. Caronia*³⁶: "The government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug" (Ref. 37, p 208).

Although these cases in the Second Circuit (New York, Connecticut, and Vermont) shifted the interpretation of the FDA's role in policing off-label promotion there, the reality is that the statutory and regulatory landscape for off-label drug promotion remains largely unchanged in other jurisdictions. The free speech protections in the Second Circuit cases noted above are limited to manufacturers within those states. The United States Supreme Court also has not taken occasion to provide further rulings on off-label prescription by physicians. Until the Supreme Court does so, manufacturers will continue to be limited to the interpretations from the courts within their respective circuits.

There has been one recent development in state law that also addresses off-label promotion of medications. In March 2017, Arizona passed a law that allows pharmaceutical manufacturers to discuss safe and effective off-label uses with health care providers, but these kinds of communications are still not permitted to be made to the public directly.³⁸ It also remains to be seen whether other states will follow or whether the FDA will be compelled to intervene and challenge the legality of Arizona's law.

According to a recent FDA draft guidance publication:

[The] FDA has long taken the position that firms (defined by the FDA as manufacturers, packers, distributors, and all their representatives), can respond to unsolicited requests for information about FDA-regulated medical products by providing truthful, balanced, non-misleading, and non-promotional scientific or medical information that is responsive to the specific request, even if responding to the request requires a firm to provide information on unapproved or uncleared indication or conditions of use [Ref. 39, p 6].

The FDA clearly warns, however, that the context of a manufacturer's communication about off-label use is a viable means of demonstrating "evidence of intended use."³⁹

Physician Liability

Physicians have been involved in several legal claims when prescribing or promoting medication for off-label use.⁴⁰⁻⁴² This is especially true when off-label prescription is the cause of injury. In that case, a patient is likely to bring a case of medical malpractice against a physician under two legal premises: lack of informed consent and negligence.

Informed Consent

To date, no appellate court has ruled that physicians must disclose off-label status as part of informed consent. As a general rule, some physicians have suggested that providing patients with information about off-label use may afford greater protection from future liability suits.⁴³ Although it may be the case that physicians are not legally required to disclose the off-label use of a medication to patients, the fact that there is not yet an appellate court decision addressing this concern does not mean there is not a clear theoretical basis for liability; the potential for liability will be judged according to the circumstances of an individual case. The matter is simply unclear, as is true of many facets of FDA-pharmaceutical company relations.

Negligence

When a patient alleges harm from an off-label use of a medication, it must be established that the prescribing physician deviated from the standard of acceptable practice. Because the FDA prohibits manufacturers from sponsoring physician

education for off-label use of their medications, physicians may find it difficult to establish how others in their area of practice use medications outside the FDA-approved indications. Peer-reviewed, published evidence focusing on a drug's off-label use and new standards of practice involving off-label use of the drug develop over time.¹⁹

Discussion

While applicable to the entire field of medicine, the matter of off-label prescription and promotion is of particular importance in the field of psychiatry. An analysis of Dr. Gleason's case using the information reviewed in this article allows for several conclusions. Dr. Gleason's use of Xyrem to treat anxiety and depressive disorders was entirely lawful, despite the medication's sole FDA approval for the treatment of narcolepsy in adults. At the time of his arrest, there was literature to support a plausible physiological mechanism to rationalize Xyrem's use in other psychiatric disorders. Further, there were no clear cases of patient injury in the doctor's widespread use of Xyrem. Neither Dr. Gleason's employment by a pharmaceutical company nor his having made presentations about Xyrem were unlawful. The content of his presentations, including his verbal statements, made on behalf of the pharmaceutical company, however, effectively served as off-label promotion of medication that was considered to be false or misleading. The court concluded that the statements made by Dr. Gleason were consistent with a direction of "intended use" of the medication for a non-FDA-approved use. This was judged to be misbranding and was the basis of legal charges against Dr. Gleason.

Given the ubiquitous nature of off-label drug use in the field of psychiatry, there is clear value in understanding the relevant legalities. Knowledge of the above principles allows for lawful and patient-centered promotion for off-label uses of medications. The following suggestions for physicians may help them better navigate the medical-legal landscape when engaged with off-label medication promotion as well as off-label prescribing.

Continue Psychopharmacology Education

Current knowledge of pharmacological advances in both the pathophysiology of psychiatric disorders and the medication's mechanisms of action permits

rational application of medication use for off-label indications. Physicians should be especially careful to review pertinent literature for precedent and supportive evidence when promoting the use of medications for off-label indications.

Obtain Appropriate Informed Consent

Given the lack of precedent establishing a legal requirement for what constitutes informed consent in off-label treatment, there is no official best practice to guide clinicians. Thus, it may be prudent to clearly communicate benefits and risks associated with off-label medications, including the lack of strong clinical evidence supporting its use for off-label purpose. Inclusion of this information in informed consent discussions may also serve to reduce the risk of a negligent practice claim. These practices should also be considered and discussed when promoting off-label prescription to other physicians.

Document the Reasoning for Off-Label Use

Clear documentation of failed medication trials and course of treatment leading to off-label drug use can help reinforce the fact that standards of practice are being met. Part of supportive documentation involves maintaining updated knowledge of the medication and having scientific literature (peer-reviewed, if possible) that supports the reasonable application of a medication and its nonexperimental status. This documentation can be useful to physicians defending themselves in malpractice cases involving alleged wrongful prescriptions for off-label indications.

Use Caution When Promoting Off-Label Use

Physicians can discuss the off-label use of medications with patients. They can also discuss, write, and organize information regarding off-label prescribing in professional journals and educational endeavors. This is based on the assumption that a clinician doing so has no statutory obligation for the labeling or distribution of the drug in interstate commerce; such an obligation exists when a physician enters a contract-based financial relationship with a pharmaceutical company.⁴⁴ Physicians must be cautious in presenting information directly related to off-label use to other physicians, however, when the act of doing so is paid for or sponsored by a pharmaceutical manufacturer. In these explicit promotional settings, physicians should clearly identify off-label use of

medications and should not themselves solicit questions or discussions of off-label use. At the same time, we encourage even clinicians unaffiliated with manufacturers to be mindful of the potential (however unlikely) downstream effect of the information they present at the level of interstate commerce.

The concept of interstate commerce has been subject to varied interpretations over the years. In 2005, the U.S. Supreme Court addressed Congress's authority under the commerce clause in *Gonzales v. Raich*,⁴⁵ noting that "regulation is squarely within Congress' commerce power because production of the commodity . . . has a substantial effect on supply and demand in the national market" (Ref. 45, p 19). Proof of the effect was not necessary; only a "rational basis" for making that conclusion was required. (Ref. 45, p 22).

In speaking about the off-label use of medications, a physician's speech, if influential to enough individuals to alter the gross demand of a medication, would theoretically violate the FDCA. Again, the burden would be on the prosecuting authority to demonstrate a reasonable direct and causal link between a physician's promotional behavior (e.g., speech as part of a presentation) and changes in supply and demand of a medication that was promoted off-label. It is possible that a physician's level of off-label promotion could be objectively shown to increase overall prescriptions (i.e., to increase demand) for a given medication in a way that could be cause for prosecution. Proving such an assertion would, however, be onerous for a resource-limited FDA.

Conclusions

Psychiatry is more and more becoming a field that is conceptualized with neuroanatomical-based circuits and intricate neurotransmitter signaling at its core. It is also a field that is in desperate need of new medications that leverage the rapidly advancing neurobiological research to provide more effective treatment options for psychiatric disorders. Because of these limitations in the evidence base, off-label prescription of psychotropic medications may be more the rule than the exception. This is especially true in particular fields of current psychiatric practice. There are relatively few medications approved for use in adolescents, and even fewer in children. The same applies in geriatric psychiatry, where medications are often prescribed, using data from nongeriatric populations, which places the elderly at high risk for negative

outcomes. The potential for considerable benefit to patient care underscores the need for opportunities where off-label medication use is presented in a systematic and peer-reviewed manner. This potential benefit must be balanced by discussion of legal risks, particularly in off-label promotion of these medications. Health care providers should understand these risks and benefits, especially when promoting off-label medication use.

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