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2020

## The Off-Label Loophole in the Psychopharmacologic Setting: Prescription of Antipsychotic Drugs in the Nonpsychotic Patient Population

Lisa E. Smilan

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# THE OFF-LABEL LOOPHOLE IN THE PSYCHOPHARMACOLOGIC SETTING: PRESCRIPTION OF ANTIPSYCHOTIC DRUGS IN THE NONPSYCHOTIC PATIENT POPULATION

*Lisa E. Smilan<sup>†</sup>*

## ABSTRACT

U.S. physicians have wide discretion in treating patients with off-label medications. Many consider off-label prescription essential in our country's health care system, and it is wholly supported by FDA and federal courts. Assumptions about physicians' expertise, judgments, and commitments to beneficence and nonmaleficence undergird laissez-faire policies that allow and support physicians' novel and innovate uses of FDA-approved drugs for purposes and populations not studied in original, strictly regulated clinical trials. Though sometimes beneficial, off-label prescribing, which flourishes in private-practice psychiatry, often harms scores of psychiatric patients. Frequently, potential harms are insufficiently disclosed to patients. In the public health sector, officials have begun to identify and warn of dangers surrounding antipsychotic use in nonpsychotic foster children. Within the government-funded

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The Author extends thanks and gratitude to Richard Boldt, Diane Hoffmann, Leslie Meltzer Henry, Francis Palumbo, Maxine Grosshans, Connie Lenz and Ellen Wright Clayton for their valuable feedback and encouragement. Thanks, also, to members of the Vanderbilt University Medical Center, Center for Biomedical Ethics and Society community for their probing questions and thoughtful comments, and Health Matrix: Journal of Law-Medicine editors, Anthony Severyn, Alayna Bridgett, and Khouloude Abboud for their careful review and constructive suggestions.

insurance apparatus there are built-in means for checking harmful physician practices. Such oversight mechanisms are deficient in the private insurance sector, and absent where treatment is paid for out-of-pocket. The Article proposes that private-practice psychiatrists' collective widespread "experimental" treatment of nonpsychotic patients with antipsychotics off label resembles clinical research without regulation or meaningful accountability. Because harmful physician practices in the off-label antipsychotics space are largely unchecked by state regulation and law, action is required to protect some of our most vulnerable patients.

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## INTRODUCTION

It is notable that consent is required of participants in a drug trial because the drug’s effects have yet to be shown, but consent is not required for a drug prescribed in a clinical setting for a purpose that has not been fully studied. . . . Without a clear stance taken by the legal establishment, the medical establishment is less able to set up a model of best practice on this issue and has less incentive to do so.<sup>1</sup>

While other specialists and general practice physicians are moving towards collaborating and conferring within partnerships

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1. Zain Mithani, *Informed Consent for Off-Label Use of Prescription Medications*, 14 *AMA J. ETHICS* 576, 578 (2012) (citing David C. Radley et al., *Off-label Prescribing Among Office-based Physicians*, 166 *ARCH. INTERN. MED.* 1021 (2006)).

or other business entities, the majority of office-based psychiatrists are in practice alone. A study analyzing data from a national survey of U.S. office-based physicians<sup>2</sup> revealed that private fee-for-service insurance, Medicare, and Medicaid acceptance rates by psychiatrists were significantly lower than acceptance rates of other specialist physicians.<sup>3</sup> Psychiatrists practicing alone were less likely to accept *any* type of insurance.<sup>4</sup> Without input from colleagues and oversight by insurance companies, psychiatrists are positioned to be practicing in isolation.

Individual psychiatrists may believe they are treating individual patients, but the collective behavior of individual psychiatrists has led to widespread prescription of antipsychotic drugs to classes of vulnerable patients who are not psychotic. This may not be the intent of the independent psychiatrist, but nonetheless it is the outcome and cause for great concern. Widespread off-label use of antipsychotics adversely affects not only the individual patients, but results in additional healthcare expenditures to treat “side-effect” illnesses (including the use of additional costly medications to treat those illnesses).<sup>5</sup> Additionally, unnecessary antipsychotic prescription can

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2. Tara F. Bishop et al., *Acceptance of Insurance by Psychiatrists and the Implications for Access to Mental Health Care*, 71 JAMA PSYCHIATRY 176, 179 (2014).
  3. *Id.* By percentage, in 2009–10 the rate of psychiatrists who accepted private fee-for-service insurance was much lower than that representing acceptance by other specialists (55.3% versus 88.7%); and that 2009–10 rate showed a decline of 17.0% compared to 2005–06. The percentage of psychiatrists accepting Medicare in 2009–10 was significantly lower than other specialists (54.8% versus 86.1%), declining by 19.5% from 2005–06. Psychiatrists’ Medicaid acceptance rates were lower than other specialists in 2009–10 (43.1% vs. 73.0%), but remained relatively stable compared to 2005–06 rates. *Id.*
  4. *Id.* 43.0% of solo practitioners accepted private fee-for-service insurance compared to 74.9% of those who practiced in groups; 45.0% of solo practitioners accepted Medicare compared to 69.5% of those who practiced in groups; and 26.8% of solo practitioners accepted Medicaid compared to 67.3% of those who practiced in groups. *Id.* In 2009–10, nearly half of psychiatrists did not accept private fee-for-service insurance, and over half did not accept either Medicare or Medicaid. *Id.*
  5. See Nevena Divac et al., *Second-Generation Antipsychotics and Extrapyramidal Adverse Effects*, BIOMED RES. INT’L 1, 2 (2014).

adversely affect productivity of patients and reduce earning potential. The Hippocratic mandate to “do no harm” is implicated here,<sup>6</sup> however, that mandate is sometimes distorted by a narrow focus on the present and not the future. For example, a “quick fix” to quell a patient’s mind or alleviate depression may lead to a lifetime of drug-induced physical ailments.

The policy of allowing individual physicians to prescribe off label for unapproved diseases and unapproved patient groups derives from several assumptions about the profession, for example, that all physicians: (1) are exceptionally intelligent and intuitive; (2) share information and decision-making with patients; (3) listen to patients’ concerns; (4) engage in appropriate screenings and long-term follow-ups with patients; (5) keep current with medical developments by reading broadly and critically; and (6) don’t have tunnel vision. In the instance of mental health treatment, off-label use can be particularly troubling, especially where the psychiatrist (or general practitioner) legally and frequently prescribes antipsychotics to the nonpsychotic patient.

In general, the psychiatric patient group experiences a heightened potential for vulnerability due to the nature of mental health illnesses and the increased sense of confidentiality and trust inherent in the psychiatrist-patient relationship. While the mentally ill patient may need additional protections against unsafe and ineffective off-label use of prescription drugs, the Food and Drug Administration (FDA) takes a hands-off approach, generally abdicating any responsibility for ensuring the welfare of those who are prescribed approved drugs for unapproved purposes.

This Article examines the “practice of medicine exception” applicable in U.S. drug law that allows licensed physicians, including psychiatrists, to write prescriptions for non-indicated purposes and non-studied patient populations, and the various bases and supports proffered for this system structure. Part I considers the purposes of the Federal Food, Drug, and Cosmetic

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6. Note that a recent Medscape poll found that of respondent-physicians under age 34, 39% viewed the Oath as “very meaningful,” whereas with respondent-physicians over age 64, 70% said the Oath was “very meaningful.” Marcia Frellick, *Youngest, Oldest Physicians Diverge on Hippocratic Oath*, MEDSCAPE (June 2, 2017), [https://www.medscape.com/viewarticle/880688#vp\\_1](https://www.medscape.com/viewarticle/880688#vp_1) [<https://perma.cc/5A5A-WENL>].

Act of 1938 and the role of physicians in the U.S. prescription-drug scheme. Part II provides an overview of antipsychotics. Part III considers the prevalence of psychiatrists prescribing antipsychotics to nonpsychotic patients, addresses the absence of safety and efficacy studies, and proposes that psychiatrists are legally conducting quasi “clinical drug trials” in the collective treatment of individual patients. Part IV contemplates who, if anyone or any entity, is willing to protect our vulnerable psychiatric patients (especially multiply vulnerable psychiatric patients), and explores how certain patient groups are “legally safe” specimens for informal “clinical drug trials.” It also reviews unsuccessful past attempts by FDA and Congress to close the off-label loophole, proposes putting the public health before the health care professional, and considers what might be done to bring about change and reform. The Article concludes with thoughts on future efforts that might protect nonpsychotic psychiatric patients from potentially harmful antipsychotics not proved to be safe or effective in this population.

## I. PURPOSES OF FDCA AND ROLE OF PHYSICIANS

The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA)<sup>7</sup> regulates drug quality, providing that “no new drug can be marketed until proved safe for use under the conditions described on the label and approved by the FDA.”<sup>8</sup> The Kefauver-Harris Amendment of 1962, also referred to as the Drug Efficacy Amendment, added the requirement that a drug not only must be safe, but it must be effective. The 1962 amendment also augmented subject protections in clinical drug investigations by requiring subjects’ informed consent and the reporting of adverse reactions related to study drugs.<sup>9</sup> Several amendments have been enacted since, but none that alter these essential protections.

### *A. Requirements for New Drugs: Safety and Efficacy*

For the purpose of protecting “the nation from harmful or worthless drugs and devices,” FDA has been charged by Congress to ensure that only drugs, devices and biologics that have been

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7. 21 U.S.C. §§ 301 *et seq.* (2018).

8. RICHARD R. ABOOD & DAVID B. BRUSHWOOD, PHARMACY PRACTICE AND THE LAW 27 (1994).

9. *Id.* at 28.

reviewed and approved by FDA for both safety and efficacy may be sold in the United States.<sup>10</sup> Sponsors file applications for an Investigational New Drug (IND) with FDA, and the agency ultimately decides the types of clinical trials that are necessary to prove that the new treatment is safe and effective for treating a particular medical ailment in a particular patient population.<sup>11</sup> FDA's rules protecting human subjects in clinical trials can be found in two locations: (1) 21 C.F.R. Part 56, relating to Institutional Review Boards (IRBs); and (2) 21 C.F.R. Part 50, relating to informed consent.<sup>12</sup> Under FDA regulations, IRBs assist the agency with human-subjects protection by reviewing and monitoring clinical trials within FDA's jurisdiction.<sup>13</sup>

Once completed, results from an FDA-approved study must be submitted to an expert panel, which then tells FDA whether or not the drug has been demonstrated to be safe and effective.<sup>14</sup> FDA's "stamp of approval" extends only to the specified medical purpose and the specified population for which the drug, device, or biologic was studied. After approval, in numerous instances, medical experts have discovered that treatments approved for one indication "may also serve other valuable medical purposes."<sup>15</sup>

FDA views its mandate as ensuring the safety and efficacy of drugs and devices under conditions set forth by the manufacturer

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10. Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, The FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J. L. & MED. 315 (2011) (referencing 21 U.S.C. §§ 335(a), 360(k), 360(e) (2018)); see CARL H. COLEMAN ET AL., *THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS* 151 (2nd ed. 2015).
  11. COLEMAN ET AL., *supra* note 10, at 251.
  12. *Id.*
  13. Richard M. Cooper & Benjamin M. Greenblum, *The Philosophy of Food and Drug Law*, in A PRACTICAL GUIDE TO FDA'S FOOD AND DRUG LAW AND REGULATION 67, 79 (Kenneth R. Piña & Wayne L. Pines eds. 2017).
  14. COLEMAN ET AL., *supra* note 10, at 151.
  15. Klasmeier & Redish, *supra* note 10, at 315 n. 2 (citing John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE L. HEALTH POL'Y L. & ETHICS 299, 304 (2010) ("[I]n some therapeutic areas off-label uses are the customary, preferred treatments and are publicly declared to be such on patient advocacy group websites and elsewhere.")).



in the IND study, not whether a medical treatment is safe for *any* use for which it may actually be prescribed.<sup>16</sup> But this “any use” permission allows for the possibility that using an approved drug in an unapproved manner may result in “worthless or even dangerous” medication of a patient.<sup>17</sup> Logic would instruct that if FDA is charged with protecting the public from harmful and useless drugs, medical devices, and biologics, then the agency should require testing and approval for any use that is outside the scope of the IND study.<sup>18</sup> While the approval process for drugs, devices, and biologics determines the safety for human use under particular parameters, uses for completely different purposes and populations could give rise to public safety issues.<sup>19</sup>

### *B. Off-Label Prescription*

Off-label use generally refers to three things: (1) the practice of a physician prescribing a legally manufactured drug for purposes other than those indicated on that drug’s FDA-mandated labeling;<sup>20</sup> (2) using a different method of applying the treatment and prescribing a drug, device, or biologic to patient groups other than those approved by FDA;<sup>21</sup> and (3) prescriptions for drug dosages that are different from the approved label-recommended dosage or for time periods exceeding the label-recommended usage.<sup>22</sup>

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16. Carol Berry, *The Dividing Line Between the Role of the FDA and the Practice of Medicine: A Historical Review and Current Analysis*, at 33–34 (1997), available at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:8846812> [<https://perma.cc/E98C-QCUE>] (unpublished Third Year paper).
  17. Klasmeier & Redish, *supra* note 10, at 316.
  18. Berry, *supra* note 16, at 35.
  19. *Id.* at 38–39.
  20. Ramune E. Barkus & Armand Derian, *Physician and Hospital Liability in Drug and Medical-Device Litigation*, in *DRUG INJURY: LIABILITY, ANALYSIS AND PREVENTION* 861, 863 (James T. O’Donnell ed., 3d ed. 2012).
  21. Richard C. Ausness, *There’s Danger Here, Cherie!: Liability For The Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*, 73 *BROOK. L. REV.* 1253, 1254 (2008) (citing Lars Noah, *Constraints on the Off-Label Uses of Prescription Drug Products*, 16 *J. PROD. & TOXICS LIAB.* 139, 141 (1994)).
  22. *Id.* (citing Elizabeth A. Weeks, *Is It Worth the Trouble? The New Policy on Dissemination of Information On Off-Label Use Under*

The accepted practice of off-label prescribing for non-indicated purposes or populations both undermines FDA's authority and mission, as well as deters pharmaceutical manufacturers from seeking on-label FDA approval for purposes the manufacturer could foresee as a widespread alternative use.<sup>23</sup> Proponents of off-label uses argue that what is "safe" and "effective" should depend partly on a physician's judgment and preferences, and not exclusively on objective fact.<sup>24</sup> These proponents state—as though inherently a positive proposition—that "[o]ff-label prescribing offers patients and doctors a choice between the judgements of the medical and scientific communities" and those of FDA.<sup>25</sup> But FDA's purpose is to protect the American public from unsafe and ineffective drugs, and the agency requires a certain level of proof before initial approval of a drug. In turn, the off-label option may cast the initial FDA approval as a mere "wedge to permit the industry's equivalent of the Wild West, where the rule of law was seen only rarely."<sup>26</sup>

The American public largely is unaware of the prevalence of off-label prescribing.<sup>27</sup> Despite the ubiquitous nature of off-label uses, a 2016 Consumer Reports survey revealed that ninety-four percent of Americans could not recall ever having been informed by a doctor that their prescriptions were for a purpose not approved by FDA and sixty-three percent said that they would refuse a doctor-prescribed drug that was not FDA-approved for their particular ailment.<sup>28</sup> So, while most patients would want to

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*the Food and Drug Administration Modernization Act of 1997*, 54 FOOD & DRUG L. J. 645, 647 (1999)).

23. Klasmeier & Redish, *supra* note 10, at 316.
24. Alexander T. Tabarrok, *Assessing the FDA Via the Anomaly of Off-Label Drug Prescribing*, 5 THE INDEP. REV. 25, 34 (2000).
25. *Id.*
26. Klasmeier & Redish, *supra* note 10, at 316.
27. Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L. J. 967, 979 (2007).
28. Christopher Robertson, *National Survey Suggests that Off-Label Status is Material to Informed Consent*, HARV. BLOG (Jan. 25, 2017), <http://blogs.harvard.edu/billofhealth/2017/01/25/national-survey-suggests-that-off-label-status-is-material-to-informed-consent/> [<https://perma.cc/65Q3-TYTY>].

know that their prescriptions are not for FDA-approved uses, this information is often withheld.<sup>29</sup> In contrast to FDA's requirement of informed, written consent for all phases of IND clinical trials, "there is no FDA requirement of informed consent to off-label prescriptions which [ ] FDA does not regulate at all."<sup>30</sup>

There are many reasons why a physician might prescribe a drug off label. For example, there may be no FDA-approved drug to treat a particular ailment.<sup>31</sup> With regard to pediatric patients, only twenty-to-thirty percent of FDA-approved drugs are labeled for pediatric use.<sup>32</sup> Without the off-label option, many pediatric diseases would go untreated.<sup>33</sup> In remarks on the Food and Drug Administration Modernization and Accountability Act of 1997, one Senator stated: "[a]s much as 90 percent of all of the uses of drugs in oncology or the treatment of cancer are used in what is called an off-label or extra-label manner."<sup>34</sup>

However, skepticism about the appropriateness of off-label uses finds support in a 2006 *Archives of Internal Medicine* survey that reviewed 150 million off-label prescriptions in the United States, finding that "73 percent had little to no scientific backing."<sup>35</sup> That study found that "off-label medication use is common in outpatient care, and most occurs without scientific support."<sup>36</sup> Without safety and efficacy studies, off-label uses of prescription drugs "can be risky, and some off-label uses have

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29. *Id.*

30. Johns, *supra* note 27, at 979.

31. Marisa A. Trasatti & Lindsey N. Lanzendorfer, *Defending Products Liability Suits Involving Off-Label Use: Does the Learned Intermediary Doctrine Apply?*, 62 FED'N DEF. CORP. COUNS. Q. 2, 5 (2011), available at [https://cdn.ymaws.com/thefederation.site-ym.com/resource/resmgr/docs/Quarterly/Archive/V62N1\\_Cover-to-Cover.pdf](https://cdn.ymaws.com/thefederation.site-ym.com/resource/resmgr/docs/Quarterly/Archive/V62N1_Cover-to-Cover.pdf) [<https://perma.cc/GM3Z-B5QC>].

32. *Id.* at 5.

33. *Id.*

34. 143 CONG. REC. S8165 (daily ed. July 28, 1997) (statement of Sen. Frist).

35. Mithani, *supra* note 1, at 577 (citing David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166(9) ARCH. INTERN. MED. 1021 (2006)); see also Johns, *supra* note 27, at 969; Wendy Teo, *FDA and the Practice of Medicine: Looking at Off-Label Drugs*, 41 SETON HALL LEGIS. J. 305, 311 (2017).

36. Johns, *supra* note 27, at 969.

turned out to be very dangerous.”<sup>37</sup> For example, in the case of the drug Fenfluramine, from the mid-to-late-1990s doctors wrote eighteen million prescriptions for its off-label use for weight loss before it was discovered that the drug had caused almost three hundred thousand people to suffer heart-valve damage.<sup>38</sup> Patients actually may be exposed to more risk after a drug, device, or biologic is FDA-approved, as opposed to still under investigation, because during clinical trials on human subjects, FDA imposes strict informed consent requirements.<sup>39</sup>

While the Federal Government could attempt to circumvent this potential danger by imposing a blanket prohibition against all off-label uses, and instead mandate that drugs, devices, and biologics be granted FDA approval for each and every use by each and every population, this alternative has its own host of problems.<sup>40</sup> Such a ban could result in potentially beneficial uses for some of our most serious diseases being tied up for years in the FDA-approval process. Another possibility would be that pharmaceuticals and device manufacturers would simply walk away, deciding that the costs outweigh any benefits that manufacturers could realize through obtaining new and separate approvals for each type of off-label use.<sup>41</sup> Terminally ill patients, for example, might be left with no treatment options at all.

There are arguments for both sides. Distinctions can be made, however, when talking about incurable, life-threatening illnesses, versus the use of mind-altering antipsychotics in the nonpsychotic patient population. Even if the psychiatric patient is severely depressed and suicidal, for example, alternative measures could be taken—even in emergency situations—to prevent death and stabilize the patient without introducing antipsychotics into the

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37. Kaspar J. Stoffelmayr, Comment, *Products Liability and “Off-Label” Uses of Prescription Drugs*, 63 U. CHI. L. REV. 275, 280 (1996) (footnote omitted).

38. Mithani, *supra* note 1, at 577 (citing Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 203 (1999) and Molly Sachdev et al., *Effect of Fenfluramine-Derivative Diet Pills on Cardiac Valves: A Meta-Analysis of Observational Studies*, 144 AM. HEART J. 1071 (2002)).

39. Berry, *supra* note 16, at 45 (citing 21 U.S.C. § 355(i)(3) (2018)).

40. Klasmeier & Redish, *supra* note 10, at 316.

41. *Id.*

already frail or troubled mind. Such alternatives include longer inpatient stays and more psychosocial interventions. In extreme situations of treatment-resistant depression, electroconvulsive therapy under anesthesia may be another effective intervention.<sup>42</sup> These suggested alternatives, however, require more time and expense compared to patients swallowing pills widely available as cheap generics. If time and cost constraints prohibit alternative treatments, another possibility is to continue allowing use of antipsychotics in the nonpsychotic patient population under emergency circumstances, but imposing limits on the duration of such treatment. Especially in the circumstance of the nonpsychotic patient taking antipsychotic drugs on a long-term basis, side effects can be deleterious, even deadly.

*C. The “Practice of Medicine Exception”*

1. FDA Deference to Physicians

Policy justifications for off-label prescribing rest on the fact that FDA does not regulate the practice of medicine. Again, once a drug is approved by FDA, use of that drug is not restricted to uses indicated on FDA-mandated labeling.<sup>43</sup> FDA has always maintained that it will not interfere with a physician’s autonomy,<sup>44</sup> and that the Practice of Medicine Exception prevents the agency from regulating a physician’s “unapproved use of an approved drug” within the confines of clinical practice.<sup>45</sup> In 1998, FDA issued guidance specifically addressing off-label use of drugs. In that paper, FDA stated that the patient’s best interests and good medical practice require that physicians have freedom to decide which prescription drugs, biologics, and devices to use, and such determination should be based on the physician’s “best

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42. Kristina Thurin et al., *How Neuroscience is Informing Treatments: Ethical Issues*, 17 FOCUS 35, 37 (2019) (“[T]he notion of ECT causing brain damage is a myth, with no scientific evidence to support it” and “[r]ecent studies show . . . that ECT is associated with increases in brain volume in regions such as the hippocampus and with increased integrity of connections between brain region[s].”).

43. Barkus & Derian, *supra* note 20, at 863.

44. Teo, *supra* note 35, at 305.

45. Berry, *supra* note 16, at 35–36; C Lee Ventola, *Off-Label Drug Information: Regulation, Distribution, Evaluation, and Related Controversies*, 34 PHARM. & THERAPEUTICS 436 (2009).

knowledge and judgment.”<sup>46</sup> FDA continued that when prescribing for a use not indicated on approved labeling, a physician must be well informed, base the off-label prescription on a firm scientific rationale and medical evidence, and then maintain records documenting the off-label use and its effects on the patient.<sup>47</sup> Further, an IND or Investigational Device Exemption (IDE) are not required if the off-label use is pursuant to the “practice of medicine.”<sup>48</sup> In 1999, FDA formally amended its regulations, clarifying decidedly, as follows: “(d) Unlabeled indication. This part does not apply to the use in the practice of medicine for the unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.”<sup>49</sup> This was one more signal that FDA was comfortable with the status quo, and would not be interjecting itself into the physician-patient relationship.

The federal government’s position is clear: FDA regulations “do not restrict a physician’s ability to prescribe drugs for off label uses,”<sup>50</sup> and federal courts reiterate this stance, without question.<sup>51</sup> For example, in *Buckman Co. v. Plaintiffs’ Legal Comm.*,<sup>52</sup> the U.S. Supreme Court noted that once a drug receives FDA approval for any use, physicians may use legally marketed drugs in any way they believe will best serve their patients, and described off-label prescribing as “an accepted and necessary corollary” of FDA’s “mission to regulate in this area without

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46. COLEMAN ET AL., *supra* note 10, at 167.

47. *Id.*

48. *Id.*

49. Klasmeier & Redish, *supra* note 10, at 323 (citing 21 C.F.R. § 312.2(d) (2019)).

50. Trasatti & Lanzendorfer, *supra* note 31, at n. 9 (citing Ausness, *supra* note 21, at n. 7).

51. *See, e.g.*, *Buckman Co. v. Plaintiffs’ Legal Comm.*, 121 S.Ct. 1012, 1018 (2001); *United States ex rel. Polansky v. Pfizer, Inc.*, 822 F.3d 613, 615 (2nd Cir. 2016) (quoting *U.S. v. Caronia*, 703 F.3d 149, 153 (2nd Cir. 2012) for the statement that “[o]nce FDA-approved, prescription drugs can be prescribed by doctors for both FDA-approved and unapproved uses; the FDA generally does not regulate how physicians use approved drugs.”).

52. *Buckman*, 121 S.Ct. at 1018–19 (2001).

directly interfering with the practice of medicine.”<sup>53</sup> In *United States v. Evers*,<sup>54</sup> the Fifth Circuit stated that though FDA “‘was obviously intended to control the availability of drugs for prescribing by physicians,’ it ‘was not intended to regulate the practice of medicine.’”<sup>55</sup> And in discussing the topic in *United States v. Regenerative Sciences*,<sup>56</sup> the D.C. District Court noted that FDA did not disagree with the proposition that “Congress has left the practice of medicine to the States to regulate.”<sup>57</sup>

Aside from the federal-state debate, long included in arguments that practitioners should control medical practice is the assertion that when government at any level—federal, state or local—limits practitioner discretion, this negatively effects the quality of medical care.<sup>58</sup> Off-label drug prescription and use is considered by some “an important part of mainstream, legitimate medical practice.”<sup>59</sup> Leaders in medicine assert, rightly so, that it would constitute medical malpractice if, in some instances, a physician failed to use a drug in an off-label manner.<sup>60</sup>

It seems rather illogical that FDA’s responsibility to safeguard the public from unsafe use of drugs has no overlap with the physician’s right to prescribe an approved medication off label within the practice of medicine.<sup>61</sup> Yet, the only substantial limits on a physician’s practice of medicine are those imposed by state

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53. Trasatti & Lanzendorfer, *supra* note 31, at n.11 (citing *Buckman*, 121 S.Ct. at 1018).
  54. *United States v. Evers*, 643 F.2d 1043, 1048 (5th Cir. 1981).
  55. Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 430 (2015) (citing *Evers*, 643 F.2d at 1048); *see also* Teo, *supra* note 35, at 324.
  56. *U.S. v. Regenerative Sciences, LLC*, 878 F. Supp. 2d 248, 255 (D. D.C. 2012), *aff’d*, 741 F.3d 1314–15 (D.C. Cir. 2014).
  57. Zettler, *supra* note 55, at 430 (citing *Regenerative Sciences*, 878 F. Supp. 2d at 255).
  58. *Id.* at 437 (citing, *cf.*, JONATHAN OBERLANDER, *THE POLITICAL LIFE OF MEDICARE 22* (2003) for the statement that “the American Medical Association lobbied against government health insurance in 1949 by arguing that it would ‘inevitably erode the quality of medical care by giving the government [rather than physicians] control over medical services.’”).
  59. Stoffelmayr, *supra* note 37, at 276.
  60. *Id.*
  61. Teo, *supra* note 35, at 306.

law regarding medical licensure and malpractice and those set by third-party payors for reimbursement standards.<sup>62</sup> But how, exactly, is “the practice of medicine” defined? One scholar poses and responds to the question aptly: “Is the ‘practice of medicine’ whatever . . . physicians say it is, or is it a question of how to properly treat patients? . . . If it is the latter, then in the name of safeguarding the public health, perhaps there is some foundation for the government to intervene and impose regulations.”<sup>63</sup> In The Belmont Report, the 1979 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the Commission drew distinctions between medical research and medical practice, the latter defined as “interventions that are designed solely to enhance the wellbeing of an individual . . . and that have a reasonable expectation of success.”<sup>64</sup> Our modern definitions of “the practice of medicine” are derived from statutory language and court decisions, and among the states there are various interpretations<sup>65</sup> that fluctuate over time.<sup>66</sup> An unequivocal determination of the scope of “the practice of medicine exception” has never been established,<sup>67</sup> and often depends on the stakeholders involved in setting the parameters.<sup>68</sup>

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62. Cooper & Greenblum, *supra* note 13, at 79.

63. Teo, *supra* note 35, at 306.

64. NAT’L COMM’N FOR THE PROTECTION OF HUM. SUBJECTS OF BIOMEDICAL AND BEHAV. RES., THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH 2 (1978), available at [https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c\\_FINAL.pdf](https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf) [<https://perma.cc/Z7S7-USU4>] [hereinafter THE BELMONT REPORT]; see also Nancy King, *The Line Between Clinical Innovation and Human Experimentation*, 32 SETON HALL L. REV. 573, 573 (2002) (footnote omitted).

65. Zettler, *supra* note 55, at 435.

66. Wendy Teo notes varying descriptions over time, from the “art of healing” to the administration of drugs or performance of surgery. “It is difficult to reach a uniform position on certain activities, and states and courts have also grappled with defining and delineating the boundaries of the practice of medicine.” Teo, *supra* note 35, at 306.

67. Berry, *supra* note 16, at 12.

68. Zettler, *supra* note 55, at 435.



Given the differences in statutory definitions and language, state courts understandably reach divergent conclusions when viewing similar activities and determining, for example, whether or not medical malpractice has been proven.<sup>69</sup> However, there are general similarities in state statutes and court determinations regarding what constitutes “the practice of medicine,” most including two physician activities: (1) the diagnosis of a disease, condition or injury, and (2) the prescribing, administration or provision of treatment for a disease, condition or injury.<sup>70</sup> Although there are nuances in how it is defined, the Practice of Medicine Exception appears to create a loophole that allows innovation and experimentation with little-to-no out-of-pocket cost to the drug manufacturer, and a huge risk reduction relating to the manufacturer’s potential liability.

## 2. Legislative Intent Underpins “Practice of Medicine Exception”

The FDCA does not explicitly support FDA’s stance on not regulating the practice of medicine; instead, “FDA’s deference to physicians is borne from Congressional intent.”<sup>71</sup> Debates preceding enactment of the FDCA make clear that Congress never intended to regulate the practice of medicine.<sup>72</sup> Considering that legislative history, the U.S. Supreme Court has stated that “FDA’s mission [is to] . . . regulate . . . without directly interfering with the practice of medicine.”<sup>73</sup> During congressional hearings in 1934, the medical profession expressed concern that the FDCA would interfere with the “prerogatives of the doctor.”<sup>74</sup>

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69. *Id.* at 435–36.

70. *Id.* at 436; *see also* Teo, *supra* note 35, at 307 n.5 (citing Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 KAN. L. REV. 149, 162 (2004) and Cynthia Marietta & Amy L. McGuire, *Direct-to-Consumer Genetic Testing: Is It the Practice of Medicine?*, 37 J. L. MED. & ETHICS, 369, 371 (2009)).

71. Teo, *supra* note 35, at 307.

72. *Id.* at 308 (citing ROBERT P. BRADY, *FUNDAMENTALS OF LAW & REGULATION: AN IN-DEPTH LOOK AT FOOD & DRUG ADMINISTRATION MODERNIZATION ACT* 423–24 (David G. Adams & Richard M. Cooper eds., 1st ed. 1997)).

73. *Buckman Co. v. Plaintiffs’ Legal Comm.*, 121 S.Ct. 1012, 1018 (2001); *see also* Teo, *supra* note 35, at 308 n. 7.

74. Berry, *supra* note 16, at 4 (citing 78 CONG. REC. NO. at 2728 (1934)).

Senator Royal Copeland, also a homeopathic physician and strong proponent of the legislation, stated that “this bill makes certain that the medical practitioner shall not be interfered with in his practice.”<sup>75</sup>

Amendments to the statutory language prior to the FDCA’s passage likewise show Congress’s intent not to interfere with the practice of medicine: “Initially section 321(b) of the 1938 Act, defining the term ‘drug,’ contained language stating that it was not intended ‘for the regulation of the legalized practice of the healing art.’”<sup>76</sup> In 1951, the Durham-Humphrey Amendment to the FDCA did not effect any changes in the practice of medicine exception.<sup>77</sup> The amendment actually exempted prescription drugs from section 352(f)’s requirements, giving physicians primary responsibility of informing patients as to directions for use and warnings about misuse.<sup>78</sup> In 1962, Congress reiterated that FDA was not to interfere with the practice of medicine.<sup>79</sup> In Section 214 of the 1997 Food and Drug Administration

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75. *Id.* at n.15 (citing Hutt, *Regulation of the Practice of Medicine under the Pure Food and Drug Laws*, 33 Q. BULL. ASS’N OF FOOD & DRUG OFF. NO.1, at 15 (1969)).

76. *Id.* at 4–5 n.18, (citing H. R. REP. NO. 2755, at 5 (1936)); *See also* Chaney v. Heckler, 718 F.2d 1174, 1180 n.13 (1983), *rev’d* 470 U.S. 821 (1985) (quoting S. REP. NO. 361, 74th Cong. (1st Sess. 1935); S. REP. NO. 646, 74th Cong. (1st Sess. 1935) and Pharmaceutical Mfrs Ass’n, 484 F. Supp. 1179, 1184 (D. Del. 1980)).

77. *Id.* at 7.

78. *Id.* at n. 28 (citing Pharmaceutical Mfrs. Ass’n v. Food & Drug Admin, 484 F. Supp. 1179, 1185 (D. Del. 1980) (citing *Hearings on H.R. 3298 Before the House Committee on Interstate and Foreign Commerce*, 82nd CONG. 1st Sess. 20–21 (1951) (remarks of Fed. Sec. Admin. Oscar Ewing)).

79. Teo, *supra* note 35, at 308 n. 8 (citing Pub. L. No. 87-781, 76 Stat. 780 (codified in scattered sections of 21 U.S.C.); Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149, 173 n. 99 (2004) (“[T]he . . . [Act] should not interfere with the professional function of the physician. FDA clearance would assure physicians that a drug effectively produces certain physiological actions, but the physician, not the FDA, would determine whether these specific physiological effects would be useful or beneficial with respect to particular patients”).

Modernization Act,<sup>80</sup> Congress directed that “nothing in [the FDCA] shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”<sup>81</sup> The Food and Drug Administration Amendments Act of 2007<sup>82</sup> states that “nothing in this section shall be construed to . . . limit the practice of medicine.”<sup>83</sup> Clearly, deference to physicians is a longstanding theme throughout the various iterations of U.S. Food and Drug law.

Other U.S. health care laws likewise confer wide latitude to the medical profession in controlling the practice of medicine, for example, laws relating to Medicare, fertility, and drug addiction treatment.<sup>84</sup> Even after a public health emergency, when drafting

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80. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 214, 111 Stat. 2296 (codified at 21 U.S.C. § 396).
81. Teo, *supra* note 35, at 308 n. 9 (citing Pub. L. No. 105-115, § 214, 111 Stat. 2296, 2348); *see also* Buckman Co. v. Plaintiffs’ Legal Comm., 121 S.Ct. 1012, 1018 (2001) (“Indeed, a recent amendment to the FDCA expressly states in part that ‘[n]othing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.’”).
82. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1111(d), 121 Stat. 823 (2007) (codified at 42 U.S.C. § 247d-5a(d)).
83. Teo, *supra* note 35, at 308 n.10 (citing Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1111(d), 121 Stat. 823, 976 (2007).)
84. *Id.* at n.11 (citing Health Insurance for the Aged Act, Pub. L. No. 89-97, § 102(a), 79 Stat. 290, 291 (1965) (codified at 42 U.S.C. § 1395) (“Nothing in [the Medicare statute] shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the practice of medicine.”)); Fertility Clinic Success Rate and Certification Act of 1992, Pub. L. No. 102-493 § 3(i)(1), 106 Stat. 3146, 3149 (1992) (codified at 42 U.S.C. § 263a-2(i)(1)) (“In developing the [federal embryo laboratory] certification program, the [Department of Health and Human Services] may not establish any regulation, standard, or requirement which has the effect of exercising supervision or control over the practice of medicine in assisted reproductive technology programs.”); To Amend the Public Health Service Act with Respect to Children’s Health, Pub. L. No. 106-310, § 3502, 114 Stat. 1222, 1226 (codified at 21 U.S.C. § 823(g)(2)(H)(i)) (“Nothing

the Drug Quality and Security Act of 2013,<sup>85</sup> Congress expressed concern about encroaching on state regulation of medical practice.<sup>86</sup> This was a measure aimed at remedying FDA's limited authority to regulate compounding pharmacies following the fatal debacle involving a fungal meningitis outbreak traced to compounded lots of injectable glucocorticoid methylprednisolone acetate, produced by the Massachusetts-based New England Compounding Center.<sup>87</sup> A proponent of the 2013 law, Senator Tom Coburn, emphasized that the Practice of Medicine remained in the ambit of state regulators, assuring that "the art and science of medicine would not be impeded" by FDA.<sup>88</sup>

*D. Physicians Regulated by State Law*

States regulate medical practice under their police powers, while the federal government regulates medical products.<sup>89</sup> FDA has been clear that it does not and will not regulate the practice

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in such regulations or practice guidelines may authorize any Federal official or employee to exercise supervision or control over the practice of medicine or the manner in which medical services are provided.")).

85. Zettler, *supra* note 55, at 430 (citing Title I of the Drug Quality and Security Act of 2013, Pub. L. No. 113-54, 127 Stat. 587 (2013), which addresses drug compounding; Title II of the act is intended to improve the security of the drug supply chain).
86. Note that state regulation is actually carried out by state medical-licensing boards, which are themselves controlled by physicians. So, in this context, state regulation equals self-regulation. See CARL ELLIOTT, *WHITE COAT, BLACK HAT: ADVENTURES ON THE DARK SIDE OF MEDICINE* at xi (2010).
87. Kevin Outterson, *Regulating Compounding Pharmacies after NECC*, 367 *NEW ENG. J. MED.* 1969, 1969 (2012).
88. Zettler, *supra* note 55, at 430–31, 443 (citing 159 *CONG. REC.* S8029-06 (Nov. 14, 2013) (statement of Sen. Coburn)) ("[t]he Social Security Amendments of 1954, for example, provided that '[n]othing in this subchapter shall be construed as authorizing the Commissioner of Social Security or any other officer or employee of the United States to interfere in any way with the practice of medicine'; The Medicare statute, the Fertility Success Rate and Certification Act of 1992; the Food and Drug Administration Modernization Act of 1997; the Drug Addiction Treatment Act of 2000; and the Food and Drug Administration Amendments Act of 2007 each included a provision with similar language.").
89. *Id.* at 430 (citing *Dent v. West Virginia*, 129 U.S. 114, 122–23, 128 (1889)).

of medicine, and that the FDCA is not a source of physician liability for harms arising from a physician's off-label prescriptions.<sup>90</sup> However, physicians are not exempt from liability arising from prescribing drugs off label.<sup>91</sup> Theoretically, remedies are available at the state level.

Medical malpractice insurance is costly, and medical literature cautions physicians that prescribing medications for off-label use has resulted in greater malpractice risk.<sup>92</sup> In order to preemptively reduce liability risks, the prudent physician would (1) remain abreast of news and developments relating to medications and their uses, (2) keep literature files relating to off-label uses, (3) inform and emphasize to the patient that the proposed treatment involves an off-label use, and (4) continually document the patient's informed consent.<sup>93</sup> Yet, in the context of mental health medical malpractice, the tort system is far from perfect due to power differentials between mentally ill patients and their psychiatrists.<sup>94</sup> Thus, the tort system cannot adequately regulate this space.

However, in instances where physicians fail to meet their obligations by inappropriately prescribing a medication, the patient's malpractice claims could sound in negligence (or in unusual circumstances strict liability) where warnings in the Physician Desk Reference or in the drug's package insert were

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90. Katherine A. Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, 18 FORDHAM INTELL. PROP., MEDIA & ENT. L. J. 116, 167 (2007).

91. *Id.*

92. James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANN. HEALTH L. 295, 319 (2003) (footnote omitted).

93. *Id.*

94. Hannah Martens & Timothy Brown, *Trusting Oneself and Others: Relational Vulnerability and DBS for Depression*, 9 AM. J. BIOETHICS NEUROSCIENCE 226 (2018) (“[T]he patient's active depressive symptoms, lesser knowledge about the [treatment], and lesser understanding of possible treatment alternatives produce a problematic power differential between the patient and their doctor.”).

disregarded.<sup>95</sup> Liability might also arise where a physician failed to obtain patient informed consent.<sup>96</sup> Laws vary from state to state, and what is negligent practice in one jurisdiction may be acceptable practice in another. A further complication, concepts of informed consent vary based on jurisdiction,<sup>97</sup> and, in some states, courts have found that nothing obliges a physician to disclose the off-label use at all.<sup>98</sup>

### 1. Strict Liability and Negligence

While FDA has at least once asserted that it retains jurisdiction to regulate off-label prescription use,<sup>99</sup> it has most often taken the position that state tort liability is the best means of controlling off-label uses.<sup>100</sup> The idea is that in prescribing

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95. O'Reilly & Dalal, *supra* note 92, at 317 (footnote omitted); See Amy E. Todd, *No Need for More Regulation: Payors and Their Role in Balancing the Cost and Safety Considerations of Off-Label Prescriptions*, 37 AM. J. L. & MED. 422, 424 (2011) (citing James B. Riley, Jr. & P. Aaron Basilius, *Physicians' Liability for Off-Label Prescriptions*, 6 HEMATOLOGY & ONCOLOGY NEWS & ISSUES 24, 26 (2007)); see also Barbara Marticelli McGarey, *Pharmaceutical Manufacturers and Consumer-Directed Information—Enhancing the Safety of Prescription Drug Use*, 34 CATHOLIC U. L. REV. 148 (1984).
96. Amy E. Todd, *No Need for More Regulation: Payors and Their Role in Balancing the Cost and Safety Considerations of Off-Label Prescriptions*, 37 AM. J. L. & MED. 422, 424 (2011) (footnotes omitted).
97. Mithani, *supra* note 1, at 579 (citing generally S. WEAR, INFORMED CONSENT: PATIENT AUTONOMY AND PHYSICIAN BENEFICENCE WITHIN CLINICAL MEDICINE (1993)).
98. Todd, *supra* note 35, at 424 (citing Ausness, *supra* note 21, at 1253; Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L. J. 967 (2007)); see also Klein v. Biscup, 673 N.E.2d 225, 231 (Ohio App. 8 Dist. 1996).
99. Stoffelmayr, *supra* note 37, at 279 n. 26; cf. Klasmeier & Redish, *supra* note 10, at 316 (“In any event, under the current regulatory framework, the FDA asserts that it lacks legal authority to restrict the ability of doctors to prescribe drugs or devices for off-label uses.” The latter is overwhelmingly the prevailing view.).
100. Stoffelmayr, *supra* note 37, at 279 n. 25, (citing 48 Fed. Reg. 26,720, FDA, Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503 (1972); and *Use of Approved*

antipsychotic or other drugs off label, psychiatrists may expose themselves to negligence liability by not fulfilling duties such as obtaining adequate medical and psychiatric histories, physical examinations, and laboratory tests.<sup>101</sup> Further failures of obligations arise when a physician prescribes a drug where indication is lacking or a contraindication is present; prescribes an improper dosage or for an unwarranted duration; or fails to recognize, monitor or treat side effects, to abate reactions and interactions, or consult with other physicians.<sup>102</sup> The patient also has a viable negligence claim against the psychiatrist-prescriber where the diagnosis itself was incorrect.<sup>103</sup> But some commentators assert that the tort system cannot effectively regulate off-label drug uses, their criticisms focused on a plaintiff's burdens in proving medical malpractice liability.<sup>104</sup>

Both the physician and drug or device manufacturer have been defendants in lawsuits claiming injury from a prescribed drug or medical device. In the products-liability actions—generally arising under theories of strict liability or negligence—the plaintiff's claims usually are based on the manufacturer's failure to warn of potential risks and dangers.<sup>105</sup> However, by prescribing a medication off-label, a physician unwittingly may be shielding the manufacturer from liability and exposing herself to state-level medical malpractice claims if the manufacturer in fact warned the physician of risks associated with the drug.<sup>106</sup>

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*Drugs for Unlabeled Indications*, 12 FDA DRUG BULL. 4, 5 (Apr. 1982)).

101. Jadwiga Najib, *Drug-Induced Movement Disorders*, in DRUG INJURY: LIABILITY, ANALYSIS AND PREVENTION, 419, 443 (James T. O'Donnell ed., 3d ed. 2012).

102. *Id.*

103. *Id.*

104. Stoffelmayr, *supra* note 37, at 281 n. 37 (citing William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L. J. 247, 260–62 (1992) and Sydney A. Shapiro, *Limiting Physician Freedom to Prescribe a Drug for Any Purpose: The Need for FDA Regulation*, 73 NW. U. L. REV. 801, 869–72 (1978)).

105. Trasatti & Lanzendorfer, *supra* note 31, at 8.

106. *Id.* at 9; see discussion of the Learned Intermediary Doctrine, *infra*, Part I.D.3.

Courts have adopted varying viewpoints regarding a drug manufacturer's duties in the context of off-label uses of prescription drugs,<sup>107</sup> and products liability cases in the off-label drug use arena are most notable for their inconsistency.<sup>108</sup> The competing goals of incentivizing manufacturers to warn of risks and minimizing penalties for failure to do so<sup>109</sup> seem more often to weigh in favor of protecting manufacturers. Criticisms of such an approach argue that the drug manufacturer should owe a duty to warn of any and all known risks associated with an off-label drug use, whether "demonstrated by the manufacturer's own research, the research of others, or physicians' experiences using the drug."<sup>110</sup>

## 2. Informed Consent

Most patients fairly assume that the drugs their physician prescribes are FDA-approved,<sup>111</sup> not understanding that once a drug is approved by FDA, it may be used for any purpose or population.<sup>112</sup> Interestingly, despite the controversial nature of off-label prescription, little has been said or published addressing informed consent for off-label use.<sup>113</sup> While FDA requires explicit written consent for drugs being tested in clinical trials, no such requirement attaches in the context of off-label prescriptions where, as in any other medical treatments, the doctor believes that he is using the drug in a manner that serves the patient's best interests.<sup>114</sup> The doctrine of informed consent imposes no

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107. Stoffelmayr, *supra* note 37, at 276 (footnote omitted).

108. *Id.* at 275–76 n. 7.

109. *Id.* at 276.

110. *Id.*

111. Mithani, *supra* note 1, at 577 (citing Wilkes & Johns, *Informed Consent and Shared Decision-Making: A Requirement to Disclose to Patients Off-Label Prescriptions*, 5 PLOS MED. e223 (2008)).

112. *Id.*

113. *Id.*; see also Berry, *supra* note 16, at 34 ("The general public is likely under the impression that if their doctor is prescribing a medical treatment, it has been tested and approved for that particular use.").

114. Am. Acad. of Pediatrics Comm. on Drugs, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, 110 PEDIATRICS 181, 182 (2002).



specific duty on the physician to inform the patient that the use of a drug, including an antipsychotic, is off label.<sup>115</sup>

Failure to obtain informed consent is a failure to advise a patient of risks and potential risks associated with a proposed treatment, which all is material information required for a patient to make an informed decision about the treatment.<sup>116</sup> In a legal proceeding, the patient-plaintiff often may assert that had he known of the risks, then he would not have consented to treatment with the offending drug.<sup>117</sup> From a legal perspective, as the risk of a treatment rises, so too does the duty to warn, monitor, and consider alternative treatments.<sup>118</sup> The physician would simultaneously best serve the patient's and his own interests by focusing on safety and efficacy, and managing risk of malpractice liability by "following the traditional golden standards of medicine": get informed consent, practice evidence-based medicine, integrate specialized medicine, and provide comprehensive follow-up care.<sup>119</sup>

Determining what qualifies as "significant or material" consent depends on the particular patient's needs, capabilities, and wishes,<sup>120</sup> as well as on the nature of the proposed treatment. Exceptions to informed consent requirements include patient incompetence,<sup>121</sup> and among the common symptoms in psychiatric illness are impaired reasoning.<sup>122</sup> However, where a psychiatrist is

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115. Helm, *supra* note 90, at 168; see Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 480 (2009) ("The few courts that have considered the question have concluded that a product's regulatory status is not part of the medical information that physicians must disclose about a proposed off-label treatment (unless it is administered in the context of research).").

116. Barkus & Derian, *supra* note 20, at 863.

117. *Id.* at 861.

118. Najib, *supra* note 101, at 443 (footnote omitted); see also Barkus & Derian, *supra* note 20, at 862 ("[A] physician is required to disclose any significant or material risks associated with the treatment, as well as any available alternatives.").

119. Najib, *supra* note 101, at 443 (footnote omitted).

120. Barkus & Derian, *supra* note 20, at 862.

121. *Id.*

122. Thurin et al., *supra* note 42, at 35.

contemplating prescription of antipsychotics, off label or not, one would think that the patient (or the patient's legal decisionmaker) must be informed of the risks of drug-induced movement disorders and other potential adverse effects, along with any potential benefits of use, before commencing antipsychotic treatment.<sup>123</sup> Too frequently, however, this risk information is not shared with the patient or surrogate. Often times, psychiatric patients are persuaded by the “‘insulin for diabetes’ metaphor,” where the psychiatrist explains that there is a chemical basis to mental illness and the psychotropic drug will fix it, just as insulin does for the diabetic.<sup>124</sup> The metaphor serves as “a summation of the risks and benefits,” and once this summary “is presented to a psychiatric patient, the patient can be understood to be misinformed about risks and benefits.”<sup>125</sup>

### 3. “Learned Intermediary Doctrine” Protects Manufacturers

The learned intermediary doctrine, first officially identified in a 1966 decision of the Eighth Circuit Court of Appeals,<sup>126</sup> recognizes that if a treating physician received adequate notice of possible risks, the manufacturer has no duty to warn the end consumer.<sup>127</sup> As such, the doctrine often affects the apportionment of liability between the physician and the pharmaceuticals manufacturer.<sup>128</sup> Using the learned intermediary doctrine as an affirmative defense, the pharmaceuticals manufacturer can shift blame for any patient injuries to the prescribing doctor. This is because liability usually will not extend to the manufacturer where it could not have foreseen the off-label use or the physician failed to convey manufacturer-recommended warnings to the patient.<sup>129</sup>

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123. Najib, *supra* note 101, at 443.

124. ROBERT WHITAKER & LISA COSGROVE, PSYCHIATRY UNDER THE INFLUENCE 157–58 (2015).

125. *Id.*

126. *Sterling Drug Inc. v. Cornish*, 370 F.2d 82, 85 (8th Cir. 1966).

127. *Barkus & Derian*, *supra* note 20, at 865 (citing Richard B. Goetz & Karen R. Growden, *A Defense of the Learned Intermediary Doctrine*, 63 FOOD & DRUG L. J. 421, 421 (2008)).

128. Helm, *supra* note 90, at 168 (citing *Marcus v. Specific Pharms. Inc.*, 77 N.Y.S.2d 508, 509–10 (N.Y. App. Term. 1948)).

129. *Id.* Note, however, that increases in DTC marketing are chipping away at protections for manufacturers, as there sometimes is no

Under the learned intermediary doctrine, pharmaceutical manufacturers generally have no duty to warn patients of risks associated with a drug's use, only a duty to warn prescribing physicians.<sup>130</sup> Several recent U.S. Circuit Court cases confirm this line of thought. For example, in *Payne v. Novartis Pharmaceuticals Corp.*,<sup>131</sup> in addressing the plaintiff's claims against a manufacturer of bisphosphonates that allegedly caused osteonecrosis of the jaw, the court stated that “[a]t base, the doctrine can shift liability from drug companies to doctors: If the drug company adequately warned and instructed the doctor but the doctor did not adequately warn and instruct the patient, the patient's quarrel is with the doctor rather than the drug company.”<sup>132</sup>

Thus, a patient who suffers a drug injury due to lack of informed consent has a cause of action against the prescribing physician for medical malpractice instead of against the drug manufacturer for products liability.<sup>133</sup> Were the manufacturer to warn the unsophisticated or uneducated patient of the potential risks, this warning would be insufficient because the patient, unlike the doctor, is not trained in appraising medical risks.<sup>134</sup> This is one reason why the manufacturer's duty is only to warn prescribing physicians, who then assume responsibility for

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real intermediary. *Id.* at 169 (“DTC advertising tends to undercut the rationale behind the doctrine.”). Interestingly, Helm notes that “the duty for pharmaceutical manufacturers to warn the patient directly is supported by the Restatement (Third) of Torts: Products Liability § 6(c)–(d) (1998).” *Id.*

130. Stoffelmayr, *supra* note 37, at 284–85 (footnote omitted).
131. *Payne v. Novartis Pharmaceuticals Corp.*, 767 F.3d 526, 531 (6th Cir. 2014).
132. *See also* *Mink v. Smith & Nephew, Inc.*, 860 F.3d 1319, 1329 (11th Cir. 2017) (holding, under the learned-intermediary doctrine, that Florida law barred the plaintiff-patient's negligence claim against a hip joint replacement system manufacturer based on the theory that the manufacturer's training of the physician was inadequate, and alleging that the manufacturer breached its duty to correctly train the plaintiff's physician on how to implant the system; any duty the manufacturer had in regards to training was owed to the physician, not the patient).
133. *Barkus & Derian*, *supra* note 20, at 865; *see also* *ABOOD & BRUSHWOOD*, *supra* note 8, at 230.
134. *ABOOD & BRUSHWOOD*, *supra* note 8, at 230.

informing patients of risks of using the drug or device.<sup>135</sup> Some argue that since the physician is in the better position to understand and weigh the risks and benefits in contemplating the specific patient's needs and conditions, the learned intermediary doctrine is valid.<sup>136</sup> Yet another rationale offered to support the doctrine is that doctors often have close and sometimes personal connections to patients and are more practically and effectively able to discuss risks and warnings than could a detached pharmaceuticals manufacturer.<sup>137</sup>

Use of the learned intermediary doctrine as a defense has allowed pharmaceuticals manufacturers to limit or decrease products-liability claims regarding pharmaceuticals since the 1966 Court of Appeals decision.<sup>138</sup> Pharmaceuticals manufacturers continue to assert this defense, successfully insulating the companies from liability in negligence and strict liability actions, including design defect, misbranding, and breach of implied warranty claims.<sup>139</sup>

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135. Trasatti & Lanzendorfer, *supra* note 31, at 9 (“For the doctrine to apply, however, the physician must be aware of the risks associated with each drug or device. This awareness does not have to come from the manufacturer. Indeed, even if a manufacturer’s warning is inadequate, the doctrine will still apply if the physician has been sufficiently warned from other sources. In essence, the learned intermediary doctrine encompasses the physician’s entire field of knowledge.”).

136. *Id.* at 9 (citing *Lee v. Baxter Healthcare Corp.*, 721 F. Supp. 89, 95 (D. Md. 1989), *aff’d*, *Lee v. Baxter Healthcare Corp.*, 898 F.2d 146 (4th Cir. 1990)).

137. Barkus & Derian, *supra* note 20, at 865.

138. Though there are exceptions—for example, cases involving mass immunization, use of certain contraceptives, and instances where FDA has mandated that a manufacturer warn the consumer-patient directly. *Id.*

139. Trasatti & Lanzendorfer, *supra* note 31, at 8 (citing *Fellows v. USV Pharm. Corp.*, 502 F. Supp. 297, 299–301 (D. Md. 1980); *but see id.* at 11–12 (“Personal injury claims increasingly allege injury from off-label use of medical products. These claims create a dilemma for pharmaceutical companies: the learned intermediary doctrine applies when physicians are aware of the risks associated with drug or device, but manufacturers are only required to warn physicians of risks associated with on-label uses and cannot know of all of the possible off-label uses of a medical product and the risks associated with those uses. In turn, this dilemma has resulted in substantial differences among state court decisions regarding a manufacturer’s

State laws and court decisions on application of the learned intermediary doctrine vary, with some considering “the totality of the circumstances, including the manufacturers’ knowledge, their promotion of the off-label use, and/or the foreseeability of the use”; some assuming that manufacturers always are duty-bound to warn, thus refusing to apply the doctrine where warnings are absent; and others always applying the doctrine on the basis that a physician must use her knowledgebase and draw from her training in determining the best course of treatment for patients.<sup>140</sup> This is troublesome because uniformity is lacking in state responses to harms arising from the same legal concept (that is directly tied to federal law on drug safety and efficacy, and permissible off-label prescription), leaving patients with similar claims in very different legal positions. As a group widely prescribed antipsychotics off label, nonpsychotic psychiatric patients—whether personally aware of it or not—are burdened by this legal uncertainty.

In the context of psychiatric practice, much in individual treatment is uncontrolled and unregulated, and the courts do little-to-nothing to reel in the potential chaos. For example, in *Boehm v. Eli Lilly & Co.*,<sup>141</sup> the Eastern District of Arkansas considered the case of a patient-plaintiff who developed tardive dyskinesia (TD)<sup>142</sup> after three years taking the atypical antipsychotic, Zyprexa, for an approved but nonpsychotic diagnosis. The drug first was prescribed by a general practitioner, then later continued by a psychiatrist. The patient-plaintiff sued the pharmaceuticals manufacturer for failure to warn about the substantial risks of developing TD, but the district court dismissed the claim based on the Arkansas learned intermediary

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liability for failure to warn claims involving off-label use.”). The authors further note, however, that “West Virginia’s highest court, the Supreme Court of Appeals, is the only court to have rejected the learned intermediary doctrine.” *Id.* at 11 (citing *Johnson & Johnson Corp. v. Karl*, 647 S.E.2d 899, 913–14 (W. Va. 2007)); *see also* *Barkus & Derian*, *supra* note 20, at 861, 865.

140. *See* *Trasatti & Lanzendorfer*, *supra* note 31, at 13–19.

141. *Boehm v. Eli Lilly & Co.*, 747 F.3d 501, 502 (8th Cir. 2014) *reh’g* and *reh’g en banc denied* (Apr. 15, 2014).

142. Tardive dyskinesia is an involuntary movement disorder long recognized as a side effect of antipsychotic drugs. *See* discussion of adverse side effects, *infra*, Part II.A.2.

doctrine.<sup>143</sup> While the plaintiff argued that he had presented substantial evidence that Lilly's warning to physicians as to the risk of developing TD after long-term use of Zyprexa was inadequate, the court disagreed, barring recovery against the manufacturer.<sup>144</sup> Ultimately, the court's reasoning was rational:

Lilly's package insert warned the prescribing doctors that though [TD] was an infrequent side effect, the risk that it would occur and become irreversible . . . was believed to increase as treatment continued over time and the patient's total cumulative dose increased. . . . No studies or other evidence existed to guide prescribers about deploying the drug for more than one month. . . . Drs. Miller and Kaczinski knew all these risks from reading the Zyprexa package insert and from their experience with first and second generation anti-psychotic medicines. They prescribed Zyprexa for Timothy Boehm across many years because, weighing the risks against the benefits of treating his bipolar disorder, in their opinion the drug helped him. These two main prescribers thought Lilly's warning adequate. Both are still prescribing Zyprexa to other patients.<sup>145</sup>

The plaintiff could have pursued claims against the prescribing physicians, but with caps in many states on medical malpractice tort claim awards, his ability to recover non-economic damages would be quite limited. Among other reasons, if the physicians were following the standard of care for treating a bipolar patient, there would be little chance the plaintiff would prevail.

In 2011, a member of Congress proposed legislation and admonished that Americans needed protection from drug manufacturers, and proposed outlawing use of the learned intermediary doctrine and allowing consumers to recover damages from pharmaceutical manufacturers directly.<sup>146</sup> "Medications are

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143. *Boehm v. Eli Lilly & Co.*, No. 4:10-CV-159-DPM, 2012 WL 12848432, at \*5 (E.D. Ark. Oct. 4, 2012), *aff'd*, 747 F.3d 501 (8th Cir. 2014).

144. *Boehm*, 747 F.3d at 507–08.

145. *Id.*

146. 157 CONG. REC. E199 (daily ed. Feb. 10, 2011) (statement of Rep. Filner).

meant to heal us,” the congressman stated, “but sometimes, something goes horribly wrong, and the medicine that was supposed to make us better, only makes us sicker. When this happens, Americans should be able to hold the drug manufacturers responsible.”<sup>147</sup> The proposed Bill went nowhere.

Drug manufacturers are in the best position to issue warnings of risks associated with using their drugs.<sup>148</sup> With the ability for broad monitoring—which is not feasible for the individual physician treating an individual patient—“drug manufacturers are, due to their superior ability to warn, the cheapest cost avoiders.”<sup>149</sup> This does not place an undue or unfair burden on the manufacturer because, if found liable, the company generally can pursue contribution and indemnity claims against the physician whose negligence gave rise to the plaintiff’s injuries.<sup>150</sup> Still, there have been instances where courts have found that a physician’s negligence—especially if unforeseeable—may absolve a manufacture of “*all* liability for failure to warn of the risks associated with the use of its drug.”<sup>151</sup> For example, in *Ferrara v. Berlex Laboratories, Inc.*,<sup>152</sup> a products liability action against manufacturers of a prescription antidepressant (Nardil) and an over-the-counter decongestant (Deconamine), for failure to warn patients of the products’ dangerous synergistic side effects, the court held that under Pennsylvania law the learned intermediary doctrine precluded manufacturer liability.

Several jurisdictions impose limits on recovering non-economic losses against health care providers, but these statutory

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147. *Id.*

148. Stoffelmayr, *supra* note 37, at 285.

149. Stoffelmayr argues, “[i]mposing a duty on manufacturers to warn of the risks of off label drug uses does not, as might be feared, turn manufacturers into insurers for physicians who carelessly prescribe dangerous off-label treatments or who negligently misprescribe drugs and later characterize their mistakes as off-label treatments. Injured patients can still bring medical malpractice suits against negligent physicians.” *Id.* at 289.

150. *Id.* (citing Charles F. Preuss, *Measures of Liability, in* PRODUCTS LIABILITY: DRUG CASES 303, 322–30 (Donald E. Vinson & Alexander H. Slaughter eds., 1988)).

151. *Id.* at 289 (emphasis added).

152. *Ferrara v. Berlex Lab., Inc.*, 732 F. Supp. 552, 553 (E.D. Pa. 1990), *aff’d*, 914 F.2d 242 (3d Cir. 1990).

limits do not apply to pharmaceuticals manufacturers; thus a physician's liability for non-economic damages might be capped at \$250,000, but the drug manufacturer's liability for those damages could be exponentially higher.<sup>153</sup> But not if that manufacturer is shielded from liability altogether.<sup>154</sup>

The learned intermediary doctrine protects pharmaceuticals manufacturers from liability, shifting the "blame" or responsibility to the doctor. It may seem at first glance that physicians are assuming great professional and financial risks by prescribing medications off-label, because they will be "left holding the bag." However, physicians have their own legally recognized means for self-protection, most significantly the accepted "standard of care."

#### 4. "Standard of Care" Protects Physicians

Courts generally consider off-label prescribing to be legitimate if it meets the standard of reasonable care.<sup>155</sup> Thus, liability usually will not extend to the physician where the off-label use is the accepted standard of care in the physician community.<sup>156</sup> In any medical malpractice action, the patient-plaintiff must establish that the physician failed to adhere to the accepted standard of care.<sup>157</sup> In order for a medical malpractice claim to succeed on these grounds, the plaintiff must demonstrate the existence of a direct physician-patient relationship and that the physician significantly departed from the standard of care of a reasonable physician.<sup>158</sup> While state laws vary in their exact determinations of accepted standards of care, generally the bar is

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153. Barkus & Derian, *supra* note 20, at 866 (citing CAL. CIV. CODE § 3333.2 (1872)).

154. In subsequent cases, major precedential developments effectively have shielded generic pharmaceuticals manufacturers from all liability for failure to warn in labeling. *See, e.g.*, Pliva, Inc. v. Mensing, 564 U.S. 604 (2011); Mutual Pharmaceutical Co. v. Bartlett, 570 U.S. 472 (2013). These developments are beyond the scope of this Article.

155. Helm, *supra* note 90, at 171; *see also* Klein v. Biscup, 673 N.E.2d 225, 231 (Ohio App. 8 Dist. 1996).

156. Helm, *supra* note 90, at 168.

157. Mark Herrmann & Pearson Bownas, *Keeping the Label Out of the Case*, 103 NW. L. REV. COLLOQUY 477, 480 (2009).

158. Helm, *supra* note 90, at 170.



set quite low, looking at what would be expected of the minimally competent physician.

In establishing the standard of care in medical malpractice actions against physicians for off-label use, peer-reviewed medical journals, introduced by expert testimony, “are generally considered the only reliable source of sound scientific and medical opinion.”<sup>159</sup> Usually, this expert testimony is required to establish the medical community’s applicable standard of care and to allow a jury to ascertain whether the off-label use and warnings provided to the patient conformed to that standard.<sup>160</sup>

Some scholars argue that FDA-approved labeling should not serve as evidence pertaining to the standard of care in litigation surrounding an off-label prescription gone wrong.<sup>161</sup> Ironically, it is the very off-label use at issue that, if widespread, becomes the standard of care: the standard of care *is* the off-label use.<sup>162</sup> If enough psychiatrists are prescribing antipsychotics to nonpsychotic patients, this becomes—and actually has become—the standard of care.<sup>163</sup> In treating individual patients, but in concert, psychiatrists have established this new standard of care, thereby insulating themselves from malpractice liability in courts of law.<sup>164</sup> It follows that the more widespread a drug’s off-label use—whether based on science, anecdote or myth—the more impervious to liability is the prescribing physician.

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159. *Id.*; Cf. Mollie E. O’Brien, *What Counts as Expert Medical Testimony?*, 6 VIRTUAL MENTOR 554, 555 (2004).

160. Barkus & Derian, *supra* note 20, at 863.

161. Herrmann & Bownas, *supra* note 157, at 480.

162. *Id.* at 486.

163. See Alex R. Thiersch, *Legal Issues: Off-Label Uses; Legal, Ethical and Informed Consent Considerations When Using Products Off-Label*, MEDESTHETICS MAG, <https://www.medestheticsmag.com/legal-issues-label-uses> [<https://perma.cc/W2XA-Y67A>] (last visited Dec. 8, 2018) (recommending that providers not put themselves in a situation where a medical board views their prescribed treatment as *too experimental*).

164. One might also consider the extension of this reasoning to informed consent. If failure to obtain informed consent has become the customary practice, is the physician’s failure to obtain the patient’s consent the new, accepted standard of care?

## II. ANTIPSYCHOTICS: PUSHING THE LIMITS

Antipsychotics serve a legitimate purpose in treating psychoses associated with mental illness after the particular drug has been scientifically shown to be safe and effective for that particular illness and study population. For the patient suffering from schizophrenia, antipsychotics can be lifechanging, for the better. For psychiatric patients not suffering from psychosis, antipsychotics can make their lives worse.

### A. History

Psychosis is marked by hallucinations, delusions, and severely disordered thought, often accompanied by extreme agitation and sleep disruption.<sup>165</sup> Symptoms of hallucination include false perceptions (for example, hearing voices that are not there), and delusions, which are “false beliefs that do not yield to a rational argument.”<sup>166</sup> With severe thought disorder there is a breakdown in logical connections between successive thoughts.<sup>167</sup> Psychosis is not limited to the experience of patients suffering from schizophrenia, but also may be a state present in illnesses such as bi-polar disorder and severe major depressive disorder.

Antipsychotics were developed in the early 1950s to treat psychoses.<sup>168</sup> For patients experiencing psychotic “breaks with reality,” particularly those associated with schizophrenia,<sup>169</sup> antipsychotics provide “a crucial and potentially life-saving treatment.”<sup>170</sup> Reducing dopamine activity within the brain is a

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165. Mary C. McCarron, *The Right to Refuse Antipsychotic Drugs: Safeguarding the Mentally Incompetent Patient's Right to Procedural Due Process*, 73 MARQ. L. REV. 477, 481 n. 24 (1990).

166. *Id.*

167. *Id.*

168. *Id.* at 477 (citing *The Forcible Medication of Involuntarily Committed Mental Patients with Antipsychotic Drugs*, 15 GA. L. REV. 739 (1981) (citing Davis, *Antipsychotic Drugs*, in FREEMAN H. KAPLAN & B. SADOCK, *COMPREHENSIVE TEXTBOOK OF PSYCHIATRY* (2d ed. 1975)).

169. *Id.* at 480–81.

170. Brendan L. Smith, *Inappropriate Prescribing: Research Shows That All Too Often, Americans Are Taking Medications That May Not Work or May Be Inappropriate for Their Mental Health Problems*, 43 MONITOR ON PSYCHOL. 36 (June 2012).

common action of all antipsychotics.<sup>171</sup> More specifically, a primary function of antipsychotics is accomplished through dopamine receptor-blocking agents—also known as neuroleptics and/or major tranquilizers—that block dopamine neurotransmission in the brain.<sup>172</sup> Earlier antipsychotics were problematic because they were difficult to tolerate due to adverse side effects, particularly extrapyramidal side effects.<sup>173</sup> In the 1990s, pharmaceutical manufacturers introduced a new wave of antipsychotics, interchangeably referred to as second generation antipsychotics (SGAs) and atypical antipsychotics.<sup>174</sup> In addition to reducing dopamine activity, SGAs work to block serotonin receptors.<sup>175</sup>

In the 1990s, major pharmaceuticals companies rolled out SGAs, such as Risperdal, Seroquel and Zyprexa, touting these new drugs as superior to first generation antipsychotics.<sup>176</sup> SGAs supposedly were better tolerated by the patient suffering from schizophrenia, with fewer adverse side effects.<sup>177</sup> But SGAs have not fully lived up to this promise, with virtually all SGAs having a propensity to cause certain degrees of adverse side effects.<sup>178</sup> In fact, widespread use of SGAs followed at least one manufacturer's now-documented suppression of unfavorable studies, and the manipulation and reporting of findings and results through academic psychiatrists with "apparent scientific legitimacy."<sup>179</sup> Some experts now assert that while less cost effective than first-generation antipsychotics, SGAs are "no more efficacious, do not

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171. DAVID HEALY, *PSYCHIATRIC DRUGS EXPLAINED* 28 (5<sup>th</sup> ed. 2009) [hereinafter HEALY—PSYCHIATRIC DRUGS].

172. Najib, *supra* note 101, at 420.

173. Divac et al., *supra* note 5, at 1.

174. *Id.*

175. H. Meltzer & B. Massey, *The Role of Serotonin Receptors in the Action of Atypical Antipsychotic Drugs*, 11 *CURRENT OPINION PHARMACOLOGY* 59, 60 (2011).

176. *See* WHITAKER & COSGROVE, *supra* note 124, at 77–85.

177. Divac et al., *supra* note 5, at 2.

178. *Id.*

179. WHITAKER & COSGROVE, *supra* note 124, at 85.

improve specific symptoms, [and] have no clearly different side effect profiles” than their predecessors.<sup>180</sup>

Antipsychotic drugs alleviate the major disruptive manifestations of psychosis, but their side effects are sometimes equally disruptive.<sup>181</sup> While they are designed for patients suffering from psychoses, within the psychiatric profession, their prescription—even to the patient suffering from psychosis—is controversial due to the long-term risks associated with their use.<sup>182</sup> Yet, SGA prescription in the U.S. almost tripled between 1995 and 2008, expanding to over 16 million prescriptions for aripiprazole (Abilify), clozapine (Clozaril) and quetiapine (Seroquel).<sup>183</sup> Disconcertingly, according to a study by Stanford University and the University of Chicago surveying over 1,700 physicians, fifty-percent of those prescriptions in 2008 were for uses not supported by scientific evidence.<sup>184</sup> If such a large number of antipsychotics prescriptions are written for indications and populations never studied, then what valid purposes are they serving? Closer examination of these off-label uses shows that

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180. *Id.* (quoting Peter Tyrer & Tim Kendall, *The Spurious Advance of Antipsychotic Drug Therapy*, 373 LANCET 4, 4-5 (2009) for the proposition that “[t]he spurious invention of the atypicals can now be regarded as invention only, cleverly manipulated by the drug industry for marketing purposes and only now being exposed. But how is it that for nearly two decades we have been beguiled into thinking they were superior?”).

181. McCarron, *supra* note 165, at 483 n. 36 (footnotes omitted). One recipient of a psychotropic injection depicts his experience this way:

There is no other feeling like it. Nothing to relate it to, no experience anyone would normally go through in their life. It affects you mentally and physically and you feel suicidal. The physical effects are so bad you can't stand it. . . . You get so tired (as if you've been up three days in a row) you lie down. But you can't stay down for more than three or four minutes because your knees begin to ache, an itching type ache. . . . Your thoughts are broken, incoherent; you can't hold a train of thought for even a minute. You're talking about one subject and suddenly you're talking about another. . . . Your mind is like a slot machine, every wheel spinning a different thought.

Opton, *Psychiatric Violence Against Prisoners: When Therapy is Punishment*, 45 MISS. L. J. 605, 641 (1974).

182. McCarron, *supra* note 165, at 477 (footnote omitted).

183. Smith, *supra* note .

184. *Id.*

claims of legitimate clinical treatment purposes are often suspect, and sometimes clearly spurious.

1. Sedation, Control, and Punishment, Not Treatment

An antipsychotic's immediate effect on patients is sedative.<sup>185</sup> By influencing chemical transmissions in the brain, antipsychotics sedate the patient suffering from schizophrenia “and suppress psychotic symptoms such as delusions, hallucinations, and other disorders.”<sup>186</sup> Antipsychotic drugs do not cure the patient of mental illness, but may limit some of the more burdensome symptoms.<sup>187</sup> Some authorities maintain that with proper drug maintenance and therapy, relapse can be prevented for a substantial number of patients who suffer from schizophrenia.<sup>188</sup> However, given the myriad severe side effects, many psychiatric patients suffering from psychosis justly wish to refuse antipsychotics and instead elect to suffer through psychotic episodes.<sup>189</sup>

Extremely problematic are uses of antipsychotic drugs for non-treatment purposes, such as convenience of nursing home staff or to discipline or control nonpsychotic persons in custody or confinement.<sup>190</sup> Extensive exposition on these questionable uses is beyond the scope of this Article, but it is noteworthy here that in many instances, clinical treatment of an individual's mental illness is not the primary purpose of prescribing antipsychotics.<sup>191</sup>

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185. McCarron, *supra* note 165, at 482 n. 33 (citing R. Byck, *Drugs and the Treatment of Psychiatric Disorders*, in THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 158 (L. Goodman & A. Gilman eds., 1975)).

186. *Id.* at 481; *See also* Vicki Anderson, *Right to Refuse Antipsychotic Medication: A Proposal for Legislative Consideration*, 17 IND. L. REV. 1035, 1038–39 (1984).

187. McCarron, *supra* note 165, at 481 (citing E. Symonds, *Mental Patient's Rights to Refuse Drugs: Involuntary Medication as Cruel and Unusual Punishment*, 7 HASTINGS CONST. L. Q. 701, 704 (1980)).

188. *Id.* at 705 n. 22.

189. *Id.*

190. *Id.* at 484 (footnote omitted); *see* Part II.B, *infra*.

191. *See, e.g.*, *US: Nursing Homes Misuse Drugs to Control Residents*, HUM. RIGHTS WATCH (Feb. 5, 2018, 3:01 AM), <https://www.hrw.org/news/2018/02/05/us-nursing-homes-misuse-drugs-control-residents> [<https://perma.cc/BCV5-GAF9>].

In prison settings, the reason of “dangerousness to others” may permissibly be used to justify forced administration of antipsychotics, despite the availability of less intrusive or harmful measures.<sup>192</sup>

## 2. Other Side Effects

While antipsychotics have some positive effects for patients—like the ability of a patient suffering from schizophrenia to function at home and even in the workforce—the increased freedom often comes with a high price.<sup>193</sup> Some negative side effects will cease upon discontinuation of medication, but others are “serious, long-lasting and potentially more disruptive than the illness itself.”<sup>194</sup> Studies have shown that when antipsychotics are used to treat patients suffering from schizophrenia, the presence of extrapyramidal side effects go undetected and, though recommended by the American Psychiatric Association (APA), documentation of significant adverse effects is not routine.<sup>195</sup>

Extrapyramidal side effects include akathisia/Parkinsonian syndrome, dystonia and akinesia.<sup>196</sup> Akathisia/Parkinsonian syndrome often is thought of as “the jitters,” and is a nonpermanent condition where the patient feels restless, cannot remain still and feels compelled to move and pace.<sup>197</sup> Interestingly, research on akathisia shows that this very side effect, caused by the antipsychotic, frequently is misdiagnosed as a symptom of psychosis.<sup>198</sup> Often, the result of this faulty inference is physician-ordered dosage increases of the culpable antipsychotic

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192. *See* *Washington v. Harper*, 494 U.S. 210, 217 (1990).

193. McCarron, *supra* note 165, at 482.

194. *Id.* at n. 29 (citing Steven Shobat, *Pathway Through the Psychotropic Jungle: The Right to Refuse Psychotropic Drugs in Illinois*, 18 J. MARSHALL L. REV. 407, 411 (1985)).

195. Najib, *supra* note 101, at 442–43.

196. McCarron, *supra* note 165, at 482 (footnotes omitted).

197. *Id.* at n. 30 (quoting E. MAGGIO, *THE PSYCHIATRY-LAW DILEMMA* 225 (1981)).

198. *Id.*; *see also* HEALY—PSYCHIATRIC DRUGS, *supra* note 171, at 31 (stating akathisia is possibly the most serious side effect of antipsychotics).

medication.<sup>199</sup> Dystonia involves muscular spasms, primarily in the head and neck, often combined with odd facial grimaces and tongue spasms.<sup>200</sup> Akinesia has the effect of restricting a patient's movements, even making the patient feel as though in a straitjacket.<sup>201</sup> Just one dose has the power to make anyone appear to be suffering from schizophrenia,<sup>202</sup> because if the akinesiac effect is severe, then it can result in a patient "sitting motionless in one place, almost like a zombie."<sup>203</sup> All three—akathesia/Parkinsonian syndrome, dystonia and akinesia—can be minimized by lowering the dosage, discontinuation, or by use of anti-Parkinsonian drugs.<sup>204</sup>

TD is the most devastating side effect, largely because oftentimes it is irreversible, even upon discontinuation of the antipsychotic.<sup>205</sup> TD includes "involuntary, rhythmic movements of the face, mouth, tongue, and jaw."<sup>206</sup> While SGAs have a lower incidence of TD than first generation antipsychotics,<sup>207</sup> the risk of developing TD with either type of antipsychotic is believed to increase as a patient's lifetime dose increases.<sup>208</sup> Serious side effects more often associated with SGAs include hormonal changes (i.e. an increase in the level of prolactin through D2 receptor binding),<sup>209</sup> in addition to metabolism changes, major

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199. McCarron, *supra* note 165, at 482 (citing Symonds, *supra* note 187, at 707–08).

200. *Id.* at n. 31 (quoting Symonds, *supra* note 187, at 707 n. 37).

201. HEALY—PSYCHIATRIC DRUGS, *supra* note 171, at 29.

202. *Id.*

203. *Id.*

204. McCarron, *supra* note 165, at 482 (footnotes omitted).

205. *Id.* at 482.

206. *Id.* (footnote omitted).

207. Maren Carbon *et al.*, *Tardive Dyskinesia Risk with First- and Second-Generation Antipsychotics in Comparative Randomized Controlled Trials: A Meta-Analysis*, 17 WORLD PSYCHIATRY 330, 336 (2018).

208. *Id.* at 332.

209. *Id.* An increased prolactin level can cause breasts to develop in boys and men (with lactation) and lactation to begin in non-nursing women. HEALY—PSYCHIATRIC DRUGS, *supra* note 171, at 34–5; *see also* Steven Brill, *America's Most Admired Lawbreaker*, HUFFINGTON POST, <http://highline.huffingtonpost.com/miracle-industry/americas-most-admired-lawbreaker/> [<https://perma.cc/>

weight gain,<sup>210</sup> and an increased risk of irreversible diabetes.<sup>211</sup> These metabolic changes are known as “metabolic syndrome.” Among other side effects are demotivation, sexual side effects, skin rashes, dry mouth and compulsive drinking, aggression and impatience, neuroleptic malignant syndrome, cardiovascular conditions, epilepsy, suicide and severe withdrawal effects.<sup>212</sup>

Though absurd and unexpected in this age of evidence-based medicine, there are instances where “evidence” has been created in order to defend against and disprove adverse events appearing in clinical-trial data.<sup>213</sup> For example, following concerns in the mid-1990s that Zyprexa, an antipsychotic, might cause diabetes, Eli Lilly dug through history to revive an association between psychosis and diabetes “documented” by Henry Maudsley in 1879.<sup>214</sup> The company then authored or sponsored articles that liberally used this anecdotal “evidence” as support for a causal connection between schizophrenia and diabetes—asserting that it was the schizophrenia “after all, and not Zyprexa, that was causing the problem.”<sup>215</sup> There were no published objections either in the U.S. or Europe from members of the psychiatric profession.<sup>216</sup> In a 2004 study examining 396 patients suffering

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D2EB-MFFB] (last visited Dec. 7, 2018) (documenting a class-action lawsuit against Johnson & Johnson for adverse side effects from Risperdal).

210. David Arterburn et al., *Antipsychotic Medications and Extreme Weight Gain in Two Health Systems*, 10 OBESITY RES. & CLINICAL PRAC. 408, 409 (2016).
211. JULIE HOLLAND, MOODY BITCHES 315–16 (2015); *See also* Najib, *supra* note 101, at 434 n. 88.
212. HEALY—PSYCHIATRIC DRUGS, *supra* note 171, at 33–41. As is the case with antidepressants, withdrawal effects from antipsychotics can be misinterpreted by both the psychiatrist and patient as evidence that the medication is needed, and can bolster the sometimes-inaccurate assumption that the treatment and not “placebo factors have brought about a clinical response.” *Id.* at 59. In such instances, where an antipsychotic is being used off-label because there have been no clinical studies to either support or refute assumptions regarding efficacy, “science” is no more than a guess.
213. DAVID HEALY, PHARMAGEDDON 218 (2012).
214. *Id.*
215. *Id.*
216. *Id.*



from psychosis, not a single one had type-2 diabetes.<sup>217</sup> Once treated with antipsychotics, these patients developed diabetes at twice the normal rate.<sup>218</sup> Yet, most physicians have been swayed by the anecdote repeatedly “reported” by pharmaceutical manufacturers.<sup>219</sup>

Psychiatric patients suffering from schizophrenia or other psychosis-inducing illnesses may feel that treatment with antipsychotics is quite beneficial. While this is not always the case, these individuals and their physicians may have assessed that the risks of adverse side effects are justified by the benefits of being able to live without psychosis. In instances where antipsychotics are used to sedate and control people in institutional settings, such as prisons and nursing homes, it is doubtful that a meaningful balancing of risks versus benefits is even contemplated: if it is, risks to the ward or patient seem to be given less weight than the benefit of alleviating burdens on institution staff-members. For any person not suffering from psychosis, justification for using antipsychotics in the risk/benefit analysis is quite thin.

*B. Prevalence of Antipsychotic Use in Nonpsychotic Patient Population*

Diagnosis in the realm of psychiatry is inexact and imperfect, thus psychiatrists often face challenges in determining which medications will be appropriate for a particular patient. In instances where definitive diagnosis is difficult, it is not uncommon that a psychiatrist attempting to achieve the best outcome might prescribe multiple medications, some of them off label.<sup>220</sup> Confronted with confusing or contradictory symptoms,

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217. *Id.* (citing Joanna Le Noury et al., *The Incidence and Prevalence of Diabetes in Patients with Serious Mental Illness in North West Wales: Two Cohorts 1875–1924 and 1994–2006 Compared*, 8 BMC PSYCHIATRY 67 (2004).).

218. *Id.*

219. *Id.*

220. Andrew McKean & Erik Monasterio, *Off-Label Use of Atypical Antipsychotics Cause for Concern?*, 26 CNS DRUGS 383, 384, (2012) (citing D.C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCH. INTERN. MED. 1021–26 (2006); D. Leslie et al., *Off Label Use of Antipsychotic Medications in the Department of Veterans Affairs Health Care System*, 60(9) PSYCHIATRIC SERVS. 1175–81 (2009); Haw C & Stubbs J., *A Survey of the Off-Label-Use of Mood Stabilizers in a Large Psychiatric*

“physicians can pull from a hat some case from the past and make their recommendation, often leading to the patient’s recovery.”<sup>221</sup> But mechanisms by which psychiatrists gather information from and about patients are uncertain, and (even if obtained from the patient directly) the information may be unreliable and merely anecdotal.<sup>222</sup> Misdiagnosis in psychiatry has been estimated to be as high as fifty percent, and nonpsychotic patients who may be perceived as exhibiting some symptoms of the disease, or none at all, may be prescribed antipsychotics inappropriately.<sup>223</sup>

1. Just a Little Bit Can’t Hurt, Can it?

Prescription of antipsychotics “should be restricted to only those patients for whom no alternative treatment is available.”<sup>224</sup> Increasingly, however, SGAs are prescribed as mood stabilizers. For example, FDA has granted approval for treating bipolar disorder with the following medications: Risperdal, Abilify and Seroquel.<sup>225</sup> While some of the newer indications are approved by FDA, most are not.

U.S. office-based psychiatrists increasingly are prescribing two or more psychotropic medications concurrently; the combination of antidepressants and antipsychotics is prevalent, and many times the antipsychotics are prescribed off label.<sup>226</sup> This

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*Hospital*, 19 J. PSYCHOPHARMACOLOGY 402–7 (2005); K. Martin-Latry et al., *A One-Day Survey of Characteristics of Off-Label Hospital Prescription of Psychotropic Drugs*, 40(3) PHARMACOPSYCHIATRY 116–20 (2007)).

221. DAVID J. ROTHMAN, STRANGERS AT THE BEDSIDE: A HISTORY OF HOW LAW AND BIOETHICS TRANSFORMED MEDICAL DECISION MAKING 7 (2003).

222. *Id.*

223. McCarron, *supra* note 165, at 483 (footnotes omitted).

224. Najib, *supra* note 101, at 443.

225. HOLLAND, *supra* note 211, at 315.

226. Lone Baandrup & Marie Kruse, *Incident Users of Antipsychotics: Who Are They and How Do They Fare?*, 51 SOC. PSYCHIATRY & PSYCHIATRIC EPIDEMIOLOGY 505, 506, 511 (2016) (citing R. Mojtabai & M. Olfson, *National Trends in Psychotropic Medication Polypharmacy in Office-Based Psychiatry*, 67 ARCH. GEN. PSYCHIATRY 26 (2010)). In addition to a lack of evidence of efficacy, the potential for drug-drug interactions and increased side effects is often a real but unnecessary burden on patients. *Id.* at 511.

is often referred to as adjunctive therapy.<sup>227</sup> A U.S. national survey concluded that efficacy was not proved for these off-label uses and risk-benefit ratios and outcomes were uncertain.<sup>228</sup> Efforts are needed to place limits on off-label uses of antipsychotics, reserving these uses for very specific and otherwise treatment-resistant conditions.

While in some instances psychiatrists are prescribing lower doses for their nonpsychotic patients than they would for treating FDA-approved indications (for example, schizophrenia),<sup>229</sup> lower doses of SGAs are not without risk. Still, these lower doses are commonly prescribed off label to “treat” anxiety, agitation, and insomnia, and there may be an assumption that the use of these drugs in lower doses will significantly mitigate risks of metabolic adverse effects.<sup>230</sup> This assumption is faulty. Chronic, low-dose use of adjunctive antipsychotic medication in treating depression has been found to result in increased blood lipids, triglycerides and glucose, with attendant weight gain and increased risk of Type II diabetes.<sup>231</sup> For example, one study looked at patients between ages nineteen and sixty-five who were prescribed low-dose quetiapine (mean daily dose of 120 mg at the end of the study) in treating insomnia: over an 11-month period there were significant changes in weight (mean increase of 4.9 pounds) and body mass index (mean increase of 0.8).<sup>232</sup> Clearly, off-label use

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227. *Id.* at 506.

228. *Id.* at 511.

229. *Antipsychotic Drugs a Last Resort for These 5 Conditions: Safety Issues Are a Concern When Used Off-Label to Treat Anxiety, ADHD, Depression, Insomnia, and PTSD, Our Analysis Finds*, CONSUMER REPORTS (Dec. 2013), <https://www.consumerreports.org/cro/2013/12/treating-anxiety-adhd-depression-insomnia-and-ptsd-with-newer-antipsychotics/index.htm> [<https://perma.cc/R92Y-AMGQ>] [hereinafter *Antipsychotic Drugs a Last Resort*].

230. McKean & Monasterio, *supra* note 220, at 387 (citing M. Cates et al., *Metabolic Consequences of Using Low Dose Quetiapine for Insomnia in Psychiatric Patients*, 45 CMTY. MENTAL HEALTH J. 25M (2009)).

231. Ping Wang, *Use of Antipsychotics in the Treatment of Depressive Disorders*, 25 SHANGHAI ARCHIVES OF PSYCHIATRY 134, 138 (2013).

232. McKean & Monasterio, *supra* note 220, at 387 (citing M. Cates et al., *Metabolic Consequences of Using Low Dose Quetiapine for Insomnia in Psychiatric Patients*, 45 CMTY. MENTAL HEALTH J. 25M (2009)); *See also* Holly V. Coe & Irene S. Hong, *Safety of Low*

of antipsychotics has potential to harm, but because these uses are not universally monitored or regulated, concrete information about side effects in the nonpsychotic population is not readily available.<sup>233</sup>

## 2. Vulnerable Populations

Particularly worrisome is the off-label prescription of antipsychotic drugs to members of vulnerable populations.<sup>234</sup> Most commonly, this is a situation in which there is no psychosis but perhaps a desire by psychiatrists, caretakers and society to control, keep still or quiet the patient. One might expect that the U.S. Department of Health and Human Services (HHS) would set an example of proper standards for addressing potential vulnerability in the psychiatric community through the department's regulation of human subjects research with this population. However, this is not the case.<sup>235</sup> HHS, and FDA for that matter, have no special regulations governing research in the psychiatric patient population.<sup>236</sup> Regarding criteria for IRB

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*Doses of Quetiapine When Used for Insomnia*, 46 THE ANNALS OF PHARMACOTHERAPY 718, 719 (2012).

233. McKean & Monasterio, *supra* note 220, at 386.

234. McCarron, *supra* note 165, at 484.

235. With recent changes to the Common Rule, 83 Fed. Reg. 28518, 28518 (June 19, 2018) (to be codified at 45 C.F.R. § 46), there is no longer reference to “mentally disabled” subjects. Now, “impaired decision-making capacity” has replaced “mentally disabled” as a new but likewise vague concept, and IRBs are tasked with delineating this concept on a protocol-by-protocol basis. See Elisa A. Hurley, *From the Director: “Vulnerability” in the Revised Common Rule*, AMP&RSAND (Sept. 12, 2017), <https://blog.primr.org/vulnerability-revised-common-rule> [<https://perma.cc/6VXZ-CC74>]. The revised Common Rule refers to impaired decision-making capacity in the context of subjects who are vulnerable to coercion or undue influence. 45 C.F.R. § 46.111(b) (2019); As with the original Common Rule (45 C.F.R. pt. 46C, § 46.111(a)(3)), the definition of vulnerability is difficult to pin down. For years, scholars have attempted to forge meaning where little guidance has been provided. See, e.g., David Wendler, *A Pragmatic Analysis of Vulnerability in Research*, 31 BIOETHICS 515, 520 (2017).

236. Philip T. Yanos et al., *Research Risk for Persons with Psychiatric Disorders: A Decisional Framework to Meet the Ethical Challenge*, 60 PSYCHIATRIC SERVS. 374, 376 (2009).

approval in the context of clinical drug research, FDA regulations state:

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or *mentally disabled persons*, or economically or educationally disadvantaged persons, are *likely to be vulnerable to coercion or undue influence* additional safeguards have been included in the study to protect the rights and welfare of these subjects.<sup>237</sup>

Our federal research regulations provide no concrete instructions on how to protect mentally disabled or mentally ill individuals in research, nor is there any department or agency guidance regarding how to limit the risks to which these subjects may be exposed in clinical research.<sup>238</sup> The term “mentally disabled persons” is not defined and could result in various interpretations. It might mean only instances involving permanent impairment of decision-making ability, for example, dementia or brain injury; or, it might also include other instances that involve temporary impairment, such as an episode of mania-induced psychosis.<sup>239</sup> Physicians, researchers and IRB members need more consistency and clarity in this area. This lack of clarity in the research setting is reflective of the wide deference that U.S. law has allowed psychiatrists in determinations relating to treatment of mentally ill patients.<sup>240</sup> It is not a stretch to conceive

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237. Note that unlike the revised Common Rule, FDA’s regulation retains its reference to “mentally disabled persons.” 21 C.F.R. § 56.111(b) (2019) (emphasis added).

238. Resnik points to the diversity within the mentally disabled and mentally ill populations that makes it not necessarily appropriate to put them in categories: “[S]ome mentally ill or disabled adults may have good decision-making abilities, while others may not. Also, some may be able to make decisions under certain conditions . . . but not [under] others.” DAVID B. RESNIK, *THE ETHICS OF RESEARCH WITH HUMAN SUBJECTS*, 218, 227 (2018).

239. See Lindy Marie Fields & James Douglas Calvert, *Informed Consent Procedures with Cognitively Impaired Patients: A Review of Ethics and Best Practices*, 69 *PSYCHIATRY & CLINICAL NEUROSCI.* 462, 463–64 (2015).

240. See, e.g., *Buck v. Bell*, 274 U.S. 200, 200 (1927) (supporting a Virginia eugenics law, allowing sterilization of people deemed by physicians to be “mentally defective” “imbeciles.”); see also *Washington v. Harper*, 494 U.S. 210, 222 n. 8 (1990) (involving

of the two disciplines—psychiatric clinical research and psychiatric clinical practice—as being inextricably intertwined in the eyes of the law.

In the field of bioethics, there are various types of vulnerability that are considered to affect a patient’s decision making. The most relevant in the context of the psychiatrist-patient relationship may be deferential vulnerability, cognitive vulnerability, economic vulnerability, and social vulnerability.<sup>241</sup> With deferential vulnerability “the subordination is affected not by *formal hierarchies* . . . but instead by *informal* ones [that may] be socially constructed,” for example, those related to “gender, race, or class inequalities,” or “inequalities of power and knowledge of the kind that occur in doctor-patient relationships.”<sup>242</sup> Deferential vulnerability may often be subtle,<sup>243</sup> but is likely present in most psychiatrist-patient relationships. With cognitive vulnerability, a patient may lack the ability to understand, for a variety of reasons, the risks of using a drug off label. A patient may lack sophisticated education and resources for learning due to economic disadvantages. With social vulnerability, a patient might possess the “cognitive capacity to consent,” yet be part of a group perceived by society through the lens of stereotypes that deflate the value of these individuals, their interests, welfare and contributions to society.<sup>244</sup> Psychiatrists are not immune to viewing patients through the lens of the stereotype.

FDA vaguely affords protections for subjects suffering from mental illness by instructing IRBs to assure adequate safeguards for the undefined category of “mentally disabled” subjects who

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forced antipsychotic medication of incarcerated inmates) (“[W]e will not assume that physicians will prescribe [antipsychotics] for reasons unrelated to the medical needs of the patients; indeed, the ethics of the medical profession are to the contrary. This consideration supports our interpretation of the State’s Policy as ensuring that antipsychotic medications will be administered only in those cases where appropriate by medical standards.”) (citations omitted).

241. COLEMAN ET AL., *supra* note 10, at 141–44 (citing ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS, NAT’L BIO. ADVISORY COMM’N 85–92 (2001)).

242. *Id.* at 143 (emphasis in original).

243. *Id.*

244. *Id.* at 144.

are likely to be vulnerable to coercion or undue influence.<sup>245</sup> However, federal law leaves the potentially vulnerable psychiatric *patient* open to possible exploitation—intentional or not—by physicians who in clinical practice prescribe antipsychotic drugs never studied for their particular disease or population.<sup>246</sup>

### 3. Children, Especially Foster Children

Among the existing antipsychotics, risperidone (the generic for Risperdal) is the drug used most frequently in the child-patient population.<sup>247</sup> There has been little official research on the use of antipsychotic drugs in the child-patient population, particularly off-label uses.<sup>248</sup> The consequence of this widespread off-label use is that many children are, in effect, enrolled “in a

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245. 21 C.F.R. § 56.111(a)(3) (2019).

246. Note that the Common Rule provides protections to everyone else, provided that the clinical study is connected to federal funding. While not applicable in the FDA setting, the revised Common Rule no longer aligns with FDA’s regulation. *See* COLEMAN ET AL., *supra* note 10, at 175–76 (“There are three ways in which a study might be subject to the federal regulations governing human subject protection: (1) the study is conducted or funded by the federal government; (2) the study is conducted at an institution that has agreed, in the assurance it entered into with the federal government, to apply the Common Rule to all research taking place at that institution; or (3) the study concerns something that brings it within the jurisdiction of the FDA.”). From the perspective of those who favor regulation, a compelling argument could be made—and perhaps has been made—regarding the chasm in protections for subjects in privately funded research that is neither drug related nor government funded, and the urgent need for protective action in this area. This inquiry is beyond the scope of the Article.

247. JASLEEN SALWAN ET AL., APPLICATION FOR INCLUSION TO THE 19TH EXPERT COMMITTEE ON THE SELECTION AND USE OF ESSENTIAL MEDICINES: RISPERIDONE, WORLD HEALTH ORG. (Jan. 6, 2013), available at [https://www.who.int/selection\\_medicines/committees/expert/19/applications/Risperidone\\_24\\_A\\_Ad\\_Final.pdf](https://www.who.int/selection_medicines/committees/expert/19/applications/Risperidone_24_A_Ad_Final.pdf) [<https://perma.cc/LV2X-DVKK>].

248. *Are Too Many Kids Taking Antipsychotic Drugs? Use Is Climbing Despite Questions About How Safe the Drugs Are and How Well They Work*, CONSUMER REPS. (Dec. 2013), <https://www.consumerreports.org/cro/2013/12/are-too-many-kids-taking-antipsychotic-drugs/index.htm> [<https://perma.cc/2SPL-PQ6X>] [hereinafter *Too Many Kids*].

sort of large, poorly controlled experiment.”<sup>249</sup> Truly evidence-based standards of care are required if there is any chance of understanding how best—if at all—to use psychotropic medications off label.<sup>250</sup> Some scholars suggest that NIH, private foundations, and the pharmaceutical industry should “study long-term clinical and developmental effects of antipsychotic use by children,<sup>251</sup> and . . . support research on potentially safer pharmacological interventions, as well as psychosocial interventions for disruptive behavior and emotional disorders of children.”<sup>252</sup>

In the early 2000s, fraudulent positive-clinical-trial results for the antidepressants Paxil and Zoloft allowed these two medications, later shown to cause suicidal thinking and addictive

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249. *Id.*

250. *Id.* (citing Helen Egger, M.D., Chief of Child and Family Mental Health and Developmental Neuroscience in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center).

251. Wacker et al., *The Protection of Subjects in Clinical Research, in DRUG INJURY: LIABILITY, ANALYSIS AND PREVENTION*, 95–109, 99 (James T. O’Donnell ed., 3d ed. 2012) (“Despite the need for pediatric drug studies, many argue that clinical studies put children at risk, for a multitude of reasons. Others believe that the benefit outweighs the risk. After all, clinical trials place a small number of children at risk (in a controlled environment). Furthermore, the children enrolled in clinical studies will have illnesses and, therefore, stand to (hopefully) benefit from the experimental treatment. The ultimate benefit will be appropriate pediatric labeling for the drug and safe use on children in the future.”). In 2013, FDA adopted a final version of rules requiring that drug trials in the child population comply with Subpart D of HHS regulations, providing additional protections for research involving children. COLEMAN ET AL., *supra* note 10, at 592 (citing Food and Drug Administration, *Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products*, 78 Fed. Reg. 12,937 (Feb. 26, 2013)). Research can (and probably should) be conducted in child populations with extra safeguards in place. *See id.* at 590–91.

252. *Use of Antipsychotic Medications for Nonpsychotic Children: Risks and Implications for Mental Health Services*, in 18 THE BROWN UNIV. CHILD & ADOLESCENT PSYCHOPHARMACOLOGY UPDATE 6 (Mar. 2016) (Jeffrey I. Hunt, M.D. ed.) [hereinafter *Brown Univ. Antipsychotics*] (citing Daviss et al., *Use of Antipsychotic Medications for Nonpsychotic Children: Risks and Implications for Mental Health Services*, PSYCHIATRY SERV. (Jan. 4, 2016)).



qualities in children, to be prescribed off label to this vulnerable group.<sup>253</sup> These examples of off-label antidepressant use in children showcase “the greatest known divide in medicine”—the discrepancies between what is reported in scientific literature and what raw data actually show—and this problem likely extends to all types of off-label treatments.<sup>254</sup> This fraudulent activity shows “how far our scientific standards have slipped and how this impinges on our ability to care for some of the most vulnerable people there are.”<sup>255</sup>

One of our most vulnerable populations, children in foster care or the juvenile justice system, are the most likely to be prescribed antipsychotic medication.<sup>256</sup> A 2011 Government Accountability Office (GAO) report found that in 2008, children in foster care in five sample states were prescribed antipsychotic drugs at higher rates than children not in the foster care system.<sup>257</sup> The report found that foster children were sometimes four-and-a-half times more likely to be prescribed psychotropic medication than their non-foster child counterparts within the Medicaid system.<sup>258</sup> The report also found that hundreds of children in the five states had drug regimens of five or more psychotropic drugs—including antipsychotics—despite the fact that there is no medical evidence supporting concurrent use of this many drugs by children.<sup>259</sup>

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253. WHITAKER & COSGROVE, *supra* note 124, at 102–07.

254. HEALY—PSYCHIATRIC DRUGS, *supra* note 171, at 148–49.

255. *Id.* (“[t]he published papers endorsing the use of Paxil, Prozac, and Zoloft remain in print in the best journals and continue to fuel a boom in off-label sales of these drugs to children. There have been efforts to get [the fraudulent] study retracted but these have failed. It continues to be built into guidelines supporting the use of antidepressants for children.”).

256. *Brown Univ. Antipsychotics*, *supra* note 252, at 6.

257. U.S. GOV'T ACCOUNTABILITY OFF., GAO-12-201, FOSTER CHILDREN: HHS GUIDANCE COULD HELP STATES IMPROVE OVERSIGHT OF PSYCHOTROPIC PRESCRIPTIONS 12 (2011) [hereinafter *GAO-12-201*]. The children studied in the GAO report—both those in foster care and not in foster care—were enrolled in the Medicaid programs of Florida, Massachusetts, Michigan, Oregon, and Texas. *Id.* at 8.

258. Smith, *supra* note 170.

259. *GAO-12-201*, *supra* note 257, at 14.

The drastic increase (an approximate tripling) in prescriptions of antipsychotic drugs to children since the early 2000s is not the result of a sudden schizophrenia epidemic or other forms of serious mental illness in children. Rather, it stems from doctors' use of these medications to "treat" behavioral issues, a "treatment" that FDA has not approved.<sup>260</sup> A disproportionate number of these prescriptions are being written for disadvantaged poor and minority children as young as age 2.<sup>261</sup> Economically disadvantaged children are increasingly vulnerable to the effects of medications because of their developing brains and bodies, and also because of stigma attached to mental illness, behavioral/adjustment issues, and the condition of living in poverty.<sup>262</sup>

According to a related 2015 Department of Health and Human Services Office of Inspector General (OIG) study on Medicaid-enrolled children, two or more quality-of-care concerns were found in 49 percent of claims for SGAs, and 53 percent of claims were identified as lacking monitoring for physiological and behavioral changes,<sup>263</sup> including measuring of height and weight, taking vital signs and blood pressure, noting abnormal involuntary movements, ordering laboratory tests (for example, tests of liver function, and for blood glucose and lipid levels), and electrocardiograms.<sup>264</sup> Amid the overwhelming lack of monitoring, reviewers identified failure of healthcare providers to recognize or manage side effects of antipsychotic use, such as akathisia, significant weight gain, insomnia, and edema.<sup>265</sup> Only eight percent of claims made for SGAs were related to prescriptions for the "limited number of medically accepted pediatric

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260. *Too Many Kids*, *supra* note 248.

261. *Id.*

262. *See id.*

263. U.S. DEP'T HHS, OFFICE OF INSPECTOR GENERAL, OEI-07-12-00320 EXECUTIVE SUMMARY: SECOND-GENERATION ANTIPSYCHOTIC DRUG USE AMONG MEDICAID-ENROLLED CHILDREN: QUALITY-OF-CARE CONCERNS 5, 9, 12 (2015), available at <https://oig.hhs.gov/oei/reports/oei-07-12-00320.pdf> [<https://perma.cc/HV7X-5BKZ>] [hereinafter *OEI-07-12-00320*]. The five States included in the OIG study were California, Florida, Illinois, New York, and Texas.

264. *Id.* at 12.

265. *Id.*

indications.”<sup>266</sup> Among the other ninety-two percent of claims, ones not related to prescriptions for medically recognized pediatric indications, SGAs most commonly were prescribed to treat “bipolar disorder (20 percent), mood disorders (13 percent), and autism spectrum disorders (8 percent).”<sup>267</sup> While the state of New York’s Medicaid coverage policy mandated that payment would only issue for SGAs prescribed for “medically accepted indications,” the state program violated its own policy and paid over 3,300 claims, totaling \$773,607.00.<sup>268</sup>

Three of the SGAs included in the OIG study had FDA warnings about an increased chance of suicidal ideation and behavior in children, adolescents, and young adults being treated with these antipsychotics while suffering from major depressive disorder or other psychiatric disorders.<sup>269</sup> However, FDA warnings do not prohibit physicians from prescribing drugs, despite specific warnings, if according to the physician’s judgment, the benefits outweigh the risks.<sup>270</sup> Thirty-seven percent of claims identified in the study were for SGAs prescribed to treat the specific conditions about which FDA had warned: for major depressive and other psychiatric disorders.<sup>271</sup> The report suggested that all children prescribed the warned-of antipsychotics, regardless of their precise diagnosis, need to be properly monitored for suicidal ideation and all other side effects.<sup>272</sup>

It is common and legal for U.S. physicians to prescribe for children drugs that have only been approved for adults.<sup>273</sup> The physician’s ethical dilemma is to withhold a drug that has not been proven safe but that may also be capable of curing disease or alleviating symptoms.<sup>274</sup> While such practices may have begun,

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266. *Id.*

267. *Id.*

268. *Id.* at 13. New York State Medicaid staff stated that because of the lack of diagnosis information on drug claims, the strict coverage policy was difficult to enforce absent a medical record review.

269. *Id.* at 14.

270. *Id.*

271. *Id.* Notably, the broad sweeping “other psychiatric disorders” could apply to any child with any sort of mental health condition.

272. *Id.*

273. Wacker et al., *supra* note 251, at 99.

274. *Id.*

with at least some level of evidence in treating a “small sub-group of youth with significant developmental disabilities,” off-label antipsychotic prescribing has been expanded to treatment of “cognitively normal” young people with a paucity of evidence on safety and efficacy.<sup>275</sup> In comparing two studies, one looking at the period 2005-2009 and one from a decade earlier, antipsychotic prescription increased by approximately 85 percent in the child and adolescent population, a much higher increase than seen in the adult population.<sup>276</sup>

Clinical trials support the efficacy of some antipsychotics for irritability associated with autism in adolescents and children; specifically, risperidone for children as young as age five, and aripiprazole for those six years old and up.<sup>277</sup> Clinical research also supports the efficacy of certain antipsychotics in treating child and adolescent bipolar mania and schizophrenia.<sup>278</sup> However, antipsychotics are *not* approved by FDA to treat attention-deficit hyperactivity disorder (ADHD).<sup>279</sup> Nonetheless, as of 2015, research<sup>280</sup> noted that boys ages 11–17 diagnosed with ADHD

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275. *Too Many Kids*, *supra* note 248 (quoting David Rubin, M.D., Associate Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania).

276. *Id.*

277. *Study Finds Most Young People Treated with Antipsychotics Lack MH Diagnosis*, 25 MENTAL HEALTH WKLY., August 17, 2015, at 1 (Valerie Canady et al., eds.) [hereinafter *Mental Health Weekly*] (citing Mark Olfson et al., *Treatment of Young People with Antipsychotic Medications in the United States*, 72 JAMA PSYCHIATRY 867 (2015)); *see also Too Many Kids*, *supra* note 248 (“Schizophrenia is rarely diagnosed until adulthood, for example. Bipolar disorder is estimated to affect less than 3% of teens, according to the National Institute of Mental Health, but the exact prevalence is unknown because of its difficulty to diagnose in children. That’s partly because the symptoms are less clear and may overlap with other conditions such as ADHD. And while about one in 110 children have some form of autistic disorder, only about 30% are affected by the aggressive impulse behavior antipsychotic drugs have been approved to treat.”).

278. *Id.*

279. *Mental Health Weekly*, *supra* note 277, at 2.

280. *Id.* at 3 (“Researchers noted that in the merged 2009 medical claims and LRx sample, most of the younger children (60%), older children (56.7%), adolescents (62%) and young adults (67.1%) treated with antipsychotics had no outpatient or inpatient claim that included a mental health diagnosis. The study found that among

represented the highest use of antipsychotic treatments in the studied population.<sup>281</sup>

There is concern among some in the psychiatrist community about the extent of off-label prescription of antipsychotics to children.<sup>282</sup> While at risk for all the adverse side effects discussed above in the context of adult patients prescribed antipsychotics, both weight gain and hormonal changes occur more significantly in children than in adults.<sup>283</sup> Additionally, the younger the patient prescribed antipsychotics off label is, “the more . . . [the drug] can affect the developing brain.”<sup>284</sup> Especially in the context of children, long-term effects are harder to determine because their current life experience is short and cannot yet have been studied. Thus, risks have “not been assessed in longitudinal follow-up studies conducted with larger samples.”<sup>285</sup>

Off-label use of antipsychotics in the child population is problematic because it is becoming commonplace, even while studies with this population are lacking. In the case of other drugs commonly prescribed off label for children, for example, to treat physical ailments, there is generally evidence of safety and efficacy through studies with adult populations. In the case of off-label use of antipsychotics, there are no underlying studies with adults, so the drugs are not proven safe or effective in *any* age group. And yet, some of the most vulnerable in the U.S. population—children who are poor—could be viewed to be serving as “human subjects” in an unofficial experiment to test safety and efficacy—at no cost to pharmaceuticals manufacturers.

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antipsychotic-treated children and adolescents with mental disorder claims, the most common diagnosis was ADHD (younger children, 52.5%; older children, 60.1%; adolescents, 34.9%). Depression was the most common diagnosis among young adults (34.5%), followed by bipolar (26.6%) and anxiety disorder (22.9%).”).

281. *Id.* at 2 (“Antipsychotics are used to manage aggression and other symptoms in ADHD.”).

282. Minji Sohn et al., *Nation Trends in Off-Label Use of Atypical Antipsychotics in Children and Adolescents in the United States*, 95 *MED.* 1, 1 (2016).

283. *Brown Univ. Antipsychotics*, *supra* note 252, at 5.

284. *Too Many Kids*, *supra* note 248 (quoting Christopher Bellonci, M.D., Assistant Professor at Tufts University School of Medicine).

285. *Brown Univ. Antipsychotics*, *supra* note 252, at 5.

#### 4. The Elderly and Poor

Although studies show an increased risk of death for elderly patients taking antipsychotic drugs, nursing home physicians across the United States continue to prescribe these drugs to “treat” psychosis and behavioral problems caused by dementia.<sup>286</sup> All antipsychotic drug labels carry the strongest warning, called a “black box” warning, about the risk of stroke and death when taken by patients with dementia.<sup>287</sup>

In the context of evaluating Medicare claims, the OIG study above noted that an earlier OIG report on SGA prescriptions for elderly nursing-home residents found that fourteen percent of those residents had Medicare claims for SGAs.<sup>288</sup> Eighty-three percent of them were prescribed SGAs off label, and eighty-eight percent were for the very conditions identified in the FDA-mandated black-box warning, like dementia.<sup>289</sup> Further, the investigation found that over one-in-five Medicare claims for antipsychotics failed to comply with federal guidelines that prohibit unnecessary or excessive medication of persons in nursing homes.<sup>290</sup>

It is often the case that antipsychotics are prescribed and administered to elderly patients, especially those in nursing homes, in order to sedate and confine the resident—which lessens the care-burden on staff. Treating a mental illness like schizophrenia is generally not the purpose.<sup>291</sup> According to the most recent APA guidelines on using antipsychotics to treat agitation or psychosis in dementia patients, these drugs should only be used in emergency settings when symptoms are severe and situations dangerous.<sup>292</sup> Yet, interestingly, under Medicare’s

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286. McCarron, *supra* note 165, at 484.

287. *Antipsychotic Drugs a Last Resort*, *supra* note 229.

288. *OEI-07-12-00320*, *supra* note 263, at 6.

289. *Id.*

290. Smith, *supra* note 170.

291. See HUM. RIGHTS WATCH, *supra* note 191.

292. Martin R. Farlow & Tatyana A. Shamliyan, *Benefits and Harms of Atypical Antipsychotics for Agitation in Adults with Dementia*, 27 EUR. NEUROPSYCHOPHARMACOLOGY 217–231 (2017) (citing V.I. Reus et al., *The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or*

Part D prescription-drug plan, antipsychotics are one of six drugs considered to belong to a “protected class,” meaning that “permissive compendium ratings may virtually guarantee reimbursement of off-label prescription claims.”<sup>293</sup>

In the case of poor families, they may lack resources and the ability for self-advocacy, and prescribers may opt to use antipsychotics as a quick and inexpensive fix to control behavior.<sup>294</sup> Economically disadvantaged people may lack access to mental health professionals who provide psychosocial interventions,<sup>295</sup> either because these professionals do not practice in underserved neighborhoods, or they do but their fees are exorbitant and prohibitive.<sup>296</sup>

A lack of financial resources appears to be a relevant factor in the likelihood that one will be prescribed an antipsychotic off label. Also significant is one’s ability to self-advocate, or the absence of such ability. Elderly persons living in nursing homes, children, and people who are economically disadvantaged lack agency due to various circumstances—confinement to the facility due to infirmity, no legal autonomy, and insufficient financial means for alternative treatment—and this makes these groups uniquely vulnerable to receiving prescriptions for drugs that are not supported by evidence of safety and efficacy.

This section reviewed the ways in which antipsychotics use has been pushed to the limits, and beyond. Medications that were originally developed to treat a specific set of symptoms and certain severe mental illnesses have quietly gained legitimacy for the treatment of less burdensome diseases, with no evidence of safety and efficacy. The balancing of risks and benefits, especially where serious and long-lasting side effects are implicated, should become a very different equation in the case of the psychiatric

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*Psychosis in Patients with Dementia*, 173 AM. J. PSYCHIATRY 543–546 (2016)).

293. Richard P. Paczynski et al., *Quality of Evidence in Drug Compendia Supporting Off-Label Use of Typical and Atypical Antipsychotic Medications*, 24 INT’L J. RISK & SAFETY MED. 137, 143 (2012).

294. *Brown Univ. Antipsychotics*, *supra* note 252, at 6.

295. *Id.*

296. *See Too Many Kids*, *supra* note 248 (citing David Rubin, M.D., Associate Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania).

patient who does not suffer from psychosis. But the market is growing exponentially, and beginning with the elderly and the poor, the U.S. government, through Medicare and Medicaid, is subsidizing this expansive use at no cost to drug manufacturers. The questions next addressed are how did we get here, and where were the regulators?

### III. OFF-LABEL SAFETY AND EFFICACY: WHO'S REALLY IN CHARGE HERE?

Significant evidence shows that pharmaceuticals manufacturers manipulated and corrupted clinical trial data and “purchased” expert consensus guidelines for the indications and patient populations ultimately receiving FDA approval relating to antipsychotics, i.e., treatment of psychosis in the patient population suffering from schizophrenia.<sup>297</sup> Because these data on safety and efficacy were distorted for the intended treatment purpose and population, this creates an even more suspect and potentially dangerous outcome for patients prescribed these drugs off label.

#### *A. Anecdotal “Evidence”*

The types of professional writings often laying the groundwork for future, rampant off-label uses range from medical journal articles describing substantive clinical research on evidence-based off-label uses to anecdotal clinical case studies regarding “successful” individual off-label use.<sup>298</sup> Determining the true sources of information can be a challenge, as ghostwriting is a critical problem. In the medical setting, ghostwriting occurs where the actual author of a medical article is not credited—thought by some scholars to be an effort to veil pharmaceutical industry involvement and create an appearance of sponsorship by academia.<sup>299</sup> Under such arrangements, a medical writer drafts the article and it is attributed to a prominent doctor, often one at a major university. While scientific journals often inform about official clinical study results, there are other types of scientific writings, such as editorials, letters to editors, and review

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297. WHITAKER & COSGROVE, *supra* note 124, at 149–50.

298. Barkus & Derian, *supra* note 20, at 863.

299. See ELLIOTT, *supra* note 86, at 33; see also WHITAKER & COSGROVE, *supra* note 124, at 158–59.



articles.<sup>300</sup> These ghostwritten articles and letters influence physicians' decisions to prescribe drugs off label.<sup>301</sup> It is estimated that off-label prescription decision-making is informed by these ghostwritten articles in "up to half of all medical prescriptions—and more for children."<sup>302</sup> Notably, in the cases of the antidepressants Paxil and Zoloft,<sup>303</sup> ghostwriters produced all of the published studies.<sup>304</sup>

In our culture, there is a tendency to associate science with truth, and commerce as something that needs some regulation by government.<sup>305</sup> "The tension between science and commerce"<sup>306</sup> is present at the intersection of the practice of medicine and the business of major pharmaceutical companies. There seems to be a general inclination in the U.S. to extend the notion that "science is truth" to "scientists are truthful."<sup>307</sup> Science, however, is quite commercialized.<sup>308</sup> A pharmaceuticals company will hire science writers to present the company in the light it desires, and favorable opinions are an assumed condition of continued employment.<sup>309</sup> Despite this potential bias, the physician "author" may give the article only a cursory review before signing her name to it. These articles have wide and enduring impacts, often

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300. ELLIOTT, *supra* note 86, at 36 ("Review articles . . . summarize the current state of knowledge about an illness or a therapy based on the author's reading of the published literature."). Elliott notes, however, that not all ghostwriting is unethical. *Id.*

301. HEALY—PSYCHIATRIC DRUGS, *supra* note 171, at 110–11.

302. *Id.* at 111.

303. *See* discussion *supra*, Part II.B.3.

304. *Id.* at 149.

305. *See generally, id.* at 128.

306. ELLIOTT, *supra* note 86, at 34.

307. *Id.*

308. *Id.*; *see also* Anthony Fletcher & Philip Bourne, *Ten Simple Rules to Commercialize Scientific Research*, 8 PLOS COMPUTATIONAL BIOLOGY 1 (2012).

309. ELLIOTT, *supra* note 86, at 36 (quoting medical writer David Bronstein (pseudonym)). Many in the industry view the medical ghostwriter as similar to a secretary, or, being generous, as an editor. *Id.* at 33.

informing decisions on inclusion of off-label uses in the pharmaceuticals compendia.<sup>310</sup>

Some scholars assert that institutional corruption within psychiatric professional organizations affects formulation of consensus practice guidelines (CPGs).<sup>311</sup> While the APA's mission is "to provide 'humane care and effective treatment for all persons with mental disorders,'" pharmaceutical-company funding and guild interests are alleged to have compromised that public health agenda.<sup>312</sup> Rather than meeting its obligations to society to conduct objective research and disseminate only "fully accurate information on the efficacy and safety of [antipsychotic] medications," the APA has allowed (and in some instances facilitated) distortions of "scientific truths" that have led to "significant social injury."<sup>313</sup> Prior to issuance of CPGs, experts in the field may create "consensus guidelines" that influence treatment, and corruption also has been documented at this point.<sup>314</sup>

Whether included in the compendia or not, a well-intentioned individual psychiatrist may read a peer-reviewed journal article—funded by the pharmaceuticals industry and sanctioned by the APA or leaders in the field—and believe he is educating himself about current trends and successes with a particular off-label treatment. Thus, individual-practice psychiatrists who are "surely motivated to see their patients do well, are harmed by this corruption, as well."<sup>315</sup> Some physicians will rely on "experience, anecdotal reports, and opinion leaders to guide their treatment

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310. *See, e.g., id.* at 37–38.

311. WHITAKER & COSGROVE, *supra* note 124, at 148–49.

312. *Id.* at 4–7.

313. *Id.* at 5–6.

314. *Id.* at 149–50 (discussing Janssen's unrestricted \$450,000 grant to three leading academic institutions that employed three prominent academic psychiatrists who "coincidentally" produced an expert consensus guideline on the use of Janssen's Risperdal as a first-line treatment for schizophrenia, later published in the *Journal of Clinical Psychiatry*; through another financial arrangement with the three psychiatrists, it is alleged that Janssen paid them over \$425,000 for speaking engagements to influence state governments' and providers' adoption of the consensus guideline recommendations).

315. *Id.* at 159.

decisions, often failing to demand solid evidence for their prescribing practices.”<sup>316</sup> Alone—with no malfeasance on the part of pharmaceuticals manufacturers or abdication of responsibility on the part of the APA—this professional approach to clinical knowledge can lead to widespread inappropriate prescribing.<sup>317</sup> Whether or not “bad actors” have intentionally manipulated prescribing practices, psychiatrists prescribe antipsychotics off label to nonpsychotic patients with no solid research basis. This has cascaded into widespread acceptance of this off-label use and, ultimately, has modified the standard of care.

*B. Compendia May be Informed by Ghostwriting and Unsubstantiated Evidence*

As stated above, “scholarly” articles that may be improperly influenced by the pharmaceuticals industry, and allowed by either the academic psychiatrist’s inattention to detail or his greed, often inform decisions about whether to include off-label uses in the pharmaceuticals compendia. Compendia are compilations that “describe the evidence and make recommendations regarding different therapeutic applications of FDA-approved drugs.”<sup>318</sup> Congress and the Centers for Medicare and Medicaid Services (CMS) have officially designated several of the compendia as authoritative to inform determinations regarding off-label prescription drug coverage.<sup>319</sup> Both public and private insurers use the drug compendia in making coverage determinations and the compendia are regarded by some as having “de facto authority in off-label reimbursement decisions across a variety of therapeutic

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316. Dresser & Frader, *supra* note 115, at 479–80 (arguing that the medical community has a responsibility to rectify situations where off-label uses lack adequate evidentiary bases, stating that “[h]igh quality evidence about off-label applications not only protects patients from harmful and ineffective interventions, it increases their access to beneficial treatments.”).

317. *Id.*

318. Paczynski et al., *supra* note 293, at 137.

319. *Id.*

classes.”<sup>320</sup> But evidence in the compendia has received scant scrutiny and can be of poor quality.<sup>321</sup>

Clearly, the compendia play an essential role today in evidence synthesis, coverage decisions, and prescription utilization. Greater oversight and effort must be committed to improving both the quality of evidence and transparency of its evaluation as contained in the compendia.<sup>322</sup> But it may already be too late, as certain states have a preference favoring off-label uses. For example, a New Hampshire statute *requires* payment of insurance claims for off-label prescriptions if those non-approved indications are listed in the compendia.<sup>323</sup> This statute provides guaranteed coverage for non-indicated uses so long as they are included in one of the compendia or “medical literature,” which, as discussed above, can be easily influenced by manufacturers through ghostwritten articles later used as “evidence” of safety and efficacy. This statutory scheme eliminates a potential oversight role for insurance companies, and leaves drug manufacturers in the driver’s seat.

### *C. Unfairness of Burdening Large Pharmaceuticals Manufacturers*

There are valid safety and efficacy concerns about introducing mind-altering chemicals approved for treating psychosis into the

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320. *Id.* at 143.

321. *Id.* at 138; *see also* Dresser & Frader, *supra* note 115, at 479 (discussing a review of Medicare-approved compendia that found a lack of consistency, quality, transparency and timeliness).

322. *See* Dresser & Frader, *supra* note 115, at 479. CMS’s Medicare Evidence Development and Coverage Advisory Committee issued guidelines in 2007 on ways to improve information quality and to rationalize processes associated with including citations relating to off-label therapies in the compendia, however, these guidelines primarily applied to drugs used off-label in treating cancer. Paczynski et al., *supra* note 293, at 138.

323. N.H. REV. STAT. ANN. § 415:6-g (1997) (“I. No insurer that issues or renews any individual policy of accident or health insurance providing benefits for medical or hospital expenses and providing coverage for prescription drugs shall: (a) Exclude coverage for any such drug for a particular indication on the ground that the drug has not been approved by the Food and Drug Administration (FDA) for that indication, if such drug is recognized for treatment of such indication in one of the standard reference compendia or in the medical literature.”).

mind of nonpsychotic patients. Multiple studies that compared adverse events relating to approved versus off-label drug uses have shown that there is a higher incidence of adverse drug reactions among patients prescribed medications for off-label purposes.<sup>324</sup> However, some engaged in the debate surrounding off-label uses suggest it is not reasonable to expect pharmaceuticals companies to devote time and financial resources to support additional clinical trials to prove the safety and efficacy of approved drugs for additional purposes.<sup>325</sup>

Those making such assertions offer the rationale that after spending hundreds of millions of dollars supporting the drug's original New Drug Application (NDA), a requirement for additional studies would necessitate replication of efforts and would cost manufacturers additional "hundreds of millions of dollars in new testing and take years."<sup>326</sup> But this is not necessarily true. For example, there exists an abbreviated pathway under FDCA §505(b)(2) for approval of drugs, where an "applicant is not restricted to reliance on published studies, but may also rely on previous FDA findings of safety and efficacy for another applicant's drug based on unpublished data in FDA's files that is no longer legally protected."<sup>327</sup> The 505(b)(2) application also could be used where "an applicant that seeks to market its version of an established drug for a *new therapeutic indication* or with some other modification requiring new clinical studies [wishes to] rely on relevant safety findings on the drug in

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324. Aishwarya Vijay et al., *Patterns and Predictors of Off-Label Prescription of Psychiatric Drugs*, 13(7) PLOS ONE 2 (2018).

325. Michael Ollove, *Pressure Mounts to Lift FDA Restrictions on Off-Label Drugs*, WASH. POST (Oct. 7, 2017, 12:00 PM), [https://www.washingtonpost.com/national/health-science/pressure-mounts-to-lift-fda-restrictions-on-off-label-drugs/2017/10/06/568204a0-a2f6-11e7-8cfe-d5b912fab99\\_story.html?utm\\_term=.46e5b955401e](https://www.washingtonpost.com/national/health-science/pressure-mounts-to-lift-fda-restrictions-on-off-label-drugs/2017/10/06/568204a0-a2f6-11e7-8cfe-d5b912fab99_story.html?utm_term=.46e5b955401e) [<https://perma.cc/B4GQ-LX28>] (reporting views of Peter Pitts, president and co-founder of the Center for Medicine in the Public Interest, a nonprofit research and advocacy organization funded by the pharmaceutical industry).

326. *Id.*

327. Geoffrey M. Levitt, *The Drugs/Biologics Approval Process*, in A PRACTICAL GUIDE TO FDA'S FOOD AND DRUG LAW AND REGULATION 125, 160 (Kenneth R. Piña & Wayne L. Pines, eds., 2017).

a previously approved NDA.”<sup>328</sup> If the 505(b)(2) process is not unduly burdensome for companies that want to market an approved drug for a new indication, then why would it be unduly burdensome to *require* the same of the original drug sponsor in order for their approved drug to be used for a new indication? This option would substantially decrease the cost-burden on the original drug sponsor,<sup>329</sup> while also allowing for FDA oversight in the matter.<sup>330</sup> It is illogical that the original sponsor is allowed to bypass FDA scrutiny through off-label uses from which the sponsor reaps financial rewards, and that FDA instead gives deference to determinations that may be supported only by a physician’s ill-informed beliefs about safety and efficacy.

In the context of the off-label *promotion* debate, those opposing such promotion argue that if a drug has not been FDA-approved for off-label uses, then the drug manufacturer has not provided evidence of safety and efficacy for those other uses.<sup>331</sup> In opposing off-label promotion, FDA itself has taken the stance

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328. *Id.* (emphasis added).

329. See U.S. FOOD & DRUG ADMIN., APPLICATIONS COVERED BY SECTION 505(B)(2): DRAFT GUIDANCE FOR INDUSTRY 3 (1999) (“This use of section 505(b)(2), described in the regulations at 21 CFR 314.54, was intended to encourage innovation without creating duplicate work.”). Note that this reference from 1999 was *draft* Guidance.

330. See 21 C.F.R. § 314.54 (2019), which states:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG. § 314.54 Procedure for submission of a 505(b)(2) application requiring investigations for approval of a new indication for, or other change from, a listed drug. (a) The Federal Food, Drug, and Cosmetic Act does not permit approval of an ANDA [Abbreviated New Drug Application, used for generics manufacturing] for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change. Any person seeking approval of a drug product that represents a modification of a listed drug (for example, a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application. This 505(b)(2) application need contain only that information needed to support the modification(s) of the listed drug.

331. Ollove, *supra* note 325 (quoting Allison Zieve, director of the litigation group at Public Citizen).

that off-label promotion may result in patients (1) being prescribed unproven therapies, or (2) being prescribed therapies with less efficacy or more risk than FDA-approved therapies.<sup>332</sup> FDA stands firm behind its concern that off-label promotion may disincentivize pharmaceutical companies from conducting additional safety and efficacy studies.<sup>333</sup> These same arguments could be made in the context of off-label *prescription*.

*D. Psychiatrists Behind Closed Doors*

During the nineteenth century, research mostly was conducted on a small scale, “with individual physicians trying out one or another remedy or procedure on a handful of persons.”<sup>334</sup> Experimentation began in the investigator’s home, using his own body, or those of relatives and neighbors.<sup>335</sup> While experimentation in current times brings to mind large-scale studies sponsored by pharmaceuticals manufacturers, much of off-label prescription is experimental in nature. The individual psychiatrist tinkers with different psychotropic medications—including antipsychotics—attempting to treat or manage a nonpsychotic patient’s mental ailments. This is perfectly legal: But when experimentation in medical practice<sup>336</sup> means potentially altering the core of a person’s being—the mind—there should be some sort of heightened oversight.

1. Innovative Treatment or Experimentation?

Off-label use sometimes constitutes the best treatment for certain patients under given circumstances and may also provide an important means of discovering effective new therapies.<sup>337</sup> Scholars of research ethics understand how difficult

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332. Wayne Pines, *Regulation of Promotion and Distribution, in A PRACTICAL GUIDE TO FDA’S FOOD AND DRUG LAW AND REGULATION* 439, 440, (Kenneth R. Piña & Wayne L. Pines, eds., 2017).

333. *Id.*

334. Rothman, *supra* note 221, at 21.

335. *Id.*

336. *See* Mithani, *supra* note 1, at 577 (noting the Fenfluramine example discussed, *supra*, at Part I.B.).

337. *See* Dresser & Frader, *supra* note 115, at 476; Stoffelmayr, *supra* note 37, at 279 (citing Christopher, *supra* note 104, at 249 (for the statement that anecdotal evidence from general practice medicine suggests off-label use often “leads to serendipitous drug discovery”))

it can be to draw clear distinctions between human experimentation and medical treatment, and that innovation that is neither clearly research nor treatment makes discerning those distinctions even more difficult.<sup>338</sup> One could argue that given the theoretical assumptions of the prescribing physician and the lack of scientific support, off-label prescription itself should be categorized as “experimental or investigational,” and this categorization would then mandate that physicians obtain consent similar to that required in research—most likely written—from patients.<sup>339</sup> Might there be a middle ground, requiring more than regular patient consent but less than the consent mandated in clinical drug trials?

The essential question is, in using antipsychotic medications off-label in private practice, when does the individual psychiatrist’s treatment of the individual patient become less about treatment and more about innovation, or, taken a step further, actual experimentation? Some scholars assert that physicians are conducting uncontrolled and unregulated experimentation within private practice; that patients are being experimented on because clinical research prior to clinical use is lacking.<sup>340</sup> As Dr. Sidney Wolf of Public Citizen observed, “huge numbers of people are going to be made guinea pigs for unapproved uses of drugs.”<sup>341</sup> Others believe, however, that there is nothing to fear. For example, one U.S. Senator—who was also

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and Shapiro, *supra* note 104, at 809 (“effective off-label drug uses may be discovered when physicians try therapies based on informal theorizing, or when a patient with multiple conditions receives a drug to treat one condition and another condition unexpectedly improves as well.”)).

338. King, *supra* note 64, at 573.

339. Mithani, *supra* note 1, at 578; *see also* Barkus & Derian, *supra* note 20, at 863.

340. Johns, *supra* note 27, at 979 (quoting Paul D. Stolley, Chair of Epidemiology and Preventative Medicine, University of Maryland School of Medicine).

341. O’Reilly & Dalal, *supra* note 92, at 307; *see* JM Beck & ED Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L. J. 71, 104 (1998) (quoting Christopher, *supra* note 104, at 255, explaining that federal regulations requiring informed consent for FDA trials do not apply to off-label treatments); *see also* Teo, *supra* note 35, at 319, 323.



a physician—offered reassurance from the Senate floor that amounted to paternalistic “because I say so” reasoning:

I have some responsibility to define for my colleagues what off-label means. Off-label scares people. Is it somebody going in some secret closet and pulling out a medicine and using it? No, it is not. That is why extra-label is probably a better term. But right now off-label is something that we in the medical profession understand is used routinely in the pediatric population and, as mentioned earlier, for inpatient hospitalization. Probably 50 percent of all pediatric drugs prescribed are off-label. So it is not a term to be scared of or to fear.<sup>342</sup>

In the context of surgery, innovation and improvisation are expected, partly because each patient’s anatomy is unique. Yet, medicine’s history is replete with examples of “medical innovators from all specialties, and popular culture likewise abounds with images of the physician-scientist as Lone Ranger.”<sup>343</sup> Perhaps innovation is common in the realm of psychopharmacologic practice, where one FDA-approved antidepressant works to treat one patient’s depression and another approved antidepressant does not. Because of this, the psychiatrist’s approach must often be “let’s try and see” if a given psychotropic medication will be effective for this particular patient. But when moving outside of FDA-approved uses of a psychotropic, such as the antipsychotic Risperdal, and prescribing and introducing the drug’s chemicals into a lucid mind, is this a step too far? Is there, or should there be, a distinction between trying to eradicate a bacterial infection or cancerous cells that are not supposed to be in the patient’s body with a drug not approved for such purposes—when nothing else works—and introducing mind-altering chemicals into the

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342. 143 CONG. REC. S8165 (daily ed. July 28, 1997) (statement of Sen. Frist).

343. King, *supra* note 64, at 574 n. 8 (“Even the FDA ‘treads lightly upon the practice of medicine and surgery,’ thus implicitly encouraging this overwhelmingly positive view of unregulated innovation” (quoting Philip D. Noguchi, *From Jim to Gene and Beyond: An Odyssey of Biologics Regulation*, 51 FOOD & DRUG L. J. 367, 392 (1996))).

patient's blood system that will change the part of the patient that uniquely defines her?<sup>344</sup>

This sort of tinkering with a person's essence is more suspect, and more in need of regulation. But the regulators are nowhere to be found. This leaves the individual psychiatrist with a great deal of power and discretion, and too often that discretion may be informed by "scientific support" that is manufactured by drug manufacturers.

2. Our Most Vulnerable in Effect "Subjects" in Private Practice  
"Clinical Trials"

Introducing chemicals into any person's brain should be done with great care and knowledge and should never amount to a mere guess regarding safety and efficacy. But patients seem to "receive the least regulatory protection in those cases where they may need it the most—namely, when individual physicians may haphazardly try out a different technique under the guise of providing innovative therapy."<sup>345</sup> Just as with actual clinical trials for a new drug or non-indicated use of an existing drug, targeting vulnerable persons for disproportionate inclusion or exclusion in studies is never appropriate.<sup>346</sup> The same argument applies when a certain vulnerable group or categories of vulnerable populations are disproportionately prescribed a drug, such as an antipsychotic, off label. This is precisely what is happening, however, to the poor, the elderly, and children in foster care. Collectively, these vulnerable individuals could be likened to uninformed "subjects" in unregulated private practice "clinical trials."

The concept of individualized treatment in good medical practice informs the physician's ethical mandate to promote an individual patient's best interests and to respect his or her

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344. Gabriel Lazaro-Munoz, *Responsible Translation of Psychiatric Genetics and Other Neuroscience Developments: In Need of Empirical Bioethics Research*, 17 AM. J. BIOETHICS 33, 33 (2017) (quoting PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES 11 (2014)) ("When you start tinkering with the brain . . . it's really tinkering with who you are.").

345. Johns, *supra* note 27, at 979 (citing Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J. L. & MED. 361, 392–93, 399–400 (2002)).

346. COLEMAN ET AL., *supra* note 10, at 146.

autonomy.<sup>347</sup> A focus on the health and best interests of individual patients is what distinguishes medicine from public health which, instead, is concerned with the well-being of an entire community or population.<sup>348</sup> As noted by one prominent physician, “the practice of medicine is carried out ‘on an individual basis, with the best interests of the patient foremost in the practitioner’s mind.’”<sup>349</sup> In contrast, FDA stresses that clinical research is designed to answer specific questions through experimentation with numerous research volunteers.<sup>350</sup> Other differences highlighted by FDA are that clinical research requires written informed consent and periodic, systematic assessment of patient data, whereas medical treatment sometimes requires no informed consent at all and patient assessment is done only as needed.<sup>351</sup> Finally, in addressing the concept of “certainty,” FDA states that while research “tests products and procedures of unproven benefit

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347. Zettler, *supra* note 55, at 437 (citing BERNARD LO, RESOLVING ETHICAL DILEMMAS: A GUIDE FOR CLINICIANS 12–14 (5th ed. 2013)); *cf.* *Canterbury v. Spence*, 464 F.2d 772, 780 (D.C. Cir. 1972) (finding that physicians have a duty to obtain informed consent from patients because “every human being of adult years and sound mind has a right to determine what shall be done with his own body”); *see* Samia A. Hurst & Marion Danis, *A Framework for Rationing by Clinical Judgment*, 17 KENNEDY INST. ETHICS J. 247, 248–51 (2007) (discussing physicians’ obligations to both ration healthcare resources and advocate for patients’ best interests); *see also* Teo, *supra* note 35, at 324.

348. Zettler, *supra* note 55, at 437 (citing LAWRENCE O. GOSTIN, PUBLIC HEALTH LAW: POWER, DUTY, RESTRAINT 4 (2d ed. 2008)); *see* COMM. FOR THE STUDY OF THE FUTURE OF PUBLIC HEALTH, INST. OF MED., THE FUTURE OF PUBLIC HEALTH 3 (1988) (noting that “public health does things that benefit everybody”); *see also* Onyebuchi A. Arah, *On The Relationship between Individual and Population Health*, 12 MED. HEALTH CARE & PHIL. 235, 235 (2009) (contending that “population health calls up images of non-individual health”).

349. *Id.* at 437 (quoting Jeffrey M. Drazen, *Government in Medicine*, 356 NEW ENG. J. MED. 2195, 2195 (2007)).

350. *Clinical Research Versus Medical Treatment*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/patients/clinical-trials-what-patients-need-know/clinical-research-versus-medical-treatment> [https://perma.cc/Z69C-CVZJ] (last updated Mar. 22, 2018).

351. *Id.*

to the patient,” medical treatment “uses products and procedures accepted by the medical community as safe and effective.”<sup>352</sup>

Though FDA has elected a hands-off approach to regulating the practice of medicine, when that practice—intentional or not—is no longer treating the individual but instead certain classes of patients who coincidentally are vulnerable, what principles should apply? This appears to be an instance of innovation bordering on experimentation (as opposed to individual treatment) with vulnerable *classes of patients* as *subjects*. If FDA continues to abstain from intervening, then one possible solution would be for Congress to amend the FDCA. A focal point of any amendment should be the Belmont Report’s distinction between medical practice and research,<sup>353</sup> with specific emphasis on the concept that a medical-practice intervention should be reasonably expected to succeed.<sup>354</sup> If off-label prescription of antipsychotics has no scientifically based evidence of safety and efficacy, then it is not “reasonable” to believe that these drugs will be “successful” in treating the nonpsychotic patient. Any amendment should address this hybrid of the practice of medicine and conducting research.<sup>355</sup>

### 3. Likelihood that Vulnerable Populations Avail Themselves of State-Law Remedies

Some commentators believe there is no need for federal regulation: the “freedom accorded to physicians does not go unsupervised, because the fear of tort liability and medical malpractice claims serves as a check on the prescribing practices of physicians.”<sup>356</sup> As discussed above, there are many hurdles over which a plaintiff-patient must leap in order to prevail in the courtroom. These obstacles are magnified in situations involving vulnerable populations who are suffering from some sort of mental

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352. *Id.*

353. King, *supra* note 64, at 573 (citing to THE BELMONT REPORT, *supra* note 64) (“The Belmont Report defines medical practice as ‘interventions that are designed solely to enhance the well-being of an individual . . . and that have a reasonable expectation of success.’”).

354. *Id.*

355. A more apt description might be “the practice of research.”

356. O’Reilly & Dalal, *supra* note 92, at 299; *see also* Teo, *supra* note 35, at 319, 322.

illness and who are taking antipsychotics with various adverse side effects. Civil litigation in such circumstances is a weak solution to a hefty problem and places the onus on the debilitated mental-health patient to stand up and fight.

If the nonpsychotic psychiatric patient is even aware of being harmed by an antipsychotic, then the synergistic effects of the psychiatric illness—depression, for example, where the patient may lack motivation, have recluse-like behaviors, feel defeated, and be unable to work—and the sedating nature of the antipsychotic will render the patient unable to summon the energy, drive, or financial means necessary to pursue litigation. Attempts to right the wrong done to the patient are extremely unlikely. The patient-plaintiff must somehow have the emotional and financial resources (or the ability to locate and retain free counsel through a legal advocacy group) to pursue litigation and the mental wherewithal to withstand the rigors and repercussions of litigation. Clearly, the hurdles for any monetary recovery are exceedingly high.

Further, in cases of children (especially foster children) and the elderly (who are dependent on others for daily needs and care, and who lack agency due to age, status, or confinement to a nursing home), the likelihood of these patients availing themselves of remedies at law is extremely low. For poor patients receiving health care through Medicaid, it may be fair to assume that they lack the resources needed to initiate legal action in order to recover for harm suffered from taking antipsychotics off label.

Regardless of who is ultimately held liable (if anyone or any entity is, at all) the patient-plaintiff in a medical malpractice suit must prove, by a preponderance of the evidence, the physician's negligence by establishing that: (1) the physician had a duty to care for the patient; (2) the physician breached that duty; (3) the injuries caused were the direct and proximate result of the physician's breach; and (4) the patient's injuries are compensable damages resulting from the physician's malpractice.<sup>357</sup> Perhaps some of the most difficult elements in medical malpractice cases are where a plaintiff must demonstrate a causal connection between the injury suffered and the physician's failure to obtain informed consent or follow the standard of care.<sup>358</sup> And then, of course, the patient-plaintiff must locate and pay a forensic "non-

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357. Najib, *supra* note 101, at 443 (footnotes omitted).

358. Barkus & Derian, *supra* note 20, at 863.

treating expert” to testify that there was a misdiagnosis of the condition and that treatment protocol for the correct diagnosis would not have invoked use of the psychotropic drug in question.<sup>359</sup> Any legal victory would turn on expert testimony establishing that prescription of the specific offending off-label treatment demonstrated the physician’s lack of skill or knowledge, or failure to exercise reasonable care or follow the accepted standard of care.<sup>360</sup> One must wonder how the mentally ill patient, especially if prosecuting her case *pro se*, will find that expert and have the financial resources to pay her.

Even in the plaintiff’s best possible legal outcome, although the physician may be held liable for malpractice after harm is caused due to use of a drug for an unapproved use, the obvious reality is an after-the-fact award of money damages.<sup>361</sup> Meanwhile, the patient-plaintiff may have sustained irreversible physical damage, endured years of lost productivity, and will carry the emotional and societal stigma of having taken an antipsychotic.

The courts do not adequately prevent, or remediate after the fact, the harms to nonpsychotic psychiatric patients from taking antipsychotics off label. Suggestions that a psychiatric patient’s right to pursue litigation can be a meaningful alternative to regulation are either disingenuous or lack consideration of the difficulties of navigating the U.S. legal system, especially as a person living with mental illness.

Behind closed doors, psychiatrists are allowed broad discretion in deciding what is best for individual patients. When many psychiatrists are making the same decisions for many individual patients without evidence of safety and efficacy, this begins to look like sloppy research with many principal investigators instead of evidence-based medical practice. There is an important ethical obligation to protect our most vulnerable patients but apparently little acknowledgement of the widespread problem of off-label antipsychotic prescription, or any sense of duty to address harms to affected populations.

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359. Najib, *supra* note 101, at 443.

360. Helm, *supra* note 90, at 171.

361. Berry, *supra* note 16, at 37–38.

#### IV. WHO PROTECTS THE MOST VULNERABLE PATIENTS?

Patients who suffer from severe mental illness should be considered potentially vulnerable in both clinical research and clinical practice. The federal government does little to protect research subjects who may have “impaired decisionmaking capacity” or are otherwise “vulnerable to coercion or undue influence,” allowing broad discretion to institutional review boards in determining if adequate protections are in place.<sup>362</sup> Likewise, U.S. common law allows the treating psychiatrist wide latitude when working with psychiatric patients. What might be done, on either the federal and state levels (or both), to curb the rampant off-label prescription of antipsychotics?

##### *A. Why Psychiatrists Need More Regulation*

Despite state informed-consent requirements, some physicians habitually fail to properly and adequately warn patients about risks and side effects associated with their prescription medications.<sup>363</sup> Psychotropic medications, and antipsychotics in particular, produce numerous adverse side effects. Perhaps these are worth the risk to the patient suffering from schizophrenia, but for the patient not experiencing psychosis, the risks may be unjustifiable where the supposed benefit is only to manage—not treat or cure—a mood state. For those patients, other alternatives may be available. Unfortunately, one cannot depend on the psychiatrist always to do what is in the patient’s best interest.

During the 1973 “Quality of Health Care—Human Experimentation” hearing conducted by Senator Edward Kennedy,<sup>364</sup> certain testimony (while not pertaining to the FDCA) illuminated problems that existed, and likely still exist, in allowing physicians unbridled discretion in the practice of medicine. In opening, Kennedy stated:

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362. 45 C.F.R. § 46.107 (2019); 45 C.F.R. §§ 46.111(a)(3), (b) (2019).

363. Barkus & Derian, *supra* note 20, at 862. This does not pertain to practices related to FDCA, but an analogous framework and lack of government oversight are present.

364. ROTHMAN, *supra* note 221, at 184 (citing pts. 1–4, Hearings Before the Senate Subcommittee on Health and the Committee on Labor and Public Welfare, 93d Cong. (1st Sess. 1973)).

Human experimentation is part of the routine practice of medicine . . . . An absence of vigorous oversight, ‘coupled with the most unlimited freedom of action which physicians have in the treatment of their patients,’ allowed dangerous practices, including the premature use of unproven and untested drugs and procedures. The question, is whether or not we can tolerate a system where the individual physician is the sole determinant of the safety of an experimental procedure. After all, it is the patients who must live the consequences of that decision.<sup>365</sup>

At those same hearings, the then head of the National Institute of Mental Health (NIMH), Bertram S. Brown, M.D., explained that the practices (even if experimental) of a private physician were beyond NIMH’s grasp and control.<sup>366</sup> The topic at issue was psychosurgery and its use to treat aggressive, uncontrollable, violent, and hyperactive behavior that did not respond to other forms of treatment.<sup>367</sup> Senator Kennedy questioned Orlando Andy, M.D., a neurosurgeon from the University of Mississippi and a major proponent of the surgery:

Q: Basically, then, you make an independent judgment whether to move ahead on this kind of operation?

A: Yes. The final decision is always mine in terms of whether or not an operation will or will not be done.

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365. *Id.* at 184–85 (citing pt. 1, Feb. 21, 1973, p. 2 of Hearings Before the Senate Subcommittee on Health and the Committee on Labor and Public Welfare). Rothman includes examples where experimental research and the practice of medicine intersect. In one case, economically disadvantaged Mexican American women who went to a clinic in Texas for contraceptives unknowingly were subjects in an experiment “to identify whether the side effects of contraceptive pills were physiological or psychological; half the women were given contraceptive pills, the other half, placebos, in order to allow the investigators to match reported side effects with the active agent or the placebo.” *Id.* “The experiment itself and the failure of the medical society to discipline the doctors involved not only confirmed the idea that ‘poor minority people’ were particularly liable to be abused but also demonstrated, yet again, the inability of the profession to police its own members.” *Id.*

366. *Id.* at 186.

367. *Id.*



Q: Do you have any board or panel that continues to review the various bases for the psychosurgery in which you have been involved?

A: No. We don't have a board of supervisors or investigators or peer review type of activity over what we are doing.<sup>368</sup>

The doctor's testimony raises the obvious ethical implications of one physician having sole discretion to decide when a patient's brain will be surgically altered. With this surgeon, who regularly tampered with the human brain in attempts to control antisocial behavior, there was no oversight by a peer group or government regulatory body.<sup>369</sup> What was once done only through psychosurgery can now, in essence, be accomplished with psychotropic medications. With the effect of sedating and controlling thoughts and behaviors of the patient suffering from psychosis, for certain psychiatric patients, the numerous SGAs can be a valuable resource. But could we endorse a little bit of brain surgery to "fix or control" a nonpsychotic patient's mood, behavior or outlook when various alternatives, such as expensive but effective psychotherapy, were available? The use of mind-altering medications instead of a scalpel is less extreme and less invasive, yet antipsychotic medications sometimes have life-altering chronic and irreversible side effects. Perhaps

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368. *Id.* (citing the questioning of Dr. Orlando Andy during "Hearings on Human Experimentation," pt. 2, 23 Feb. 1973, p. 354).

369. *Id.* Rothman notes that while Senator Kennedy's version of the legislative proposal calling for the creation of a National Commission for the Protection of Human Subjects passed the Senate intact, the House had different ideas. The compromise resulted in a temporary commission and advisory to the secretary of HEW, with no independent enforcement powers. "Even in its reduced state, however, the commission represented a critical departure. First, it made apparent that the monopoly of the medical profession in medical ethics was over. The issues were now public and national—the province of an extraordinary variety of outsiders . . . . Finally, although the commission was not permanent and was charged to investigate not all of medicine but only human experimentation, it had a vital and continuing presence. When its mandate was about to expire in 1978, Kennedy was able to transform it into the President's Commission for the Study of Ethical Problems in Medicine." *Id.* at 189.

psychiatrists' habitual practice of prescribing antipsychotics off label warrants closer scrutiny.

While there are plenty of honest and well-intentioned physicians, “honesty is getting harder all the time.”<sup>370</sup> Whether intentional or not, our country has created a medical system “in which deception is often not just tolerated but rewarded,”<sup>371</sup> and through a series of social and legislative changes, medicine has been transformed into a business permitted primarily to operate within state boundaries and under self-regulation.<sup>372</sup> Self-regulation, occurring via a state's delegation of oversight responsibilities to “the medical profession itself is another way states oversee—or decline to oversee—medical practice.”<sup>373</sup> Little is done within the self-regulating psychiatric-physician group to protect vulnerable nonpsychotic psychiatric patients from being prescribed dangerous antipsychotics; rather, this physician group has made such prescribing practices *the* standard of care, and has made these patients “legally safe” specimens for informal, unregulated “clinical drug trials.”

*B. Congress and FDA Attempted to Close the Loophole*

In 1968, a member of Congress alerted FDA of a medical journal article that encouraged the use of Methotrexate—a drug approved solely for treating particular cancers—to treat a non-life-threatening skin condition, psoriasis.<sup>374</sup> FDA had authorized only “highly limited and tightly regulated investigational use of the drug” in the treatment of psoriasis and rheumatoid arthritis.<sup>375</sup> While major side effects associated with Methotrexate (for example, bone marrow suppression, leucopenia, thrombocytopenia and anemia) might be outweighed by benefits in the treatment of a cancer patient, these were not justifiable for

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370. ELLIOTT, *supra* note 86, at xi.

371. *Id.*

372. *Id.*

373. Zettler, *supra* note 55, at 453.

374. Klasmeier & Redish, *supra* note 10, at 321 (citing New Drugs Used for Nonapproved Purposes (Methotrexate for Psoriasis), Hearings before a Subcomm. of the H. Comm. on Gov't Operations, 92nd Cong. 5 (1971)).

375. *Id.*

a patient suffering a much less severe condition.<sup>376</sup> In 1971, a House subcommittee finally initiated hearings to consider the unique questions and dangerous situation surrounding Methotrexate, a drug legally marketed for restricted purposes that was commonly being used to treat a different, non-indicated (and thus, non-approved) medical condition.<sup>377</sup>

Dissatisfied with FDA's handling of the issue (opting for a physician educational campaign instead of inserting itself into the doctor-patient relationship), members of Congress insisted that FDA "develop a more coherent position on the Agency's ability to constrain prescriber decisions" in prescribing approved drugs off label.<sup>378</sup> While FDA's witnesses asserted authority under the FDCA for FDA to limit off-label uses, they conceded that FDA officials had wavered on this position in the past.<sup>379</sup> Congress pressed FDA to establish clear policy regarding off-label use, and FDA considered new regulations that would have given FDA the ability to interfere directly in medical practice by controlling particular off-label uses with which it disagreed.<sup>380</sup> However, "the medical community continued its vigorous campaign of resistance" to FDA's appropriate efforts to constrain a prescriber's clinical judgment.<sup>381</sup>

Aiming to balance conflicting influences, FDA proposed a new rule that would allow it to restrict physician-prescribing under certain circumstances, although FDA strongly denied any intention to interfere with the practice of medicine.<sup>382</sup> The proposed rule stated that if FDA "determined that an 'unapproved use of a new drug may pose a danger to the patients receiving the medication, [then] the agency may confine

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376. *Id.*

377. *Id.* Eventually, FDA approved the use of Methotrexate for the treatment of severe psoriasis. Gerald Weinstein, *Methotrexate*, 86 ANN. INTERNAL MED. 199, 199 (1977).

378. Klasmeier & Redish, *supra* note 10, at 322.

379. *Id.*

380. *Id.*

381. *Id.*

382. *Id.*; see Berry, *supra* note 16, at 9 n. 36 (citing *Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration*, 37 Fed. Reg. 16,503 (1972)).

distribution of the drug to specified channels or restrict the physicians who are able to prescribe the drug.”<sup>383</sup> Under the proposed rule, FDA would have had authority to limit the ability to prescribe, dispense or administer certain drugs to physicians possessing specified, specialized qualifications.<sup>384</sup> This action would have impacted physicians by effectively allowing FDA into doctors’ offices, limiting their freedom to prescribe as they deemed fit.<sup>385</sup>

Physicians “vociferously objected” to FDA’s interference with physician decisions regarding which lawfully marketed drugs would be used, for whom, and for what conditions.<sup>386</sup> In an attempt to satisfy both physicians and members of Congress, FDA backed down,<sup>387</sup> taking the position that “its statutory authority to control the market introduction and labeling of new drugs did not encompass the power to restrict the uses to which approved drugs might be put.”<sup>388</sup> FDA never issued the final rule;<sup>389</sup> instead, it issued a series of statements that appeared to be an effort “to soothe the medical community,” denying that the

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383. Berry, *supra* note 16, at 9.

384. *Id.* (footnote omitted).

385. *Id.*

386. Klasmeyer & Redish, *supra* note 10, at 323, 356 n. 35 (“According to David Kessler, FDA ‘was concerned’ about ‘improper prescribing,’ but ‘was under great pressure from the American Medical Association not to tell the doctor what he or she could prescribe.’ Kessler indicated that FDA ‘chose to deal with the problem [of off-label prescribing] as an educational matter.”); See also Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149, 175 (2004) (“Physicians have gone so far as to pursue litigation against the government when they viewed FDA initiatives as threatening their right to practice medicine without federal interference.”).

387. Rodney A. Smolla, *Off-Label Drug Advertising and the First Amendment*, 50 WAKE FOREST L. REV. 81, 90 (2015) (“[O]n the few occasions in history in which the FDA has venturesomely threatened to cross the fateful threshold into the actual regulation of medical practice, the political pushback, led by the medical profession, has been so intense that the FDA has beat a swift retreat.”); see Teo, *supra* note 35, at 311.

388. Klasmeyer & Redish, *supra* note 10, at 322 (citing 37 Fed. Reg. 16,503 (Aug. 15, 1972)).

389. *Id.* at 323.

failed proposal had represented any real threat to the doctor's autonomy in prescribing decisions.<sup>390</sup>

In 1991, FDA issued a Notice of Intent to withdraw certain proposed rules for which no final rule or notice of withdrawal had been issued; among the rules in the notice was the one regarding restrictions on prescription of certain drugs for uses unapproved by FDA.<sup>391</sup> Months later, FDA determined that it would not withdraw that particular proposed rule but also would not proceed to a final rule.<sup>392</sup> FDA noted that it had established an "Unlabeled Use Task Force" to examine promotion and use of prescription drugs for non-approved indications and stated that FDA would delay considering the withdrawal of the proposed regulation until sometime after the task force had completed the review.<sup>393</sup> Based on extensive legal research, it appears that nothing came of this task force. Further, there is no mention of subsequent activities in any of FDA's public communications or in the scholarly legal literature.

*C. Putting the Public Health Before the Healthcare Professional*

States regulate medical practice, and physician groups hold dear the autonomy of their members to practice medicine based on best judgments. There are instances, however, where a state is not able to adequately regulate a given space or profession. When considering whether or not to wield federal power, Congress and federal agencies should ask whether a given activity implicates national public health concerns that are beyond the scope of what individual states properly can address.<sup>394</sup> Some scholars argue that "Article I, Section 8 [of the U.S. Constitution] empowers Congress to enact those policies that individual states are structurally ill-suited to resolve as a result of interstate

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390. This 1982 "drug bulletin" issued by FDA emphasized that the Agency regarded off-label use as "accepted medical practice." *Id.* n. 38 (citing *Use of Approved Drugs for Unlabeled Indications*, 12 FOOD & DRUG ADMIN. DRUG BULL. 4, 5 (Apr. 1982)); see Zettler, *supra* note 55, at ns. 71, 72.

391. Berry, *supra* note 16, at 10 (citing 56 Fed. Reg. 42,668-43,701 (1991)).

392. *Id.* (citing 56 Fed. Reg. 67,440 (1991)).

393. *Id.* (citing 56 Fed. Reg. 67,442 (1991)).

394. Zettler, *supra* note 55, at 432.

externalities.”<sup>395</sup> Where activities are beyond the capacity of individual states to regulate, federal authority is appropriate and permissible.<sup>396</sup> While the narrative continues that medical practice is an individualized and local endeavor, medical practice contributes “to problems that cross state boundaries and require nationally coordinated or uniform solutions.”<sup>397</sup> The widespread prescription of antipsychotics in the nonpsychotic patient population is a serious threat to our nation’s public health, and setting parameters on the sale, prescription and use of antipsychotic drugs is a national concern that crosses state lines.

1. Progress in the Works on Federal Level

There is some interest within the federal government to address the unbridled use of antipsychotics in the nonpsychotic patient population. While federal studies and initiatives do not extend to the private health-insurance market or to psychiatric treatment paid for by patients out-of-pocket, they provide a starting point.

One federal initiative, The Centers for Education and Research on Therapeutics (CERTs), conducts research and provides education to advance optimal use of drugs, medical devices, and biological products.<sup>398</sup> Funded and run as a

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395. Leslie Meltzer Henry & Maxwell L. Sterns, *Commerce Games and the Individual Mandate*, 100 GEO. L. J. 1117, 1121–22 n.11 (2012) (citing Neil Siegel, *Free Riding on Benevolence: Collective Action Federalism and the Individual Mandate*, 75(3) L. & CONTEMP. PROBS. 29 (2012)).

396. See KATHRYN ARMSTRONG & JENNIFER STAMAN, CONG. RESEARCH SERVS., R43609, ENFORCEMENT OF THE FOOD, DRUG, AND COSMETIC ACT: SELECT LEGAL ISSUES 7 (2018) (noting the FDCA’s “requirement that articles be in interstate commerce poses ‘no obstacle’ to FDA enforcing the Act with respect to seemingly wholly intrastate activities.”).

397. Zettler, *supra* note 55, at 479.

398. U.S. DEP’T HEALTH & HUM. SERV., AGENCY FOR HEALTHCARE RESEARCH AND QUALITY: FY 2012 ONLINE PERFORMANCE APPENDIX (2012). The CERTs receive funds from both public and private sources, with AHRQ providing core financial support. The research conducted by the CERTs program has three major aims: (1) increase awareness of both the uses and risks of new drugs and drug combinations, biological products, and devices, as well as of mechanisms to improve their safe and effective use; (2) provide clinical information to patients and consumers; health care providers; pharmacists, pharmacy benefit managers, and

cooperative agreement by the Agency for Healthcare Research and Quality (AHRQ), in consultation with FDA, the program has six research centers and a CERTs Scientific Forum.<sup>399</sup> In 2010, sixteen States, the Rutgers University Center for Education and Research on Mental Health Therapeutics, and Medicaid Medical Directors Learning Network (MMDLN) collaborated on a report titled “Antipsychotic Medication Use in Medicaid Children and Adolescents: Report and Resource Guide From a 16-State Study.”<sup>400</sup> This report contains data on utilization patterns and treatment practices that raise clinical concerns, including “polypharmacy, wrong dosages, and the prescribing of antipsychotic drugs to very young children.”<sup>401</sup>

In 2011, the OIG commissioned a study regarding prescription of antipsychotics to Medicaid-covered children to ensure the quality of care provided to children receiving SGAs.<sup>402</sup> As a result, in 2015 the OIG made three recommendations to CMS, the agency that partially funds State Medicaid programs. The OIG recommended that CMS work with State Medicaid programs to (1) perform utilization reviews of SGAs prescribed to children; (2) conduct periodic reviews of medical records associated with claims for SGAs prescribed to children; and, (3) consider other methods of enhanced oversight

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purchasers; health maintenance organizations (HMOs) and health care delivery systems; insurers; and government agencies; (3) improve quality while reducing cost of care by increasing the appropriate use of drugs, biological products, and devices and by preventing their adverse effects and consequences of these effects (such as unnecessary hospitalizations). *Id.* at 32–33.

399. *Id.* at 33.

400. *OEI-07-12-00320*, *supra* note 263, at 5. The Rutgers group and MMDLN receive funding from the Agency for Healthcare Research and Quality. The 16 collaborating states were Alabama, California, Colorado, Illinois, Indiana, Maine, Massachusetts, Missouri, New Hampshire, New York, Oklahoma, Oregon, Pennsylvania, Tennessee, Texas, and Washington. States prominently featured in the study were California, Illinois, New York, and Texas.

401. *Id.*

402. *Id.* at 31.

of SGAs prescribed to children, such as implementing peer-review programs.<sup>403</sup> CMS concurred with these recommendations.<sup>404</sup>

The OIG intervention could influence prescribing practices because it affected reimbursement policy. Specifically, the influence derived from the policies that: (1) “[a]ll State Medicaid programs cover outpatient prescription drugs,” provided that said outpatient drugs are prescribed for medically accepted indications;<sup>405</sup> and (2) State Medicaid programs *may* pay for outpatient drugs not prescribed for medically accepted indications.<sup>406</sup> The Social Security Act defines “medically accepted indications” as FDA-approved uses and off-label uses supported in one of the compendia.<sup>407</sup> At the time of the OIG review, only one of the SGAs prescribed to children—risperidone—had “medically accepted” indications for use in pediatric patients beyond what FDA had approved.<sup>408</sup> Now there are more antipsychotics designated to have “medically accepted indications” for use in children, but still the list of indications is far narrower than uses in actual practice.<sup>409</sup> Given the alarming

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403. *Id.* at 32–33.

404. *Id.*

405. *Id.* at 2 (citing the Social Security Act, Pub. L. 89-97, 79 Stat. 286, § 1905(a)(12) (1965)); *Prescription Drugs*, MEDICAID.GOV (May 12, 2014), <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/ByTopics/Benefits/Prescription-Drugs/Prescription-Drugs.html> [<https://perma.cc/D8AN-MGGB>]; see *United States ex rel. Polansky v. Pfizer, Inc.*, 822 F.3d 613, 615 (2d Cir. 2016) (citing 42 U.S.C. § 1396r-8(d)(1)(B)(i) (2018)).

406. *OEI-07-12-00320*, *supra* note 263, at 5.

407. *Id.* (citing § 1927(g)(1)(B)(i)(I)–(III) of the Social Security Act). The three compendia are (1) the American Society of Health System Pharmacists, Inc.’s American Hospital Formulary Service Drug Information, (2) the United States Pharmacopeia—Drug Information (or its successor publications), and (3) DrugDEX Information System. See 42 U.S.C. §§ 1396r-8(k)(2), (3), (6), 1395w-102(e)(1), (4) (2018).

408. *Id.* n.10 (“Medically accepted indications for risperidone include its FDA-approved uses as well as its use to treat (1) behavioral syndrome-mental retardation and (2) pervasive developmental disorder.”).

409. *CTRS. FOR MEDICARE AND MEDICAID SERVS., ATYPICAL ANTIPSYCHOTIC MEDICATIONS: USE IN PEDIATRIC PATIENTS 1, 2* (Oct. 2015), available at <https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity->



number of Medicaid-recipient children prescribed antipsychotics off-label, it appears that government reimbursement practices are lenient and lacking in oversight.

While federal Medicaid requirements governing the prescribing of SGAs to children are deficient, federal and state agencies and professional associations, such as the American Academy of Child and Adolescent Psychiatry, the National Committee for Quality Assurance, and the Administration for Children and Families, have provided guidance and information on prescribing these drugs to child-patients.<sup>410</sup> In 2012, the Administration for Children and Families released a memorandum titled “Promoting the Safe, Appropriate, and Effective Use of Psychotropic Medication for Children in Foster Care.”<sup>411</sup> This memorandum spotlighted three “outlier practices” that could signify red flags of inappropriate physician prescribing practices of SGAs: (1) prescribing multiple drugs concurrently with the antipsychotic; (2) prescribing dosages that are too high; and, (3) prescribing SGAs to very young children.<sup>412</sup>

Hope for economically disadvantaged nonpsychotic patients of all ages who indiscriminately (and perhaps automatically, with little forethought) are prescribed antipsychotics, may rest in future Medicaid reimbursement policies. As of December 2019,

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Education/Pharmacy-Education-Materials/Downloads/atyp-antipsych-pediatric-factsheet11-14.pdf [https://perma.cc/UJ77-SA5R]. As of October 2015, six atypical antipsychotics had FDA-approved indications for use in children and adolescents: aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, and risperidone, for various combinations of Tourette’s disorder, schizophrenia, Bipolar I disorder, and irritability with autistic disorder. *Id.*

410. *Id.* at 3; *OEI-07-12-00320*, *supra* note 263, at 4 n.14 (“The guidance discussed here covers all psychotropic drugs—a category that includes SGAs and several other types of drugs. Other classes of psychotropic drugs include attention deficit/ hyperactivity disorder (ADHD) drugs, antianxiety drugs, antidepressants, first-generation antipsychotics, hypnotics, and mood stabilizers. This study focuses specifically on SGAs.”)

411. *Id.* (citing ACF, PROMOTING THE SAFE, APPROPRIATE, AND EFFECTIVE USE OF PSYCHOTROPIC MEDICATION FOR CHILDREN IN FOSTER CARE, LOG NO. ACYF-CB-IM-12-03 (Apr. 11, 2012), available at <http://www.acf.hhs.gov/sites/default/files/cb/im1203.pdf> [https://perma.cc/U65A-GJAX]).

412. *Id.* at 4–5.

over 71.6 million individuals were enrolled in Medicaid and the Children’s Health Insurance Program (CHIP).<sup>413</sup> This is a sizable population that can benefit from federal oversight in this area. CMS determines what services and treatments are “reasonable and necessary,” and with regard to the elderly and disabled, Medicare is supposed to reimburse only for those services that are deemed “reasonable and necessary.”<sup>414</sup> These payors could change their policies, for example by hinging reimbursement for off-label antipsychotic drugs on a requirement that manufacturers demonstrate safety and efficacy—evidence of *reasonableness and necessity*—through rigorous studies.<sup>415</sup>

The federal government may also legally impose certain limits on health-care practitioners who are paid through Medicare and Medicaid.<sup>416</sup> But, as discussed above, the majority of psychiatrists in the U.S. do not accept either Medicare or Medicaid; and some do not accept insurance at all.<sup>417</sup> It is quite possible, however, that studies and recommendations like those done by the GAO in 2011 and OIG in 2015, with regard to child Medicaid recipients and off-label antipsychotic prescriptions, could be applicable to Medicare recipients in a less direct way. The total number of U.S. citizens covered by Part D Medicare coverage, including stand-

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413. *December 2019 Medicaid & CHIP Enrollment Data Highlights*, MEDICAID.GOV, <https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index.html> [<https://perma.cc/4LCY-NFNF>] (last visited Apr. 6, 2020).

414. Zettler, *supra* note 55, at 470–71 (citing 42 U.S.C. § 1395g (2018)) and 42 U.S.C. § 1395nn (2018)).

415. Joshua Wallach & Joseph Ross, *Gabapentin Approvals, Off-Label Use, and Lessons for Postmarketing Evaluation Efforts*, 319 J.A.M.A. 776, 777 (2018).

416. *Id.*; See also Ass’n of Am. Physicians & Surgeons v. Weinberger, 395 F. Supp. 125 (N.D. Ill. 1975), *aff’d sub nom*, Ass’n of Am. Physicians & Surgeons v. Mathews, 423 US. 975 (1975) (affirming a district court holding that setting forth conditions under federal Professional Standards Review Law for compensating physicians with federal funds under Medicare and Medicaid did not bar physicians from practicing their profession and was not so patently arbitrary and totally lacking in rational justification as to be violative of due process clause of Fifth Amendment, as there was no coercion by the government making physicians participate in the program).

417. See generally Bishop et al., *supra* note 2.

alone prescription plans and Medicare Advantage with prescription drug coverage, was 39,246,296 as of May 2015.<sup>418</sup> While it may be a viable solution to have the federal government impose limits on medical practice,<sup>419</sup> history suggests that the strong physician lobby would adamantly and effectively oppose such an agenda. At this point in time, it is widely accepted that federal agencies such as FDA and HHS cannot interfere with the practice of medicine; that is relegated to the states.<sup>420</sup> HHS, however, through CMS, *can* restrict prescription coverage.<sup>421</sup>

While a doctor is free to prescribe an antipsychotic off label to a nonpsychotic patient, the government does not need to pay for that prescription. While the compendia have strong influence on reimbursement of off-label claims, “there is no strict legal requirement that these uses be reimbursed under current CMS rules and regulations.”<sup>422</sup> Were CMS to refuse to pay for these drugs, this would be a powerful way for the federal government to impose restrictions on the use of antipsychotics without directly interfering with the practice of medicine.

Federal oversight in this area would not automatically preempt all state oversight.<sup>423</sup> In circumstances of both national public-health concerns and inadequate state oversight, a limited proposal can provide a solution to expand “federal options for addressing public health problems, avoiding ineffective federal interference with medical practice, and preserving well-functioning state regulation consistent with federalism values.”<sup>424</sup>

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418. *On Its 50th Anniversary, more than 55 Million Americans Covered by Medicare*, CTRS. FOR MEDICARE & MEDICAID SERVS. NEWSROOM (July 28, 2015), <https://www.cms.gov/newsroom/press-releases/its-50th-anniversary-more-55-million-americans-covered-medicare> [<https://perma.cc/D2EB-MFFB>].

419. Zettler, *supra* note 55, at 480–81.

420. Since the late 1800s, the U.S. Supreme Court has recognized a state’s right to exercise its police powers in regulating the practice of medicine. *See Dent v. West Virginia*, 129 U.S. 114, 128 (1889).

421. *See Todd*, *supra* note 95, at 434–45.

422. Paczynski et al., *supra* note 293, at 143.

423. Zettler, *supra* note 55, at 482 (citing GOSTIN, *supra* note 348, at 4); *see also* COMM. FOR THE STUDY OF THE FUTURE OF PUBLIC HEALTH, INST. OF MED., *THE FUTURE OF PUBLIC HEALTH* 3 (1988); Onyebuchi A. Arah, *supra* note 348, 235.

424. Zettler, *supra* note 55, at 482.

As federal government oversight in the area would be in stark contrast with existing schemes, such regulation may serve to spotlight that area's significance in public health and educate physicians and patients about increased risks or need for vigilance.<sup>425</sup>

The federal government response to the Opioid epidemic provides a good example of HHS stepping in, attempting to regulate a pharmaceutical public-health disaster that is spiraling out of control. In mid-2016, after two days of hearings, FDA's Drug Safety and Risk Management Advisory Committee recommended that physicians be required to complete specialized training in order to be able to prescribe Opioids.<sup>426</sup> While FDA is not required to follow or implement advisory-panel recommendations, it often does so.<sup>427</sup> This particular mandate, however, could not simply be accomplished through the regulatory process, but would require congressional action.<sup>428</sup> Given the current political climate that opposes regulation of any sort,<sup>429</sup> the likelihood of FDA moving forward with the recommendations is slim. In a different political climate, however, perhaps a similar plan of attack could be implemented by HHS to address the problem of antipsychotic use in the nonpsychotic patient population.<sup>430</sup>

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425. *Id.* at 488–89.

426. Stephen Loiaconi, *Physicians Warn Mandatory Opioid Prescription Training Could Have Unintended Effects*, WJLA (May 5, 2016), <http://wjla.com/news/nation-world/physicians-warn-mandatory-opioid-prescription-training-could-have-unintended-effects> [<https://perma.cc/3U6P-EF2T>].

427. *Id.*

428. *Id.* (“Despite a similar expert panel recommendation in favor of mandatory training in 2012, the FDA had opted to make educational courses on safe pain prescription voluntary. As of March 2015, less than half of the 80,000 doctors the agency wanted to complete that training had done so.”).

429. See Kathy Wagner Hill, *The State of the Administrative State: The Regulatory Impact of the Trump Administration*, 6 EMORY CORP. GOV'T & ACCOUNTABILITY REV. 25, 26–7 (2019).

430. Interestingly, the Substance Abuse and Mental Health Services Administration (“SAMHSA”), an agency within the U.S. HHS that leads public health efforts to advance the behavioral health of the nation, and whose mission is to reduce the impact of substance abuse and mental illness on America's communities, advocates for shared decision-making. On the SAMHSA website is a link to an

## 2. Reform at State Level—What Could be Done?

States are in a unique position to foster needed changes in the prescribing habits surrounding antipsychotics in the nonpsychotic patient population. A desire to keep citizens healthy while keeping down costs should incentivize states to seriously consider options for intervention, which may include State Medicaid policy adjustments. Other areas of influence include state legislation and regulation, and the ability of a state to modify physician practices through physician state-licensing boards. Other options are for states to explicitly define what is experimental in medical practice, and how that must be disclosed to patients. It may require some creativity to identify what will work in a particular state, and how implementation of new policy should proceed, but a state-based solution to harms caused by off-label prescription of antipsychotics, where FDA refuses to intervene, may be one of the best options available for realizing meaningful change and reform.

### *a. State Medicaid Services*

State Medicaid Services have a compelling interest in preventing the needless adverse side effects stemming from unnecessary use of antipsychotics in the nonpsychotic patient population. The adverse side effects that can and do result from use of antipsychotics contribute to increased healthcare claims for avoidable physical illnesses directly caused by antipsychotics. Physicians should be provided disincentives for unnecessarily prescribing antipsychotic drugs, and should be held accountable through refusal of payment where Medicaid determines there is a lackadaisical attitude in the physician's prescribing practices.

In the 2015 OIG report, insufficient or non-existent monitoring was the most common quality-of-care issue, identified in more than half of claims for SGAs prescribed to Medicaid recipient children.<sup>431</sup> As a result, the OIG recommended that CMS

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online tool "Considering the Role of Antipsychotic Medications in My Recovery Plan" for people using or seeking treatment services involving antipsychotic medications, with recommendations on how to speak to one's doctor about the use of antipsychotics in treatment. *Considering the Role of Antipsychotic Medicine*, SAMHSA, <https://www.samhsa.gov/brss-tacs/recovery-support-tools/shared-decision-making> [<https://perma.cc/C5SW-H765>] (last visited Mar. 27, 2020).

431. *OEI-07-12-00320*, *supra* note 263, at 12.

work with State Medicaid programs to perform utilization reviews of SGAs prescribed to children, focusing on the children's ages, duration of their treatment with SGAs, and their overall drug regimens.<sup>432</sup> The OIG review criteria could be useful in crafting state guidelines. Specifically, conducting periodic reviews of medical records associated with claims for SGAs prescribed to children to ensure: (1) clear rationales exist for prescribing the SGAs; (2) patients are being properly monitored; and (3) children's dosages are properly adjusted.<sup>433</sup> The OIG also encouraged states to consider other methods of enhanced oversight of SGAs prescribed to children, including implementing peer-review programs (through which prescribers encourage one another to improve quality of care) and undertaking voluntary reporting of the Healthcare Effectiveness Data and Information Set (HEDIS)<sup>434</sup> measures regarding children's use of antipsychotic drugs or adopting the HEDIS measures in State oversight of SGAs.<sup>435</sup>

These same guidelines could be extended to adult recipients of State Medicaid services who are not suffering from psychoses but nonetheless are prescribed antipsychotics off label. And the extension of policies to the adult Medicaid population could then be a model for new standards of care in the private sector. The 2015 OIG report is a rich and readily available resource, and its thoughtful recommendations could be put to use beyond the original focal population.

*b. Other Ideas for State Influence in Addressing Problem*

States could enact laws requiring *specific* informed consent for off-label prescription of antipsychotics, especially prescriptions to nonpsychotic patients. Nonpsychotic patients would benefit

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432. *Id.* at 15 (“The previously described guidance and information on using SGAs to treat children—such as the utilization guidelines developed by the Florida and Texas Medicaid programs— may be of use to CMS and to other State Medicaid programs in developing guidelines for such utilization reviews.”).

433. *Id.*

434. *HEDIS and Performance Measurement*, NAT'L COMM. QUALITY ASSURANCE, <https://www.ncqa.org/hedis/> (last visited Dec. 7, 2018) [<https://perma.cc/6SNX-DGTZ>] (“The Healthcare Effectiveness Data and Information Set (HEDIS) is one of health care's most widely used performance improvement tools.”).

435. *OEI-07-12-00320*, *supra* note 263, at 15.

from playing a larger role in decision-making (even by guardians or surrogates) regarding the use of antipsychotics. This may be a critical juncture for treatment decision-making in that long-term adverse side effects might be put into motion, and in some instances be irreversible.

Some states, through legislation, have delineated the general disclosure required in certain procedures and treatments, but physicians have not been given any clear directive as to precisely what must be disclosed to patients.<sup>436</sup> Even in these states, because the medical community sets its own standards within the practice of medicine, physicians still are given latitude in deciding what information to disclose to patients.<sup>437</sup> States could require more, directly through their statutes, or through mandates to medical- and psychiatric-licensing boards.

Closer and systematic attention to informed consent and decision-making is required in the context of medical practice.<sup>438</sup> Alone, intent to benefit the patient does not supply sufficient justification for an intervention, regardless of whether it is called research, innovation, or treatment.<sup>439</sup> Consent-related discussions regarding the nature, magnitude, and likelihood of benefit—in both standard and innovative treatment—are quite often insufficient.<sup>440</sup> Individuals (patients, parents, or guardians) faced with difficult decisions need information about expected benefits and the sources of information that allegedly support such expectations.<sup>441</sup> There must be substantial, candid discussion regarding all likely and possible adverse side effects.

A state's legislative authority is limited only by the federal constitution and the state's constitution.<sup>442</sup> Thus, a state legislature that deems it "appropriate to regulate research beyond the scope of existing federal regulations is unquestionably free to do so as an aspect of its sovereign power."<sup>443</sup> The State of

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436. Barkus & Derian, *supra* note 20, at 862.

437. *Id.*

438. King, *supra* note 64, at 581.

439. *Id.*

440. *Id.* at 582 (footnote omitted).

441. *See id.* at 581–82.

442. COLEMAN ET AL., *supra* note 10, at 179 (quoting *Township of Pine Grove v. Talcott*, 86 U.S. 666, 676 (1873)).

443. *Id.*

California has done this by imposing a higher bar for informed consent relating to off-label uses.<sup>444</sup> In California, physicians are required to describe off-label uses as experimental before obtaining informed consent from patients.<sup>445</sup> Other states should consider California's example in crafting their own heightened protections for nonpsychotic psychiatric patients, including the designation of off-label prescription of antipsychotics as "experimental" and the requirement that physicians include patients in meaningful discussion of the risks and the benefits.

On the other hand, there may be intermediate options that "involve[e] intraprofessional peer review and consent guidelines, at the level of a division, department, institution, or professional association."<sup>446</sup> The OIG recommendations take into consideration some of these strategies in implementing controls in the prescription of antipsychotic drugs to the nonpsychotic-child Medicaid recipient.<sup>447</sup> This approach can be extended to and modeled by state medical- and psychiatric-licensing boards.

Through legislation, regulation, and medical-licensing boards, a state can regulate what is required of physicians within that state's borders. More stringent informed consent requirements will alert a nonpsychotic psychiatric patient that the antipsychotic their doctor is about to prescribe has not been proven safe or effective for a given condition. By arming the patient with knowledge, and requiring a meaningful conversation between doctor and patient, the state may substantially influence decisions regarding off-label use of antipsychotics.

*c. States Can Impose Regulations on Non-Federally-Funded Clinical Research*

As in the case with the California informed consent law, state protections may exceed those set by federal law, and what is not clinical research according to FDA can be deemed "experimental" by a state. Another area open for state regulation is clinical research that is *not* (1) conducted or funded by agencies that have adopted the Common Rule;<sup>448</sup> (2) under FDA's exclusive

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444. Barkus & Derian, *supra* note 20, at 863–64.

445. *Id.*

446. King, *supra* note 64, at 576 (footnote omitted).

447. *OEI-07-12-00320*, *supra* note 263, at 16.

448. *See* 45 C.F.R. § 46 (2019).



jurisdiction; or (3) conducted at an institution that has agreed, in an assurance to the Office for Human Research Protections, that all research at the institution will be conducted in line with the Common Rule.<sup>449</sup> Privately funded research is generally outside the purview of federal government regulation, which means the federal government cannot know the number of Americans who are subjects in private research, influence subject recruitment practices, ensure that research subjects are informed of risks, or ascertain if these subjects suffer harm.<sup>450</sup> Among venues listed by the National Bioethics Advisory Commission where non-government funded research could take place and where federal regulation has no force are *private offices of some physicians and psychotherapists*.<sup>451</sup>

Clearly, state law is relevant to the research enterprise, and states can regulate privately funded research or any other activities within their borders.<sup>452</sup> For research endeavors not falling within federal jurisdiction, “state law (if any) becomes the *only* legally applicable regulatory regime.”<sup>453</sup> When federal law does apply to research, it expressly preserves any additional state protections. For example, the Common Rule specifically addresses preemption: “[t]his policy does not affect any state or local laws or regulations (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) that may otherwise be applicable and that provide additional protections for human subjects.”<sup>454</sup>

Further, under the Common Rule, informed consent requirements “are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.”<sup>455</sup> Preserving a role for states in research regulation is

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449. COLEMAN ET AL., *supra* note 10, at 178.

450. *Id.* at 178 (quoting the Nat’l Bioethics Advisory Comm’n).

451. *Id.* at 176.

452. *Id.* at 179.

453. *Id.* at 178 (quoting JACK SCHWARTZ, OVERSIGHT OF HUMAN SUBJECT RESEARCH: THE ROLE OF THE STATES IN NATIONAL BIOETHICS ADVISORY COMMISSION; ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS § 3.05 (2001)).

454. *Id.*; see Revised Common Rule, 45 C.F.R. Pt. A § 46.101(f) (2019).

455. COLEMAN ET AL., *supra* note 10, at 178.

wholly appropriate given that one of a state's core functions is to protect its citizens—including human subjects—from harm.<sup>456</sup> While this may result in greater variability in clinical research requirements, which may complicate implementation of multisite studies, state interpretations of what constitutes research and what informed consent must include provide potential avenues for states to step in and offer protections to the scores of nonpsychotic psychiatric patients who are prescribed antipsychotics off label.

Besides delineating the scope of medical practice, licensing requirements, and medical board disciplinary power, states may regulate medical practice in a multitude of manners.<sup>457</sup> California, for example, requires physicians to distribute to patients standardized pamphlets regarding blood transfusions, breast cancer, gynecological cancers, silicone implants, prostate cancer, and patients' rights and remedies if they have been in a sexual relationship with their therapist.<sup>458</sup> States may also impose requirements for specific procedures and the timeframes in which they must be performed, for example, treating infants with eyedrops immediately, within an hour, or within two hours of birth.<sup>459</sup> Also, each state has mandated newborn medical screening tests to detect genetic and metabolic disorders, but the specific mandates vary by state.<sup>460</sup> States could require certain screening

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456. *Id.*; see *Panhandle Eastern Pipe Line Co. v. St. Highway Comm'n*, 294 U.S. 613, 622 (1935) (“It springs from the obligation of the state to protect its citizens and provide for the safety and good order of society. Under it there is no unrestricted authority to accomplish whatever the public may presently desire. It is the governmental power of self-protection and permits reasonable regulation of rights and property in particulars essential to the preservation of the community from injury”).

457. Zettler, *supra* note 55, at 451.

458. *Id.* at 452 (citing MED. BD. OF CAL., GUIDE TO THE LAWS GOVERNING THE PRACTICE OF MEDICINE BY PHYSICIANS AND SURGEONS 70–71 (7th ed. 2013), available at <http://perma.cc/K3WB-YHSK>).

459. *Id.* (citing N.H. REV. STAT. § 132:6 (2006)); MICH. COMP. LAWS ANN. § 333.5125 (West 2001); MASS. GEN. LAWS ANN. ch. 111, § 109A (West 2003)).

460. *Id.* (citing *About Newborn Screening: Conditions Screened by State, BABY'S FIRST TEST*, <http://www.babysfirsttest.org/newborn-screening/states> [<http://perma.cc/9RNC-BG4H>] (last visited Feb. 18, 2020) and Jennifer Kraszewski et al., *Legal Issues in Newborn*

procedures to determine whether use of an antipsychotic would be the best first-, second- or third-line defense in treating the nonpsychotic patient. States could also require physician education hours on the topic of using antipsychotics in the nonpsychotic patient population and channel resources to awareness-raising campaigns.

States have many underutilized tools to shape policies and practices relating to off-label prescription of antipsychotics to nonpsychotic patients. States could get out ahead of the escalating off-label prescription of antipsychotics by recalibrating the parameters for (1) provision of publicly funded psychiatric services (making psychotherapy less costly or free); (2) reimbursement policies under State Medicaid (making reimbursement contingent on evidence-based justifications for treatments, including prescription of off-label antipsychotics); and (3) determining what is appropriate and acceptable medical practice in the context of nonpsychotic psychiatric patients (influencing psychiatrists' prescribing practices and consideration of alternative methods). By doing so, states could wield substantial influence in treatment decisions and improve outcomes for many individual patients.

#### CONCLUSIONS AND THOUGHTS ON FUTURE EFFORTS

Illuminating the incidence of inappropriate and harmful off-label prescription of antipsychotic drugs and their indiscriminate use in the nonpsychotic patient population may also depend on efforts of consumer advocacy groups and media reports. In order to accurately portray this as a valid concern for all mental-health patients in the U.S., it would be prudent to enlist the support of liberal, mainstream, and conservative groups and news outlets alike. The media could play a critical role in spotlighting this mostly under-the-radar issue. If the public knows that antipsychotic use is frequent in the nonpsychotic population, and oftentimes not in patients' best interests, public opinion could influence the way doctors conduct the practice of medicine. Lobbying efforts at the individual state level will be required to

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*Screening: Implications for Public Health Practice and Policy*, 121 PUB. HEALTH REP. 92, 92–93 (2006), available at <http://www.publichealthreports.org/issueopen.cfm?articleID=1585> [<http://perma.cc/QMF9-GY63>] (discussing the legal issues raised by state newborn screening programs)).

effect any sort of meaningful change in how antipsychotics are prescribed to nonpsychotic patients and to frame the issue of what oversights should be established through state statutory mandates, then implemented by medical and psychiatric boards.

While it is heartening to see that there are both federal and state government agencies aware of the problems associated with antipsychotic use in the nonpsychotic patient population, and that studies and some guidance have been undertaken, follow-through with purposeful, meaningful action is needed. Further, much more must be done to reach and advocate on behalf of the millions of patients who pay solo practice psychiatrists out-of-pocket for treatment. Private health-insurance companies must question prescriptions and restrict payment/reimbursement.<sup>461</sup> That alone would have a negative effect on the nonpsychotic patient's pocketbook and might spur discussion between the patient and psychiatrist regarding the off-label nature of the prescription and the evidence of safety and efficacy—or lack thereof.

Efforts to address widespread off-label use of potentially harmful antipsychotics are the responsibility of many, including physicians, government regulators, policy makers and advisors, public health experts, scholars, politicians, payors, drug manufacturers, the media, and patients and their advocates; but, it is physicians who “wield the prescribing pen.”<sup>462</sup> Medical associations and boards strongly resist efforts of non-physicians to participate in discussions regarding off-label prescriptions, but in performing their duty to self-regulate, these medical professionals are falling short. Therefore, invited or not, more people *must* enter the off-label-prescription conversation, and change it.

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461. In their recent study, Vijay et al., found that private insurance was billed for 41.3% of the psychiatric- patient appointments in their study sample. There is a large group of patients that will not be reached by changes in CMS coverage decisions. Vijay et al., *supra* note 324, at 5.

462. Joshua Wallach & Joseph Ross, *Reply to Karen Maschke: Off-Label Use of Medications*, 320 JAMA 306, 307 (2018).

