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Promoting, Prescribing, and Pushing Pills: Understanding the Lessons of Antipsychotic Drug Litigation

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PROMOTING, PRESCRIBING, AND PUSHING PILLS: UNDERSTANDING THE LESSONS OF ANTIPSYCHOTIC DRUG LITIGATION

Douglas Mossman, M.D.*

Jill L. Steinberg†

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ABSTRACT

Ineffectiveness of prescription drugs, hidden drug hazards, and advertising violations have led to several drug recalls and numerous lawsuits against pharmaceutical companies in recent years. These suits have involved several varieties of medications, but psychoactive medications have figured especially prominently. A recent \$1.4 billion settlement by Eli Lilly & Company related to improper promotion of its top-selling drug olanzapine included the largest individual corporate criminal fine in U.S. history.

Improper promotion is far from the sole reason why olanzapine and other "second-generation" antipsychotic (SGA) drugs have become so successful. Rather, the widespread adoption of SGAs represents a collective judgment error by the medical profession. For policymakers, the olanzapine litigation is important because it provides an impetus for learning what makes certain drugs successful and for understanding processes that determine medication choices, physicians' judgments, and expenditures for drugs. Litigation will not solve problems with these processes, so understanding them is crucial if regulatory agencies and other entities wish to avert future medical judgment errors and suboptimal uses of healthcare dollars.

To promote this understanding, we first describe the rapid switch from older drugs to SGAs and summarize recent evidence suggesting that the switch was improvident. We then review the lawsuits brought against Lilly, which exemplify the many types of liability claims that drugs may generate. We next describe marketing techniques that drug companies use to get physicians to prescribe their products, the special features of SGAs that have contributed to their huge success, and the ways that pharmaceutical companies exercise virtually total control over the information doctors use to prescribe drugs. Increased funding for independent, comparative effectiveness studies and better incentives for pharmaceutical companies to generate and disclose more information about their products' flaws might produce better medications, help physicians make better treatment decisions, and improve patient safety.

I. INTRODUCTION

In recent years, numerous popular press accounts have reported on ineffectiveness of prescription drugs,¹ hidden drug hazards,² drug recalls,³ and repeated violations of advertising regulations⁴ by pharmaceutical companies. Other reports have described the methods that pharmaceutical sales forces use to influence, "corrupt,"⁵ or "bribe"⁶ physicians who prescribe their products. These stories report on problems with several types of medications and on marketing to practitioners of several medical specialties. But psychoactive medications—the types of drugs typically prescribed by psychiatrists to treat mental disorders—have figured especially prominently in stories reporting large judgments against pharmaceutical companies and unseemly links between physicians and commercial interests.

1. See, e.g., Alex Berenson, *Study Reveals Doubt on Drug for Cholesterol*, N.Y. TIMES, Jan. 15, 2008, at A1, available at 2008 WLNR 786340 (apparent ineffectiveness of ezetimibe [Zetia®]).

2. See, e.g., Gardiner Harris, *Report Backs Up Warnings About Drug Avandia and Heart Attack Risk*, N.Y. TIMES, Jul. 27, 2007, at A19, available at 2007 WLNR 14402147 (increased risk of heart attacks related to rosiglitazone, a medication for diabetes).

3. See, e.g., Gardiner Harris, *Studies Lead to Withdrawal of Drug for Bowel Ailment*, N.Y. TIMES, Mar. 31, 2007, at A12, available at 2007 WLNR 6102138 (prescription drug tegaserod [Zelnorm®] removed from market).

4. See, e.g., Tom Murphy & Marley Seaman, *Lilly Settles Zyprexa Suit For \$1.4 Billion*, HUFFINGTON POST, Jan. 15, 2009, http://www.huffingtonpost.com/2009/01/14/lilly-said-to-be-near-14_n_158032.html (last visited Feb. 28, 2009).

5. Marcia Angell, *'Drug Companies & Doctors': An Exchange*, N.Y. REV. BOOKS, Feb. 26, 2009 (reply to letter), available at <http://www.nybooks.com/articles/22363> ("[P]ervasive conflicts of interest corrupt the medical profession, not in a criminal sense, but in the sense of undermining the impartiality that is essential both to medical research and clinical practice.").

6. Carl Elliott, *The Drug Pushers*, ATLANTIC, Apr. 2006, available at <http://www.theatlantic.com/doc/200604/drug-reps/3>.

For example, the recent settlement⁷ in which Eli Lilly & Company agreed to pay \$1.415 billion dollars in civil and criminal penalties related to improper promotion of the psychotropic drug olanzapine⁸ represented “a record sum for so-called corporate whistle-blower cases”⁹ and the largest individual corporate criminal fine in U.S. history.¹⁰ A recent book review illustrates how drug makers influence physicians using the behavior of three nationally prominent psychiatrists¹¹ whose objectivity and ethics have been questioned following revelations about their extensive financial connections to pharmaceutical firms.¹²

Popular press reports focus on events that are remarkable, sensational, or extreme, and they often oversimplify outcomes of complex processes. Litigation focuses on rectifying or punishing perceived wrongs by one party against another, rather than on the various forces that induce the alleged misbehavior. Understandably then, published stories about drug litigation and physicians’ susceptibility to drug company blandishments typically paint a picture of evil actions caused by moral turpitude. Drug makers and physicians may deserve criticism and even vilification for some of their behavior, but responses to their actions should not end with condemnation alone. Some actions of drug companies have violated public trust, but violating public trust cannot be these companies’ main intent. Drug makers’ self-interests lie in selling good, safe, effective products, not bad ones. Similarly, a few doctors may be amoral, evil, or corrupt, but the vast majority—including the many physicians who have accepted meals, lecture fees, and other favors from drug companies—want to better the lives and health of their patients.

7. See U.S. v. Eli Lilly and Co., <http://news.findlaw.com/nytimes/docs/drugs/zyprexa11509guiltyplea.html> (last visited Feb. 23, 2009).

8. In accordance with the usual practices of academic publications, this article usually refers to specific medications using their “generic” or nonproprietary names (e.g., olanzapine), rather than their trade names (e.g., Zyprexa®).

9. Gardiner Harris & Alex Berenson, *Settlement Called Near on Zyprexa*, N.Y. TIMES, Jan. 15, 2009, at B1, available at 2009 WLNR 773474. “The settlement resolves four *qui tam* actions filed in the Eastern District of Pennsylvania: United States *ex rel.* Rudolf, *et al.*, v. Eli Lilly and Company, Civil Action No. 03-943 (E.D. Pa.); United States *ex rel.* Faltaous v. Eli Lilly and Company, Civil Action No. 06-2909 (E.D. Pa.); United States *ex rel.* Woodward v. Dr. George B. Jerusalem, *et al.*, Civil Action No. 06-5526 (E.D. Pa.); and United States *ex rel.* Vicente v. Eli Lilly and Company, Civil Action No. 07-1791 (E.D. Pa).” Press Release, U.S. Dep’t of Justice, Eli Lilly and Company Agrees to Pay \$1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa (Jan. 15, 2009), available at <http://www.usdoj.gov/opa/pr/2009/January/09-civ-038.html>.

10. See U.S. Dep’t of Justice, *supra* note 9.

11. See Angell, *supra* note 5 (discussing psychiatrists Joseph Biederman, Alan Schatzberg, and Charles Nemeroff).

12. One such instance received front-page coverage in *The New York Times*. Gardiner Harris, *Top Psychiatrist Didn’t Report Drug Makers’ Pay, Files Show*, N.Y. TIMES, Oct. 4, 2008, at A1, available at 2008 WLNR 18884180 (reporting that, in 2000 - 2007, “One of the nation’s most influential psychiatrists,” Dr. Nemeroff, “earned more than \$2.8 million in consulting arrangements with drug makers” that he did not report to his employer, Emory University).

This article provides legal audiences with a detailed examination of the uses and prescribing patterns of olanzapine and other “second-generation” antipsychotic (SGA) medications,¹³ a group of drugs which, since their introduction in the 1990s, have come to account for a huge share of all money spent on *all* pharmaceuticals.¹⁴ This huge market success is not justified by markedly superior treatment results; older and cheaper medications might do just as well (or poorly).

Though Eli Lilly may have improperly promoted olanzapine, improper promotion is far from the sole reason why olanzapine and other SGAs have become so successful. Rather, the widespread adoption of SGAs represents a collective judgment error by the medical profession, something that litigation has very limited power to remedy. Legal audiences need to understand that sensational reports about drug company fines and physicians’ dubious actions arise from a larger context in which salesmanship has acquired a dominant role in determining medical practice and patient/consumer choices about treatment. For policymakers, the potential value of the olanzapine litigation is that the drug’s success offers a window into the complex, interacting processes that influence medication use, medical decision-making, treatment choices, and expenditures for all kinds of drugs. An accurate understanding of these processes is crucial if regulatory agencies and funding entities wish to develop mechanisms and processes that might avert future mass medical judgment errors and suboptimal uses of healthcare dollars.

We proceed as follows. In Part II, we review the introduction into the American pharmacopeia of two waves of antipsychotic medication, describe why psychiatrists switched from the first to the second type, and summarize recent evidence that suggests that the switch was improvident. In Part III, we summarize the olanzapine-related litigation brought against the drug’s manufacturer, which exemplifies the various legal claims for which product liability suits can be brought. In Part IV, we describe the costly but successful marketing techniques that drug companies have used to get physicians to prescribe their products. We also describe several other factors that have been crucial to the huge success of SGAs. In Part V, we show why pharmaceutical companies enjoy virtually total control of the information practicing physicians use in prescribing medications. We suggest that enhanced funding for independent drug studies and incentives for pharmaceutical companies to generate and disclose more information about their products’ flaws might produce better medications, help physicians make better treatment decisions, and improve patient safety.

13. We explain the meaning of “generation” *infra* note 62. The first - and second - generation antipsychotic medications are discussed in Part II.

14. See *infra* note 119 and accompanying text.

II. FIRST- AND SECOND-GENERATION ANTIPSYCHOTIC DRUGS¹⁵

Olanzapine is one of several medications¹⁶ that physicians call “anti-psychotic drugs” and that physicians have used since the 1950s¹⁷ to treat psychoses. A psychosis is

a mental disorder characterized by gross impairment in reality testing as evidenced by delusions, hallucinations, markedly incoherent speech, or disorganized and agitated behavior, usually without apparent awareness on the part of the patient of the incomprehensibility of his behavior.¹⁸

Psychoses, or psychotic disorders, are a group of psychiatric syndromes each of which reflects “different aspects of the various definitions of *psychotic*.”¹⁹ Psychotic symptoms occur in several mental disorders,²⁰ and antipsychotic drugs have varying levels of effectiveness in quelling manifestations of these conditions. Because of their mood-stabilizing and anti-anxiety properties, antipsychotic drugs can also ameliorate conditions in which psychotic

15. This section focuses on the medical features of these medications. For a summary of legal contexts in which antipsychotic drugs figure importantly, see Douglas Mossman, *Unbuckling the “Chemical Straitjacket”: The Legal Significance of Recent Advances in the Pharmacological Treatment of Psychosis*, 39 SAN DIEGO L. REV. 1033, 1035-37 (2002) (discussing legal categories and citing main cases); see also *Sell v. U.S.*, 539 U.S. 166, 180-81 (2003) (describing conditions under which involuntary medication to restore trial competence is permissible, and noting that “[d]ifferent kinds of antipsychotic drugs may produce different side effects and enjoy different levels of success”).

16. Generic names of other antipsychotic medications mentioned in this article include fluphenazine, perphenazine, trifluoperazine, haloperidol, loxapine, molindone, thiothixene, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole.

17. The first of these drugs was chlorpromazine, more commonly known by its proprietary name, Thorazine®. Its discovery and initial use is mentioned in *Williams v. U.S.*, 133 F. Supp. 319, 322 (E.D. Va. 1955) (noting “an interesting article appearing in Time magazine (March 7, 1955) involving the use of new drugs referred to as chlorpromazine and reserpine which have been very effective in certain types of schizophrenia cases.”).

18. DORLAND’S ILLUSTRATED MEDICAL DICTIONARY 1489 (29th ed. 2000) [hereinafter DORLAND’S]. A delusion is:

a false belief based on incorrect inference about external reality that is firmly sustained despite what almost everyone else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary. The belief is not one ordinarily accepted by other members of the person’s culture or subculture (e.g., it is not an article of religious faith).

AM. PSYCHIATRIC ASS’N, DIAGNOSTIC AND STATISTICAL MANUAL FOR MENTAL DISORDERS 821 (4th ed., text rev. 2000) [hereinafter DSM-IV-TR]. A hallucination is “[a] sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ.” *Id.* at 823.

19. *Id.* at 827.

20. A partial list: psychotic disorders caused by general medical conditions, *id.* at 334-38; psychotic disorders induced by medications or intoxicants, *id.* at 338-43; schizophreniform disorder, *id.* at 317-19; schizoaffective disorder, *id.* at 319-23; mood disorders with psychotic features, *id.* at 411-17; delusional disorder, *id.* at 323-29; and brief psychotic disorder, *id.* at 329-32.

symptoms do not occur, including manic episodes, refractory depression, dementia with severe agitation, and severe anxiety.²¹ In several cases, drugs first approved for treatment of psychoses have received subsequent approval for treatment of other psychiatric conditions.²²

For simplicity of exposition, we focus here on the role of antipsychotic medications in treating schizophrenia. Schizophrenia is a logical choice for three reasons. First, recent advances in understanding schizophrenia typify psychiatrists' current thinking about many severe mental disorders. Second, schizophrenia frequently is the principal condition for which new antipsychotic drugs undergo efficacy testing prior to receiving FDA approval.²³ Third, the clinical manifestations of schizophrenia—that is, the types of symptoms experienced and the signs of illness exhibited by persons with the disorder—make it a paradigmatic instance of the role that pharmacotherapy plays in the treatment of a psychotic disorder.

A. Schizophrenia

Schizophrenia affects approximately 1 out of 200 persons,²⁴ and usually makes its appearance in a person's late teenage years or young adulthood. The classic signs of schizophrenia are hallucinations, delusions, and disorganized speech or behavior.²⁵ Over the last two decades, however, it has become increasingly clear that impaired cognition, loss of emotionality, diminished speech production, and reduced initiative explain much of the disability caused by schizophrenia.²⁶

21. JERROLD F. ROSENBAUM ET AL., HANDBOOK OF PSYCHIATRIC DRUG THERAPY 17, 23-25 (5th ed. 2005).

22. We discuss the use of newer antipsychotic drugs to treat other conditions *infra* Part II.D.3.

23. See, e.g., Guy Chouinard et al., *A Canadian Multicenter Placebo-Controlled Study of Fixed Doses of Risperidone and Haloperidol in the Treatment of Chronic Schizophrenic Patients*, 13 J. CLINICAL PSYCHOPHARMACOLOGY 25, 35 (1993) (reporting results of pre-approval study); Charles M. Beasley, Jr. et al., *Olanzapine Versus Placebo and Haloperidol: Acute Phase Results of the North American Double-Blind Olanzapine Trial*, 14 NEUROPSYCHOPHARMACOLOGY 111, 114-20 (1996) (reporting pre-marketing results in patients with schizophrenia).

24. Dinesh Bhugra, *The Global Prevalence of Schizophrenia*, 2 PUB. LIBR. SCI. MED. 372, 372 (2005), available at <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0020151> (citing study results of 0.0046 for point prevalence, 0.0033 for period prevalence, and 0.0072 for lifetime morbid risk).

25. Psychiatrists often call these "positive" symptoms because they involve the presence of something pathological. Schizophrenia may be diagnosed when an individual has experienced positive symptoms for six months or longer and has undergone marked deterioration in his social or occupational functioning, provided that the diagnostician can rule out other conditions—including medical conditions, intoxicants, and mood disorders—that might be potential causes of the symptoms. DSM-IV-TR, *supra* note 18, at 299, 312.

26. See, e.g., Victoria Villalta-Gil et al., *Neurocognitive Performance and Negative Symptoms: Are They Equal in Explaining Disability in Schizophrenia Outpatients?* 87 SCHIZOPHRENIA RES. 246, 246

Like most mental disorders, schizophrenia is an illness with biological, psychological, and social causes. Evidence of substantial biological causation includes:

- rates of schizophrenia among relatives that suggest a substantial genetic contribution to the illness;²⁷
- gene variations that influence the probability of developing schizophrenia;²⁸
- seasonal variation, i.e., people born in winter or spring are more likely to develop schizophrenia;²⁹
- the impact of *in utero* exposure to certain infections;³⁰
- the ability of cannabis to trigger the onset of schizophrenia;³¹
- the capacity of some pharmaceuticals to induce symptoms that mimic schizophrenia in persons who do not have the disorder;³²
- differences in brain configurations³³ and neural activity³⁴ among people diagnosed with schizophrenia;

(“Negative symptoms are the major source of disability of our sample.”). These features are termed “negative” symptoms because they reflect the absence of normal psychological features.

27. See, e.g., Alastair G. Cardno & Irving I. Gottesman, *Twin Studies of Schizophrenia: From Bow-and-Arrow Concordances to Star Wars Mx and Functional Genomics*, 97 AM. J. MED. GENETICS 12, 13 (2000) (high concordance in monozygotic twins; lower but substantial concordance in dizygotic twins; heritability estimates of 80-85%); Judy L Thompson et al., *Indicators of Genetic Liability to Schizophrenia: A Sibling Study of Neuropsychological Performance*, 31 SCHIZOPHRENIA BULL. 85, 85 (2005) (studies of twins and adoptions show that genes play a major role in causing schizophrenia).

28. See, e.g., Xiao-Wei Chen et al., *DINBP1, a Schizophrenia Susceptibility Gene, Affects Kinetics of Transmitter Release*, 181 J. CELL BIOLOGY 791, 798-99 (2008) (schizophrenia-dysbindin gene link offers possible causal mechanism for the illness).

29. Geoffrey Davies et al., *A Systematic Review and Meta-Analysis of Northern Hemisphere Season of Birth Studies in Schizophrenia*, 29 SCHIZOPHRENIA BULL. 587, 588 (2003) (excess risk for winter/spring births).

30. Alan S. Brown, *Prenatal Infection as a Risk Factor for Schizophrenia*, 32 SCHIZOPHRENIA BULL. 200, 200-01 (2006) (prenatal rubella, influenza, and toxoplasmosis associated with schizophrenia).

31. Sven Andréasson et al., *Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts*, 330 LANCET 1483, 1484 (1987) (heightened risk for schizophrenia among cannabis users); Stephen M. Eggen et al., *Reduced Cortical Cannabinoid 1 Receptor Messenger RNA and Protein Expression in Schizophrenia*, 65 ARCHIVES OF GEN. PSYCHIATRY 772, 779-83 (2008) (relationship between marijuana and schizophrenia may stem from fewer cannabinoid receptors); Louisa Degenhardt & Wayne Hall, *Is Cannabis Use a Contributory Cause of Psychosis?* 51 CAN. J. PSYCHIATRY 556, 563 (2006) (marijuana use can precipitate schizophrenia in biologically vulnerable persons).

32. Adrienne C. Lahti et al., *Effects of Ketamine in Normal and Schizophrenic Volunteers*, 25 NEUROPSYCHOPHARMACOLOGY 455, 463-65 (2001) (in normal persons, ketamine causes short-term psychotic symptoms like those of schizophrenia).

33. Laura A. Flashman & Michael F. Green, *Review of Cognition and Brain Structure in Schizophrenia: Profiles, Longitudinal Course, and Effects of Treatment*, 27 PSYCHIATRIC CLINICS N. AMER. 1, 3-4 (2004) (reviewing many studies examining neuroanatomy of schizophrenia).

- the impact of medications—especially drugs that block the brain’s dopamine D₂ receptor—on some symptoms of schizophrenia.³⁵

Though biological factors create individual vulnerability, social and individual psychological factors influence the risk of developing schizophrenia and the impact of the illness:

- urban settings, poverty, and minority status increase the risk of developing schizophrenia;³⁶
- childhood abuse or trauma influences the severity of schizophrenia later;³⁷
- unsupportive family relationships increase risk for relapse following an episode of psychosis;³⁸
- impaired capacity to appreciate one’s own and other persons’ mental states adversely affects social competence of persons with schizophrenia;³⁹
- depressed mood, low self-esteem, and negative attitudes correlate with severe, preoccupying persecutory delusions;⁴⁰
- some symptoms of schizophrenia can be viewed as biased cognitive or emotional states and may be amenable to verbal therapies.⁴¹

Contemporary psychiatry’s view of schizophrenia reflects the perspective of Eugen Bleuler, a Swiss psychiatrist who coined the term “schizophrenias”

34. Heather C. Whalley et al., *Correlations Between fMRI Activation and Individual Psychotic Symptoms in Un-medicated Subjects at High Genetic Risk of Schizophrenia*, 7 BMC PSYCHIATRY 61, 69 (2007) (altered lateral temporal cortex functioning related to hallucinations; altered medial temporal lobe function related to other psychotic symptoms).

35. H.M. Jones & L.S. Pilowsky, *Dopamine and Antipsychotic Drug Action Revisited*, 181 BRIT. J. PSYCHIATRY 271, 271-73 (2002) (noting that all effective antipsychotics block dopamine D₂ receptors to some degree, and discussing abnormal dopamine transmission in schizophrenia).

36. Jim van Os, *The Schizophrenia Envirome*, 18 CURRENT OPINION PSYCHIATRY 141 (2005) (discussing evidence for increased risk and suggesting biological pathways that may mediate or transmit impact of environment).

37. Lindsay S. Schenkel et al., *Histories of Childhood Maltreatment in Schizophrenia: Relationships with Premorbid Functioning, Symptomatology, and Cognitive Deficits*, 76 SCHIZOPHRENIA RES. 273, 281, 283 (2005) (childhood maltreatment influences specific forms of cognitive dysfunction).

38. Ronald L. Butzlaff & Jill M. Hooley, *Expressed Emotion and Psychiatric Relapse: A Meta-Analysis*, 55 ARCHIVES GEN. PSYCHIATRY 547, 549, tbl. 1, 551 (1998) (synthesizing results from twenty-seven studies of expressed emotion).

39. Martin Brüne et al., *Mental State Attribution, Neurocognitive Functioning, and Psychopathology: What Predicts Poor Social Competence in Schizophrenia Best?* 92 SCHIZOPHRENIA RES. 151, 152, 158 (2007).

40. Ben Smith et al., *Emotion and Psychosis: Links Between Depression, Self-Esteem, Negative Schematic Beliefs and Delusions and Hallucinations*, 86 SCHIZOPHRENIA RES. 181, 185-86 (2006).

41. Aaron T. Beck, *A Cognitive Model of Schizophrenia*, 18 J. COGN. PSYCHOTHERAPY 281 (2004).

early in the twentieth century.⁴² The term's Greek roots, *schizein* and *phren*,⁴³ connote a mind divided or torn apart, or, as Bleuler put it, a "splitting of the psychic functions."⁴⁴ For the past century, psychiatrists have used "schizophrenia" to denote a severe, debilitating disorder characterized by a pervasive impairment in thinking, behavior, and interpersonal relationships.⁴⁵ Modern psychiatrists still endorse Bleuler's approach to understanding schizophrenia because of its emphasis on "an underlying cognitive process" rather than often variable outward manifestations.⁴⁶

In the current U.S. diagnostic system, schizophrenia is divided into five subtypes. Persons with the *paranoid* subtype retain normal displays of emotion, and their speech, behavior, and thinking are usually organized and coherent.⁴⁷ When symptomatic, however, they typically have delusions of persecution and fear potential harm by their putative persecutors.⁴⁸ The other four subtypes of schizophrenia usually are much more disabling, and nonclinicians often recognize that sufferers with these subtypes of schizophrenia suffer from severe mental problems. In *disorganized* schizophrenia, persons exhibit disorganized speech and behavior, along with inappropriate emotional responses. Persons with *catatonic* schizophrenia have motor immobility, stupor, rigid posturing, mutism, stereotyped and repetitive movements, and/or excessive-but-poorly-organized activity ("catatonic excitement"). Persons with *undifferentiated* schizophrenia hallucinate and have disorganized thinking and lack initiative or interest in extended, determined activity. Individuals with *residual* schizophrenia display reduced verbal production, initiative, and im-

42. EUGEN BLEULER, *DEMENTIA PRAECOX OR THE GROUP OF SCHIZOPHRENIAS* 8 (Joseph Zinkin trans., Int'l U. Press 1950) (1911). The plural form "schizophrenias"—"schizophrenien" in German—reflects the multiple manifestations of the illness.

43. 2 THE COMPACT EDITION OF THE OXFORD ENGLISH DICTIONARY 2159, 2664 (1989).

44. BLEULER, *supra* note 42, at 9-10. His description, which still rings true, continues: In every case we are confronted with a more or less clear-cut splitting of the psychic functions Often ideas are only partially worked out, and fragments of ideas are connected in an illogical way to constitute a new idea.

This results in associations which normal individuals will regard as incorrect, bizarre, and utterly unpredictable. Often thinking stops in the middle of a thought; or in the attempt to pass to another idea, it may suddenly cease altogether, at least as far as it is a conscious process (blocking). Instead of continuing the thought, new ideas crop up which neither the patient nor the observer can bring into any connection with the previous stream of thought.

In the severest cases emotional and affective expressions seem to be completely lacking.

Id. at 9-10.

45. Susan K. Schultz & Nancy C. Andreasen, *Schizophrenia*, 353 LANCET 1425, 1425 (1999).

46. Nancy C. Andreasen, *A Unitary Model of Schizophrenia: Bleuler's "Fragmented Phrene" as Schizencephaly*, 56 ARCHIVES GEN. PSYCHIATRY 781, 782 (1999).

47. That is, the *form* of their thoughts and behavior are normal. The *content* of their thoughts can be quite irrational, and their actions may be motivated by delusional ideas.

48. DSM-IV-TR, *supra* note 18, at 299, 312-13.

paired motivation, though they do not experience pronounced delusions or hallucinations.⁴⁹

Although schizophrenia manifests itself in disturbances of thought and action, Bleuler conceptualized the condition as a medical disorder—he thought schizophrenia could be understood by cataloging patients’ signs, symptoms, clinical course, and ultimate outcomes.⁵⁰ By the end of the twentieth century, scientific evidence had provided overwhelming support for this viewpoint.⁵¹ Psychiatrists now recognize that persons with schizophrenia do not act irrationally because they have unusual, socially inappropriate, or crazy beliefs. Rather, these symptoms reflect the underlying core problem in schizophrenia, which is malfunctioning brain circuitry.⁵²

Evidence that has accumulated over decades shows that schizophrenia is a brain-based condition that can be addressed effectively, though not cured, with pharmacological agents⁵³ that alter neuronal⁵⁴ functioning. By continuing to take antipsychotic medication after initial remission of symptoms, persons with schizophrenia can greatly reduce their risk of having a relapse of symptoms.⁵⁵ Research also shows that individual psychotherapy, behavioral treat-

49. *Id.* at 313-17.

50. For a short description of Bleuler’s contributions to the modern conception of schizophrenia, see J. Hoenig, *The Concept of Schizophrenia: Kraepelin-Bleuler-Schneider*, 142 BRIT. J. PSYCHIATRY 547, 549-52 (1983).

51. For a discussion of the various perspectives extant in the 1960s, see Mossman, *supra* note 15, at 1047-48 (reviewing viewpoints).

52. As psychiatrist Nancy Andreasen observes,

[t]he symptoms and signs of schizophrenia are very diverse, and they encompass the entire range of human mental activity. . . . These symptoms and signs occur in patterns that may not overlap; one patient may have hallucinations and affective flattening, whereas another has disorganized speech and avolition [lack of motivation]. The diversity and nonoverlapping pattern of symptoms and signs suggest a more basic and unifying problem: abnormalities in neural circuits and fundamental cognitive mechanisms.

Nancy C. Andreasen, *Understanding the Causes of Schizophrenia*, 340 NEW ENG. J. MED. 645, 646 (1999).

For additional discussion of the significance of this shift in perspective, see Mossman, *supra* note 15, at 1056-59 (discussing current conceptualization of schizophrenia as malfunctioning neurocircuitry).

53. For a summary of early research, see generally Jonathan O. Cole et al., *Phenothiazine Treatment in Acute Schizophrenia*, 10 ARCHIVES GEN. PSYCHIATRY 246 (1964). For more recent summaries concerning older antipsychotic medications, see generally John M. Davis et al., *Important Issues in the Drug Treatment of Schizophrenia*, 6 SCHIZOPHRENIA BULL. 70 (1980); and John M. Kane, *Treatment of Schizophrenia*, 13 SCHIZOPHRENIA BULL. 133 (1987) (noting both pooling and summarizing studies showing that antipsychotic drugs are effective for approximately seventy percent of patients in acute episodes of schizophrenia).

54. The word “neuronal” means “pertaining to a neuron or neurons.” DORLAND’S, *supra* note 18, at 1212. Neurons are “the conducting cells of the nervous system.” *Id.* at 1211.

55. See, e.g., Patricia L. Gilbert et al., *Neuroleptic Withdrawal in Schizophrenic Patients: A Review of the Literature*, 52 ARCHIVES GEN. PSYCHIATRY 173, 184, tbl. 2 (1995) (after 9.7 months, patients who continued to take antipsychotic drugs had 16% relapse rate; 53% of patients not taking medication relapsed); Delbert Robinson et al., *Predictors of Relapse Following Response From a*

ments, and family therapy are very useful; these nonpharmacological interventions help many patients and their families cope with the consequences of schizophrenia and reduce symptoms that medication alone does not completely alleviate.⁵⁶ However, antipsychotic medication is the “mainstay” of current treatment for schizophrenia.⁵⁷

B. Development of “First-Generation” Antipsychotic Drugs

Symptoms of psychotic disorders were recognized in antiquity,⁵⁸ but effective and specific pharmacological treatments for these conditions only be-

First Episode of Schizophrenia or Schizoaffective Disorder, 56 ARCHIVES GEN. PSYCHIATRY 241, 245 (1999) (stopping antipsychotic medication therapy hazard increased ratio for relapse by almost 5 times).

The relapse studies generally refer to recurrence of delusions, hallucinations, and disorganized thought. These are often termed “positive symptoms” because they involve the presence of abnormal clinical findings or “distortions of normal functioning.” Samuel J. Keith, *Pharmacologic Advances in the Treatment of Schizophrenia*, 337 NEW ENG. J. MED. 851, 851 (1997). By contrast, the “negative symptoms” of schizophrenia—social withdrawal and apathy—involve the absence of normal findings or “the loss of normal functioning.” *Id.* Relapse studies focus primarily on reduction and control of positive symptoms; negative symptoms are much less responsive to medication.

56. See, e.g., Sukhwinder S. Shergill et al., *Auditory Hallucinations: A Review of Psychological Treatments*, 32 SCHIZOPHRENIA RES. 137, 143, 147 (1998); Dennis G. Dyck et al., *Management of Negative Symptoms Among Patients with Schizophrenia Attending Multiple-Family Groups*, 51 PSYCHIATRIC SERVICES 513, 513-14 (2000) (multifamily educational groups reduce negative symptoms).

57. For years, medical publications have consistently referred to antipsychotic medications as the “mainstay” of schizophrenia treatment. See, e.g., Kane, *supra* note 53, at 133 (“Antipsychotic medication remains a mainstay of treatment in both acute and chronic schizophrenia”); Robin McCreadie, *Schizophrenia: What’s New?*, 6 ADVANCES PSYCHIATRIC TREATMENT 81, 81 (2000) (“Drugs have always been a mainstay of treatment of schizophrenia”); Mahesh B. Jayaram et al., *Risperidone Versus Olanzapine for Treatment of Schizophrenia*, 33 SCHIZOPHRENIA BULL. 1274, 1274 (2007) (“Antipsychotic medication is a mainstay of treatment for schizophrenia”); DAVID GILL & JENNIFER BARRACLOUGH, HUGHES’ OUTLINE OF MODERN PSYCHIATRY 61 (5th ed. 2007) (“Antipsychotic drugs remain the mainstay of treatment”); and Peter B. Jones et al., *Randomized Controlled Trial of the Effect on Quality of Life of Second- vs First-Generation Antipsychotic Drugs in Schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUiLASS 1)*, 63 ARCHIVES GEN. PSYCHIATRY 1079, 1079 (2006) (“Antipsychotic drugs have been the mainstay of schizophrenia treatment for almost 50 years.”).

58. See, e.g., 1 Samuel 21:11–22:1, which describes David’s successful effort to feign a severe mental disorder. The account, whether factually true or not, implies that madness was recognized at the time of Saul or at the latest when the books of *Samuel* were set down. Current biblical scholarship places Saul’s reign in the latter half of the eleventh century B.C.E., 10 NEW ENCYC. BRITANNICA 475 (15th ed. 1998), and places the writing of I *Samuel* in the sixth century B.C.E., *id.* at 382.

See also THE AMERICAN PSYCHIATRIC PUBLISHING TEXTBOOK OF PSYCHIATRY 408 (Robert E. Hales et al., eds. 2007) (citing recent authors who believe that what we now call schizophrenia was widely recognized by the first century C.E.); FREDERICK K. GOODWIN ET AL., MANIC-DEPRESSIVE ILLNESS: BIPOLAR DISORDERS AND RECURRENT DEPRESSION 3-5 (2nd ed. 2007) (reviewing ancient descriptions of severe mental illness).

came available in the 1950s, when scientists and clinicians recognized that chlorpromazine alleviated symptoms of psychosis.⁵⁹ Within just a few years, pharmaceutical companies had produced several other phenothiazine derivatives⁶⁰ and other medications with different chemical structures but similar actions.⁶¹

Until this “first generation”⁶² of antipsychotic drugs became available, “most individuals with schizophrenia were destined to spend their entire adult lives within large, often remote psychiatric hospitals.”⁶³ In 1955, U.S. state mental hospitals housed more than 550,000 persons,⁶⁴ many of whom had psychotic disorders. Many patients spent years or decades at these facilities living in wretched conditions. Today, fewer than 55,000 persons are commit-

59. Chlorpromazine is the nonproprietary (or “generic”) name of a compound better known by its trade name, Thorazine®. *Medline Plus Drug Information*, <http://www.nlm.nih.gov/medlineplus/print/druginfo/medmaster/a682040.html> (last visited Jan. 7, 2009). For a fascinating account of the success, impact, and marketing of chlorpromazine in the 1950s, see ANN BRADEN JOHNSON, *OUT OF BEDLAM: THE TRUTH ABOUT DEINSTITUTIONALIZATION* 40–52 (1990).

60. Phenothiazine antipsychotic drugs all share a basic tricyclic structure. ROSENBAUM ET AL., *supra* note 21, at 6. Among the better known phenothiazines are fluphenazine (marketed as Prolixin®), perphenazine (marketed as Trilafon®), and trifluoperazine (marketed as Stelazine®).

61. In the 1980s, commonly prescribed non-phenothiazine antipsychotic compounds included haloperidol (Haldol®), loxapine (Loxitane®), molindone (Moban®), and thiothixene (Navane®). ROSENBAUM ET AL., *supra* note 21, at 9–10. Though older antipsychotic drugs differ in *potency* (and therefore in their typical dosages), “each ... has been found to be equally effective in treating psychotic disorders.” *Id.* at 8.

62. Pharmacologists and physicians often describe phases in drug development as “generations.” See, e.g., Johannes G. Ramaekers, *Behavioural Toxicity of Medicinal Drugs: Practical Consequences, Incidence, Management and Avoidance*, 18 *DRUG SAFETY* 189, 195–96, 199–202 (1998) (referring to generations of antidepressants, antipsychotic drugs, and antihistamines); Lorenzo Drago & Elena De Vecchi, *The Safety of Cefepime in the Treatment of Infection*, 7 *EXPERT OPINION ON DRUG SAFETY* 377, 377 (2008) (referring to an antibiotic, cefepime, as a “fourth-generation cephalosporin”).

In the 1990s, it was common to contrast “standard,” “conventional,” “typical,” or “traditional” antipsychotics—that is, the antipsychotic drugs used in the U.S. before the late 1980s—with “newer,” “novel,” or “atypical” antipsychotics that had just come into use. The appellations “first-generation” and “second-generation” were first applied to antipsychotic drugs around the turn of the present century. See, e.g., Hubert H. Fernandez & Joseph H. Friedman, *The Role of Atypical Antipsychotics in the Treatment of Movement Disorders*, 11 *CNS DRUGS* 467, 476 (1999) (one of the first articles that refers to “first-generation antipsychotics”); and Eric T. Edgell et al., *Olanzapine versus Risperidone: A Prospective Comparison of Clinical and Economic Outcomes in Schizophrenia*, 18 *PHARMACOECONOMICS* 567, 568 (2000) (describing and contrasting “first-generation” and “second-generation” antipsychotic medications).

63. Donald C. Goff, *A 23-Year-Old Man With Schizophrenia*, 287 *J. AM. MED. ASS'N* 3249, 3253–54 (2002).

64. H. Richard Lamb & Linda E. Weinberger, *Persons With Severe Mental Illness in Jails and Prisons: A Review*, 49 *PSYCHIATRIC SERVICES* 483, 486 (1998) (stating that 559,000 patients were in state psychiatric hospitals in 1955).

ted to state and county psychiatric hospitals.⁶⁵ Though several factors have reduced the census of public sector hospitals,⁶⁶ “the new drugs made the wholesale removal of patients from hospitals imaginable and then possible.”⁶⁷ As a 1961 report by the Joint Commission on Mental Illness and Health put it, “Unquestionably, the drugs have delivered the greatest blow for patient freedom, in terms of nonrestraint, since Pinel struck off the chains of the lunatics in the Paris asylum 168 years ago.”⁶⁸

C. Limitations of Early Antipsychotic Drugs

Though it was quickly apparent *that* first-generation antipsychotics (FGA) quelled psychosis, what these compounds did—*why* they helped—was not clear. One hypothesis, which suggested that schizophrenia resulted from excessive dopamine,⁶⁹ drew support from findings that high doses of drugs that increase brain levels of dopamine mimic some symptoms of schizophrenia.⁷⁰ Also, the potency of FGAs was directly proportional to their blockade of the brain’s dopamine D₂ receptor.⁷¹ Over subsequent decades, however, it

65. GARY MELTON ET AL., *PSYCHOLOGICAL EVALUATIONS FOR THE COURTS* 328 (3d ed. 2007). In 1955, the U.S. population numbered 166 million. 1955, <http://www.infoplease.com/year/1955.html> (last visited Nov. 16, 2008). In 2007, the U.S. population was estimated at 301,621,157. *Factfinder*, <http://factfinder.census.gov/servlet/SAFFPopulation> (last visited Nov. 16, 2008). Thus, over 50 years, the U.S. per capita rate of public sector psychiatric hospitalization fell nearly ninety-five percent, from 3.3 to 0.18 persons per 1,000 population.

66. In 1963, Congress passed the Community Mental Health Centers Act, which recognized that community services was a preferable treatment alternative for many mentally ill persons. In the 1970s, Medicare, Medicaid and Social Security laws created financial support for mentally ill persons to receive community-based care; also, new civil commitment laws made involuntary psychiatric hospitalization contingent on dangerous behavior rather than need for treatment. In the 1990s, managed care organizations used financial pressures to get physicians to shorten hospitalizations. See Mossman, *supra* note 15, at 1087.

67. JOHNSON, *supra* note 59, at 45-46.

68. *Id.* at 46, quoting JOINT COMMISSION ON MENTAL ILLNESS AND HEALTH, *ACTION FOR MENTAL HEALTH* 39 (1961).

69. See Arvid Carlsson & Margit Lindqvist, *Effect of Chlorpromazine and Haloperidol on Formation of 3-Methoxytyramine and Normetanephrine in Mouse Brain*, 20 ACTA PHARMACOLOGICA ET TOXICOLOGICA 140 (1963) (finding that after administration of antipsychotic drugs, extracellular dopamine was not increased, but its metabolites were, which suggested that the drugs blocked dopamine receptors and activated feedback pathways); GOODMAN AND GILMAN’S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 389 (7th ed. 1985).

70. *Id.* at 168, 553–54. See also Yoshimoto Sekine et al., *Methamphetamine-Related Psychiatric Symptoms and Reduced Brain Dopamine Transporters Studied with PET*, 158 AM. J. PSYCHIATRY 1206 (2001) (discussing the long-term impact of methamphetamine on dopamine transporter density, and its relationship to psychotic symptoms).

71. Aspects of the dopamine hypothesis remain valid. For confirmatory findings from brain imaging studies, see Anissa Abi-Dargham et al., *Increased Baseline Occupancy of D₂ Receptors by Dopamine in Schizophrenia*, 97 PROC. NAT’L ACAD. SCI. U.S. 8104, 8109 (2000) (also showing “direct *in vivo* evidence that schizophrenia is associated with excessive stimulation of D₂ recep-

was recognized that other types of drugs—including phencyclidine (PCP) and the anesthetic ketamine—could induce psychoses even though these drugs have little direct effect on brain dopamine activity.⁷² Also, psychiatrists recognized that “negative” symptoms—deficits in interest in surroundings, volume of communication, and social relationships⁷³—often influenced the long-term functioning of persons with schizophrenia far more than the positive symptoms—delusions and hallucinations—that high doses of dopaminergic drugs could induce.⁷⁴ Indeed, negative symptoms also seemed related to a relative *lack* of dopamine activity in some areas of the brain.⁷⁵

tors by dopamine [as opposed to excess dopamine *simpliciter*], and that this dysregulation is predictive of good treatment response to antipsychotic drugs.”); Oliver D. Howes et al., *Elevated Striatal Dopamine Function Linked to Prodromal Signs of Schizophrenia*, 66 ARCHIVES GEN. PSYCHIATRY 13, 18 (2009) (dopaminergic abnormality particularly evident in the associative striatum, which regulates information flow to and from the prefrontal cortex; this provides a plausible link to prefrontal dysfunction in schizophrenia and indicates why dopamine-blocking drugs attenuate symptoms of prodromal schizophrenia).

72. In 1979, the ability of ketamine and phencyclidine to mimic psychoses was found to be related to interaction by the drugs with a unique receptor; once bound to this receptor, phencyclidine is not displaced by dopamine or other chemically similar neurotransmitters. J. P. Vincent et al., *Interaction of Phencyclidine (“Angel Dust”) with a Specific Receptor in Rat Brain Membranes*, 76 PROC. NAT’L. ACAD. SCI. U.S. 4678, 4678 (1979); S. R. Zukin & R. S. Zukin, *Specific [β H]Phencyclidine Binding in Rat Central Nervous System*, 76 PROC. NAT’L. ACAD. SCI. U.S. 5372, 5372 (1979). For this reason, antipsychotic drugs do not reverse the psychotic symptoms induced by phencyclidine. For a recent study comparing and distinguishing the actions of ketamine and phencyclidine, see Wulf Hevers et al., *Ketamine, But Not Phencyclidine, Selectively Modulates Cerebellar GABA_A Receptors Containing $\alpha 6$ and δ Subunits*, 28 J. NEUROSCIENCE 5383, 5389-91 (2008) (both induce analgesia, psychosis-like behavior, and a catatonic unconsciousness, but ketamine’s better anesthetic properties relate to unique actions on specific receptors).

73. One of the first articles to contrast positive and negative symptoms states, “Positive schizophrenia is characterized by prominent delusions, hallucinations, positive formal thought disorder, and persistently bizarre behavior; negative schizophrenia, by affective flattening, avolition, anhedonia, and attentional impairment.” Nancy C. Andreasen & Scott Olsen, *Negative v. Positive Schizophrenia: Definition and Validation*, 39 ARCHIVES GEN. PSYCHIATRY 789, 789 (1982).

74. Wayne S. Fenton & Thomas H. McGlashan, *Antecedents, Symptom Progression, and Long-Term Outcome of the Deficit Syndrome in Schizophrenia*, 151 AM. J. PSYCHIATRY 351, 351 (1994) (deficits associated with poor outcomes and disability); Wayne S. Fenton & Thomas H. McGlashan, *Natural History of Schizophrenia Subtypes. II. Positive and Negative Symptoms and Long-Term Course*, 48 ARCHIVES GEN. PSYCHIATRY 978, 978 (1991) (negative symptoms are linked to poorer functioning prior to onset of illness and a “progressive course leading to permanent disability”).

75. See David Pickar et al., *Neurochemical and Neural Mechanisms of Positive and Negative Symptoms in Schizophrenia*, in 24 MODERN PROBLEMS OF PHARMACOPSYCHIATRY 124–51 (Nancy C. Andreasen ed., 1990) (linking deficit symptoms to functional frontal dopamine dysfunction); Terry E. Goldberg et al., *Cognitive and Behavioral Effects of the Coadministration of Dextroamphetamine and Haloperidol in Schizophrenia*, 148 AM. J. PSYCHIATRY 78, 78, 81-82 (1991) (finding that the addition of amphetamine, a dopaminergic drug, to schizophrenic patients’ medication regimen improved some aspects of cognition, motivation, and affect); Jonathan D. Cohen & David Servan-Schreiber, *A Theory of Dopamine Function and its Role in Cognitive Deficits in Schizophrenia*, 19 SCHIZOPHRENIA BULL. 85, 99 (1993) (noting that a computer model suggests that dopamine deficiency is responsible for cognitive deficits observed in persons with schizophrenia); Kenneth

The benefits of FGAs come with significant drawbacks. FGAs do not help all patients who have schizophrenia or other psychotic disorders; ten to fifty percent of patients who take FGAs experience only partial remission of positive symptoms or no response at all,⁷⁶ and many patients see little improvement in their cognition or negative symptoms.⁷⁷ FGAs also consistently cause “extrapyramidal symptoms,”⁷⁸ a constellation of side effects including stiffness, diminished facial expression, tremors, and restlessness.⁷⁹ Such side effects were among the reasons that patients often quit taking FGAs.⁸⁰ In addition, many patients who take FGAs develop permanent and sometimes disabling neuromotor syndromes such as tardive dyskinesia (TD),⁸¹ and a few

L. Davis et al., *Dopamine in Schizophrenia: A Review and Reconceptualization*, 148 AM. J. PSYCHIATRY 1474, 1474 (1991) (suggesting “that schizophrenia is characterized by abnormally low prefrontal dopamine activity (causing deficit symptoms) leading to excessive dopamine activity in mesolimbic dopamine neurons (causing positive symptoms)”).

76. Studies reviewing FGAs typically reported that fifty to seventy-five percent of schizophrenic patients have “a moderate to excellent response and up to ninety percent of patients show[] some response.” Daniel P. Van Kammen & Stephen R. Marder, *Dopamine Receptor Antagonists*, in 2 COMPREHENSIVE TEXTBOOK OF PSYCHIATRY/VI, at 1987 (Harold I. Kaplan & Benjamin J. Sadock eds., 6th ed. 1995). This implies that 10 to 50 percent of patients show no response or only a partial one.

77. Lisa B. Dixon et al., *Conventional Antipsychotic Medications for Schizophrenia*, 21 SCHIZOPHRENIA BULL. 567, 572 (1995); Herbert Y. Meltzer & Susan R. McGurk, *The Effects of Clozapine, Risperidone, and Olanzapine on Cognitive Function in Schizophrenia*, 25 SCHIZOPHRENIA BULL. 233, 235 (1999) (seeing “some evidence” that neuroleptics “cause selective impairment of some cognitive functions”).

78. The term “extrapyramidal” refers to those neurons that control movements outside the “pyramidal tracts.” DORLAND’S, *supra* note 18, at 638. The pyramidal tract “provides for direct cortical control and initiation of skilled movements, especially those related to speech and involving the hand and fingers.” *Id.* at 1861. “Extrapyramidal system” is “an imprecise term referring to a functional rather than an anatomical part of the central nervous system,” including brain structures that “control and coordinate especially the postural, static, supporting, and locomotor mechanisms.” *Id.* at 1776.

79. Keith, *supra* note 55, at 851. The pronounced effects of these drugs on the nervous system led to their being termed “neuroleptics,” a combination of the Greek words *neuron* (nerve) and *leptis* (to take hold). DORLAND’S, *supra* note 18, at 1210. The French psychiatrists Delay and Deniker coined the term “neuroleptic” in 1955. JOHNSON, *supra* note 59, at 40.

80. The classic study on this topic is Theodore Van Putten, *Why Do Schizophrenic Patients Refuse to Take Their Drugs?*, 31 ARCHIVES GEN. PSYCHIATRY 67, 70-71 (1974) (antipsychotic noncompliance strongly associated with extrapyramidal involvement, especially akathisia, the subjective experience of restlessness).

81. TD rarely occurs in young individuals who have been exposed to neuroleptics for fewer than three months. ROSENBAUM ET AL., *supra* note 21, at 45. Approximately one-fifth of patients undergoing long-term treatment with FGAs develop TD; the risk of developing TD is roughly five percent per year of FGA exposure. Dilip V. Jeste and Michael J. Caligiuri, *Tardive Dyskinesia*, 19 SCHIZOPHRENIA BULL. 303, 303 (1993) (mean prevalence of TD among long-term FGA patients is approximately twenty-four percent; annual incidence in young adults is four to five percent). The risk for elderly patients is much higher. *See, e.g.*, Robert A. Sweet et al., *Duration of Neuroleptic Treatment and Prevalence of Tardive Dyskinesia in Late Life*, 52 ARCHIVES

patients develop “neuroleptic malignant syndrome,” a severe and sometimes fatal reaction to the drugs.⁸²

D. Arrival of “Second-Generation” Antipsychotic Drugs

The FDA’s approval of clozapine in late 1989⁸³ paved the way for a striking change in psychiatrists’ prescribing over the next decade. Clozapine was the first really new antipsychotic medication to become available in thirty-five years. Clozapine was distinctive—or “atypical”—because it could alleviate psychotic symptoms without inducing the extrapyramidal side effects that usually accompanied treatment with FGAs.⁸⁴ Moreover, clozapine worked better than FGAs: thirty to sixty percent of schizophrenic patients who had not responded to FGAs improved when they took clozapine.⁸⁵ Also, the incidence of extrapyramidal side effects with clozapine was much low-

GEN. PSYCHIATRY 478, 482, tbl. 3 (1995) (twenty-nine percent risk in 3-12 months of drug exposure).

82. This syndrome occurs in one-tenth to one percent of persons receiving neuroleptics, and includes development of fever, muscle stiffness, unstable vital signs, altered consciousness, elevated muscle enzymes, and elevated white blood cell count.” Herbert Y. Meltzer & S. Hossein Fatemi, *Treatment of Schizophrenia*, in THE AMERICAN PSYCHIATRIC PRESS TEXTBOOK OF PSYCHOPHARMACOLOGY 760–61 (Alan F. Schatzberg & Charles B. Nemeroff eds., 2d ed. 1998); see also ROSENBAUM ET AL., *supra* note 21, at 43.

83. Stuart L. Nightingale, *Approval of Clozapine for Refractory Schizophrenia*, 263 J. AM. MED. ASS’N 202, 202 (1990) (requiring FDA approval); F.D.A. Approves a Backup Therapy for Severe Schizophrenia, N.Y. TIMES, Oct. 4, 1989, at A24, available at 1989 WLNR 2032721 (reporting FDA approval).

84. Michael J. Owens & S. Craig Risch, *Atypical Antipsychotics*, in THE AMERICAN PSYCHIATRIC PRESS TEXTBOOK OF PSYCHOPHARMACOLOGY 323, 333 (Alan F. Schatzberg & Charles B. Nemeroff eds., 2d ed. 1998). In 1993, psychiatrist Jeffrey Lieberman suggested that the following characteristics defined an atypical or second-generation antipsychotic drug: (1) “pre-clinical” (that is, laboratory findings often worked out in animals) evidence of efficacy and nontoxicity, (2) effectiveness in reducing psychotic symptoms, (3) low incidence of extrapyramidal symptoms and TD, and (4) no elevation of prolactin (a hormone involved in breast milk production, secretion of which is increased in men and women who take typical antipsychotics). Jeffrey A. Lieberman, *Understanding the Mechanism of Action of Atypical Antipsychotic Drugs: A Review of Compounds in Use and Development*, 163 BRIT. J. PSYCHIATRY 7–18 (Supp. 22, 1993).

85. The landmark study reporting clozapine’s efficacy in patients who had failed to benefit from neuroleptics is John Kane et al., *Clozapine for the Treatment-Resistant Schizophrenic: A Double-Blind Comparison with Chlorpromazine*, 45 ARCHIVES GEN. PSYCHIATRY 789, 794 (1988) (demonstrating improvement in thirty percent of previously refractory patients over a six-week period, compared with just four percent of patients who received chlorpromazine). Subsequent studies looking at treatment refractory patients treated with clozapine for longer periods have yielded higher estimated rates of improvement. See, e.g., John M. Kane et al., *Clozapine and Haloperidol in Moderately Refractory Schizophrenia: A 6-Month Randomized and Double-Blind Comparison*, 58 ARCHIVES GEN. PSYCHIATRY 965, 970 (2001) (showing a fifty-seven percent response rate); Jeffrey A. Lieberman et al., *Clinical Effects of Clozapine in Chronic Schizophrenia: Response to Treatment and Predictors of Outcome*, 151 AM. J. PSYCHIATRY 1744 (1994) (showing a fifty percent response rate in treatment refractory patients).

er, as was the likelihood of the damaging neuromotor syndromes associated with FGAs.⁸⁶

Patients who take clozapine for extended periods incur a small risk of developing a potentially fatal side effect involving a loss of the white blood cells responsible for fighting bacterial infections.⁸⁷ Therefore, when clozapine was released in the U.S., it was “bundled”⁸⁸ by its manufacturer with a mandatory monitoring system that included weekly blood tests.⁸⁹ The combined cost of the drug plus was initially around \$9,000 a year.⁹⁰

Costs,⁹¹ blood testing, medical risks,⁹² FDA restrictions,⁹³ and initial reluctance of third-party payers⁹⁴ have meant that psychiatrists would prescribe

86. Daniel E. Casey, *Effects of Clozapine Therapy in Schizophrenic Individuals at Risk for Tardive Dyskinesia*, 59 J. CLINICAL PSYCHIATRY 35–36 (Supp. 3, 1998).

87. Though clozapine had been available for prescription in other countries, it “had not been marketed [in the U.S.] because it carried approximately a 1% risk of potentially lethal agranulocytosis.” ROSENBAUM ET AL., *supra* note 21, at 5–6. Clozapine was introduced for use in several European countries in the 1970s. See J. Idänpään-Heikkilä et al., *Agranulocytosis During Treatment with Clozapine*, 11 EUROP. J. CLINICAL PHARMACOLOGY 1432, 1432 (1977). Agranulocytosis is a potentially fatal side effect in which the bone marrow stops making the white blood cells responsible for fighting bacterial infections. *MedlinePlus Medical Encyclopedia: Agranulocytosis*, <http://www.nlm.nih.gov/medlineplus/ency/article/001295.htm> (last visited Jan. 3, 2009).

88. The initial “bundling” of clozapine raised antitrust issues. See Michael A. Sanzo, *Antitrust Law and Patent Misconduct in the Proprietary Drug Industry*, 39 VILL. L. REV. 1209, 1224–25 (1994) (bundling clozapine to a patient monitoring system violated the *Jefferson Parish* test); Robert N. Swidler, *Medical Innovations and Ethics: A State Government Perspective*, 57 ALB. L. REV. 655, 668–72 (1994) (commenting on ethical issues surrounding New York state’s concerns about the cost of clozapine); Mark A. Hurwitz, Note, *Bundling Patented Drugs and Medical Services: An Antitrust Analysis*, 91 COLUM. L. REV. 1188, 1219 (tying clozapine to lab tests does not violate “rule of reason” test articulated in *Jefferson Parish Hosp. Dist. No. 2 v. Hyde*, 466 U.S. 2 (1984)).

89. Carl Salzman, *Mandatory Monitoring for Side Effects: The “Bundling” of Clozapine*, 323 NEW ENG. J. MED. 827, 827 (1990).

90. Hurwitz, *supra* note 88, at 1189; Daniel Goleman, *Outcry Grows Over Method of Selling New Drug*, N.Y. TIMES, Sep. 27, 1990, at B9, available at 1990 WLNR 2973991 (annual cost of bundled treatment was \$8,944).

Clozapine therapy was subsequently “unbundled” (allowing testing by a variety of agencies). Because Sandoz’s bundling had made the drug very expensive in the United States, the program had been assailed by physicians, patient advocacy groups, and Congress. Milt Freudenheim, *Maker of Schizophrenia Drug Bows to Pressure to Cut Cost*, N.Y. TIMES, Dec. 6, 1990, at A1, available at 1990 WLNR 2991484. Blood testing frequency has been reduced, and generic versions of the compound are now available. However, clozapine remains available only through monitoring protocols under which pharmacists dispense the medication only when they have determined that a patient’s blood has been tested and that the laboratory values are satisfactory. For a discussion of current monitoring requirements, see Yael Waknine, *Clozaril Monitoring Schedule Modified to Include ANC Reporting*, Medscape Alert, Jan. 17, 2006, available at <http://www.clozaril.com/pdfs/monthlymonitoring.pdf> (last visited Jan. 3, 2009).

91. In 1997, Keith estimated the cost of clozapine to be “about \$6,000 a year at [his] institution—and the additional cost of the weekly blood monitoring [was] about \$1,000 a year.” Keith, *supra* note 55, at 852. In a study conducted at VA facilities, per capita pharmacy costs in clozapine treated patients were \$3,199 a year. Robert Rosenheck et al., *A Comparison of Clozapine*

clozapine only to patients who could not benefit from or tolerate other available antipsychotic drugs. In the early 1990s, these drugs included only FGAs, which remained the primary drug therapy for schizophrenia. But clozapine's arrival made both psychiatrists and patients realize that antipsychotic drugs could be more effective and less neurotoxic than the preceding decades had led them to assume.

1. Second-Generation Antipsychotics for "First-Line" Use

In January 1994, risperidone entered the U.S. pharmacopeia, allowing U.S. psychiatrists to prescribe a second-generation antipsychotic drug as *initial* therapy for schizophrenia.⁹⁵ As of June 2009, six other SGAs--olanzapine⁹⁶

and Haloperidol in Hospitalized Patients with Refractory Schizophrenia, 337 NEW ENG. J. MED. 809, 812 (1997).

92. Clozapine has several other potential adverse effects. Risk of seizures was known when the drug was released in the U.S., as were other less serious but potentially troublesome problems (e.g., sedation and drooling). Medical Letter, Inc., *Clozapine for Schizophrenia*, 32 MED. LETTER DRUGS & THERAPEUTICS 3-4 (1990). Potential for weight gain and associated medical problems (for example, diabetes mellitus and hyperlipidemia) became better appreciated after several years of the drug's use. Michael Davidson, *Risk of Cardiovascular Disease and Sudden Death in Schizophrenia*, 63 J. CLINICAL PSYCHIATRY 5, 6-8 (Supp. 9, 2002) (summarizing results of studies); David C. Henderson et al., *Clozapine, Diabetes Mellitus, Weight Gain, and Lipid Abnormalities: A Five-year Naturalistic Study*, 157 AM. J. PSYCHIATRY 975, 979-80 (2000) (reporting high rates of weight gain, diabetes, and hyperlipidemia in patients who take clozapine for extended periods).

93. The FDA "required a demonstration of efficacy in patients whose disease was refractory to treatment with standard antipsychotic drugs. No other antipsychotic drug had ever been required to meet such a standard." Keith, *supra* note 55, at 852. The Physicians' Desk Reference still contains a black-box warning to reserve clozapine therapy for "use in (1) the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment, or (2) for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of re-experiencing suicidal behavior." *Physician's Desk Reference 2008*, 2193 (62nd ed. 2007) [hereinafter *PDR*]. However, clozapine has proved useful in treating other serious mental conditions, including refractory bipolar disorder, psychotic depression, and psychosis in Parkinson's Disease, see RONALD W. PIES, HANDBOOK OF ESSENTIAL PSYCHOPHARMACOLOGY 189-90 (2nd ed. 2005), and borderline personality disorder. K. N. Roy Chengappa et al., *Clozapine Reduces Severe Self-Mutilation and Aggression in Psychotic Patients with Borderline Personality Disorder*, 60 J. CLINICAL PSYCHIATRY 477, 483 (1999); George F. Parker, *Clozapine and Borderline Personality Disorder*, 53 PSYCHIATRIC SERVICES 348-49 (2002).

94. After some state Medicaid programs were initially to financially support clozapine therapy, courts ruled that Medicaid programs were obligated to make clozapine available to beneficiaries when doctors felt that the drug was medically necessary. *Visser v. Taylor*, 756 F. Supp. 501, 507 (D. Kan. 1990); *Alexander L. v. Cuomo*, 588 N.Y.S.2d 85, 88 (N.Y. Sup. Ct. 1991).

95. Reuters, *Johnson & Johnson Drug for Schizophrenia Is Approved*, N.Y. TIMES, Jan. 4, 1994, at D5, available at 1994 WLNR 3520024. Risperidone is the nonproprietary name for the product originally marked as Risperdal® by Janssen Pharmaceutica. *PDR, supra* note 93, at 1715.

quetiapine,⁹⁷ ziprasidone,⁹⁸ aripiprazole,⁹⁹ paliperidone,¹⁰⁰ and iloperidone¹⁰¹—had received marketing approval in the U.S. and were available for first-line use. None of these SGAs carry a substantial risk of agranulocytosis, and their recipients do not need medical monitoring as intensive as is required for clozapine.¹⁰²

Through the early years of the 21st century, psychiatrists were confident that SGAs had several advantages over FGAs. Based on premarketing studies used to achieve FDA approval, the SGAs appeared to treat positive symptoms as effectively as did FGAs, but with a lower incidence of noxious neuromotor side effects, including TD.¹⁰³ Psychiatrists thought that patients preferred

96. Olanzapine is marketed as Zyprexa® by Eli Lilly & Company. *PDR, supra* note 93, at 1816. It was approved for general use in October 1996. Associated Press, *A New Drug for Schizophrenia Wins Approval From the F.D.A.*, N.Y. TIMES, Oct. 2, 1996, at A21, available at 1996 WLNR 4385816.

97. Quetiapine received FDA approval in 1997. *Zeneca Given FDA Go-Ahead for Seroquel*, INDEPENDENT, Aug. 2, 1997, at 19. The drug is marketed as Seroquel® by AstraZeneca Pharmaceuticals LP. *PDR, supra* note 93, at 3451.

98. Ziprasidone, marketed by Pfizer Inc. as Geodon®, was introduced in the U.S. in early 2001. *PDR, supra* note 93, at 2506; Scott Hensley, *Schizophrenia Drug From Pfizer Wins FDA's Approval*, WALL ST. J., Feb. 6, 2001, at B21, available at 2001 WLNR 2013345.

99. Aripiprazole received FDA approval in November 2002. *Bristol-Meyers Schizophrenia Drug Receives Approval*, N.Y. TIMES, Nov. 16, 2002, at C4, available at 2002 WLNR 4100623. The compound is marketed as Abilify® by Bristol-Meyers. *PDR, supra* note 93, at 872.

100. The FDA approved paliperidone on December 20, 2006. Press Release, Food & Drug Admin., *FDA Approves New Drug for Schizophrenia* (Dec. 20, 2006), available at <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01534.html>. Paliperidone is the active metabolite of risperidone, *id.*, and marketed by Janssen as Invega®. *PDR, supra* note 93, at 1711.

101. Iloperidone, marketed by Vanda Pharmaceuticals as Fanapt®, received FDA approval on May 6, 2009. Press Release, Food & Drug Admin., *FDA Approves Fanapt to Treat Schizophrenia* (May 6, 2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149578.htm>.

102. In the 1990s, psychiatrists believed very little medical monitoring was necessary absent indications of problems. Marvin I. Herz et al., *Practice Guideline for the Treatment of Patients with Schizophrenia*, 154 AM. J. PSYCHIATRY 20-23 (Supp. Apr. 1997). By 2004, however, the risk of weight gain and metabolic problems with SGAs had been recognized. *See infra* Part II.E.1.

103. For examples of studies from the 1990s, *see* Mossman, *supra* note 15, at 1073 n.201. For a more recent study, *see* Christoph U. Correll et al., *Lower Risk for Tardive Dyskinesia Associated With Second-Generation Antipsychotics: A Systematic Review of 1-Year Studies*, 161 AM. J. PSYCHIATRY 414, 419 (2004) (mean annual TD risk with SGAs was below one percent, compared to a five percent risk with FGAs).

These studies usually compared SGAs to 20-mg/day doses of the high-potency FGA haloperidol that are well above patients' "neuroleptic threshold," that is, the minimum dose needed to produce modest extrapyramidal side effects. In an important study of the neuroleptic threshold dosing, McEvoy and colleagues found that the average dose needed to treat patients with schizophrenia was just 3.7 mg/day. Joseph P. McEvoy et al., *Optimal Dose of Neuroleptic in Acute Schizophrenia: A Controlled Study of the Neuroleptic Threshold and Higher Haloperidol Dose*, 48 ARCHIVES GEN. PSYCHIATRY 739, 741 (1991). Some writers recognized that the side effect evidence might have been less favorable to SGAs had the studies used lower haloperidol doses.

SGAs¹⁰⁴ and were “better off” for taking them.¹⁰⁵ Psychiatrists also believed that SGAs left patients less affected by negative symptoms than did FGAs¹⁰⁶ and were better than FGAs at ameliorating cognitive deficits in schizophrenia.¹⁰⁷

Shitij Kapur et al., *Clinical and Theoretical Implications of 5-HT₂ and D₂ Receptor Occupancy of Clozapine, Risperidone, and Olanzapine in Schizophrenia*, 156 AM. J. PSYCHIATRY 286, 291-92 (1999). However, the full significance of this has been appreciated only in the last few years. See *infra* notes 181, 366, and accompanying text.

Why SGAs are novel drugs, that is, why they cause fewer neurological side effects than the FGAs, is still not agreed upon. One explanation: SGAs “clinically help patients by transiently occupying D₂ receptors and then rapidly dissociating to allow normal dopamine neurotransmission.” Philip Seeman, *Atypical Antipsychotics: Mechanism of Action*, 2 FOCUS 48, 48 (2004). For other theories, see Herbert Y. Meltzer, *What’s Atypical about Atypical Antipsychotic Drugs?* 4 CURRENT OPINION PHARMACOLOGY 53, 55-56 (2004) (discussing effects on serotonin, acetylcholine, and N-methyl-D-aspartate receptors). Aripiprazole derives its atypicality from being a mixed agonist-antagonist of the dopamine-D₂ receptor. Kevin D. Burris et al., *Aripiprazole, a Novel Antipsychotic, Is a High-Affinity Partial Agonist at Human Dopamine D₂ Receptors*, 302 J. PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 381, 381 (2002).

104. See, e.g., Shitij Kapur & Gary Remington, *Atypical Antipsychotics: Patients Value the Lower Incidence of Extrapyramidal Side Effects*, 321 BRIT. MED. J. 1360 (2000); Piper S. Meyer et al., *Comparison Between the Effects of Atypical and Traditional Antipsychotics on Work Status for Clients in a Psychiatric Rehabilitation Program*, 63 J. CLINICAL PSYCHIATRY 108, 114 (2002).

105. A. George Awad & Lakshmi N.P. Voruganti, *Quality of Life and New Antipsychotics in Schizophrenia: Are Patients Better Off?* 25 INT’L J. SOC. PSYCHIATRY 268, 273-74 (1999). Subsequent studies have suggested that SGAs may not contribute to loss of gray matter volume in the way that FGAs apparently do. See, e.g., Jeffrey A. Lieberman et al., *Antipsychotic Drug Effects on Brain Morphology in First-Episode Psychosis*, 62, 62 ARCHIVES GEN. PSYCHIATRY 361 (2005) (in first-episode psychosis, haloperidol treatment was associated with reduced gray matter volume, but olanzapine treatment was not; findings could be due to haloperidol-associated toxicity or therapeutic effects of olanzapine).

106. Steven R. Hirsch et al., *A 28-Week Comparison of Ziprasidone and Haloperidol in Outpatients with Stable Schizophrenia*, 63 J. CLINICAL PSYCHIATRY 516, 519 fig.3 (2002) (reporting that in previously stable patients, ziprasidone reduced negative symptoms more than did haloperidol); Beng-Choon Ho et al., *A Comparative Effectiveness Study of Risperidone and Olanzapine in the Treatment of Schizophrenia*, 60 J. CLINICAL PSYCHIATRY 658, 662 (1999) (reporting that olanzapine and risperidone reduced negative symptoms). However, some authors thought SGAs merely avoided the neurological side effects of FGAs. William T. Carpenter et al., *Patient Response and Resource Management: Another View of Clozapine Treatment of Schizophrenia*, 152 AM. J. PSYCHIATRY 827, 827 (1995) (“Treatment of primary negative symptoms is not supported by the current experimental data.”).

107. See Mossman, *supra* note 15, at 1075 n.207 (citing studies).

More recent studies question these findings. See, e.g., Terry E. Goldberg, *Cognitive Improvement After Treatment With Second-Generation Antipsychotic Medications in First-Episode Schizophrenia: Is It a Practice Effect?* 64 ARCHIVES GEN. PSYCHIATRY 1115, 1115 (2007) (findings that cognitive improvements appeared attributable to practice — exposure, familiarity, and/or procedural learning — rather than SGA therapy; differences between risperidone and olanzapine were small); Richard S. E. Keefe et al., *Neurocognitive Effects of Antipsychotic Medications in Patients With Chronic Schizophrenia in the CATIE Trial*, 64 ARCHIVES GEN. PSYCHIATRY 633, 641-42 (2007) (after 2 months of treatment, both recipients of SGAs and the FGA perphenazine showed small but significant improvement in cognition; reasons may have included broad

Because SGAs seemed to offer a clear pharmacological advance in the treatment of psychoses, most psychiatrists concluded that these drugs had created new standards for treatment of psychotic disorders. In the mid-1990s, psychiatrists began suggesting that the SGAs should be psychiatrists' first choice when selecting an antipsychotic therapy,¹⁰⁸ and, a few years later, this view became dominant.¹⁰⁹ One can appreciate how rapid and dramatic this change was by noting that (1) in a 1995 psychopharmacology handbook, discussion of risperidone occupies less than one page in a 38-page chapter on antipsychotic medications;¹¹⁰ and (2) in its 1997 guideline for treating schizophrenia, the American Psychiatric Association (APA) states that "conventional antipsychotic medications and risperidone are all reasonable first-line medications for patients in acute phases of schizophrenia."¹¹¹ In the APA's 2004 version of the schizophrenia guideline, however, the preference for SGAs seems clear: "The second-generation antipsychotics should be considered as first-line medications for patients in the acute phase of schizophrenia,

inclusion criteria and more reasonable dosing of FGA compared with previous studies). The latter study contains approximately forty earlier references asserting improved cognition with SGAs. *Id.* at 645 n.10, 646 nn.15-53.

108. Jeffrey A. Lieberman, *Atypical Antipsychotic Drugs as a First-Line Treatment of Schizophrenia: A Rationale and Hypothesis*, 57 J. CLINICAL PSYCHIATRY 68, 68 (Supp. 11 1996) (offering "a rationale and hypothesis for the use of atypical antipsychotic drugs as a first-line treatment of schizophrenia").

109. Rowland Pearsall et al., *A New Algorithm for Treating Schizophrenia*, 34 PSYCHOPHARMACOL. BULL. 349, 349 (1998) (suggesting "that the newer atypical antipsychotic agents may now be the treatment of choice for initiating therapy in most clinical situations"); Alexander L. Miller et al., *The Texas Medication Algorithm Project (IMAP) Schizophrenia Algorithms*, 60 J. CLINICAL PSYCHIATRY 649, 652 (1999); Steven P. Shon et al., *Mental Health Care from the Public Perspective: The Texas Medication Algorithm Project*, 60 J. CLINICAL PSYCHIATRY 16, 18 (Supp. 3 1999); John A. Chiles et al., *The Texas Medication Algorithm Project: Development and Implementation of the Schizophrenia Algorithm*, 50 PSYCHIATRIC SERVICES 69, 72-73 (1999); Joseph P. McEvoy et al., *The Expert Consensus Guideline Series: Treatment of Schizophrenia 1999: 1, Strategies for Selecting Medications*, 60 J. CLINICAL PSYCHIATRY 12, 12 (Supp. 11 1999); Neil S. Kaye & Thomas J. Reed, *Tardive Dyskinesia: Tremors in Law and Medicine*, 27 J. AM. ACAD. PSYCHIATRY L. 315, 316 (1999); David N. Osser & Carlos A. Zarate, Jr., *Consultant for the Pharmacotherapy of Schizophrenia*, 29 PSYCHIATRIC ANNALS 252, 253 (1999). See also Roger S. McIntyre, *Psychotropic Drugs and Adverse Events in the Treatment of Bipolar Disorders Revisited*, 63 J. CLINICAL PSYCHIATRY 15 (Supp. 3 2002) ("Novel antipsychotics are now the antipsychotics of choice in the treatment of bipolar disorders, having displaced the conventional antipsychotic agents."); David N. Osser & Robert Sigadel, *Short-Term Inpatient Pharmacotherapy of Schizophrenia*, 9 HARV. REV. PSYCHIATRY 89 (2001) ("For initial oral treatment, monotherapy with one of the new 'atypical' antipsychotics is favored."); Renée E. Snow & Sumer Verma, *Late-life Psychosis: It's Efficacy vs. Cost in the Tug-of-War Over Treatment*, 1 CURRENT PSYCHIATRY 10, 16 (2002) ("In general, atypical antipsychotics are considered first-line therapy [for treating psychotic disorders in elderly patients], unless there is a compelling reason not to use them in an individual patient.").

110. STEVEN E. HYMAN ET AL., HANDBOOK OF PSYCHIATRIC DRUG THERAPY 30 (3d ed. 1995). This edition is a predecessor of ROSENBAUM ET AL., *supra* note 55.

111. Hertz, *supra* note 102, at 23.

mainly because of the decreased risk of extrapyramidal side effects and tardive dyskinesia. . . ."¹¹²

2. Changes in Prescribing Patterns and Drug Expenditures

These changes in official treatment recommendations merely followed the prescribing patterns of American psychiatrists, who, by the late 1990s, had made SGAs their first-line choice for antipsychotic therapy. In the early 1990s, most FGAs were off-patent; many were available in "generic" form, and the daily cost for an oral FGA was sometimes just a few pennies. The costs of SGAs were up to 100 times higher, depending on the specific drug and dosage.¹¹³ Accordingly, annual expenditures for antipsychotic drugs rose substantially in the years during which SGAs were introduced. In 1994, when risperidone became available, annual U.S. expenditures for all antipsychotic medication was \$1.4 billion, and only a small fraction of patients with schizophrenia were taking SGAs. A decade later, about 90% of patients with schizophrenia received SGAs at a cost exceeding \$10 billion.¹¹⁴ In 2006, U.S. total sales of SGAs reached \$11.5 billion.¹¹⁵

Because schizophrenia is such a debilitating illness, most sufferers of the condition do not work; family members and/or public health funds pay most of their health care expenses. Between 1994 and 2003, the number of individuals receiving Social Security benefits for schizophrenia increased from

112. Anthony F. Lehman et al., *Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition*, 161 AM. J. PSYCHIATRY 1, 28 (Supp. Feb. 2004). This phenomenon was not restricted to the U.S. See, e.g., *Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia*, May 2002, National Institute for Health and Clinical Excellence, <http://www.nice.org.uk/Guidance/TA43> (last visited Jan. 6, 2009) (United Kingdom recommendations for using a SGA for persons newly diagnosed with schizophrenia); Stephan Heres et al., *Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics*, 163 AM. J. PSYCHIATRY 185, 185 (2006) (noting that SGAs "are now defined as the gold standard in most aspects of treatment, at least in highly industrialized countries").

113. See, e.g., Douglas Mossman & Douglas S. Lehrer, *Conventional and Atypical Antipsychotics and the Evolving Standard of Care*, 51 PSYCHIATRIC SERVICES 1528, 1529 tbl.1 (2000). Justifications for higher prices included the high expectations for SGAs (that is, that they were more effective, less toxic drugs), cost-savings from lower uses of other healthcare resources, and the costs of drug development. See *infra* notes 121-124, notes 364-371, and accompanying text.

114. Robert H. Rosenheck, *Outcomes, Costs, and Policy Caution: A Commentary on the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUILASS 1)*, 63 ARCHIVES GEN. PSYCHIATRY 1074, 1074 (2006).

115. *Vital Signs: Seroquel Led Antipsychotics Sales in 2006*, 35 CLINICAL PSYCHIATRY NEWS 1 (May 2007). For some perspective, in 2005, about 633,000 physicians (5.1% of them psychiatrists) held jobs in the U.S., and the median psychiatrists' income was \$180,000. BUREAU OF LABOR STATISTICS, *Physicians and Surgeons*, in U.S. DEP'T OF LABOR, OCCUPATIONAL OUTLOOK HANDBOOK, 2008-09 EDITION 4 tbl.1, available at <http://www.bls.gov/oco/ocos074.htm>. Thus, total earnings of all psychiatrists was $633,000 \times 0.051 \times \$180,000 = \$5.8$ billion — about half of what was spent on just antipsychotic medication.

400,000 to 550,000.¹¹⁶ Between 1993 and 2001, as use of SGAs by Medicaid beneficiaries with schizophrenia climbed from 0 to 69%, annual per-patient drug costs climbed from \$586 to \$2,854.¹¹⁷ In 2002, the Medicaid program spent \$3.73 billion on antipsychotic medications.¹¹⁸ Risperidone, olanzapine, and quetiapine accounted for 88% of these dollars, and the costs for these SGAs ranked first, second, and fourth, respectively, among *all* prescription drugs paid for by Medicaid.¹¹⁹ By 2001, antipsychotic medications accounted for more government spending than any other category of drugs because of a 610% increase in Medicaid spending fueled largely by the switch to SGAs.¹²⁰

At the time, the switch and the added costs seemed justified, given what psychiatrists believed. The arrival of the SGAs was accompanied by dozens of studies that reported lower rates of adverse effects,¹²¹ better patient acceptance, and greater effectiveness¹²²—and by concerted, elaborate promotional efforts by the pharmaceutical companies that manufactured and sold SGAs.¹²³ The FGAs had produced relatively modest benefit (and did not seem to reduce disability a great deal), so treating schizophrenia had often been relegated to the unglamorous wards of state hospitals. The SGAs gave clinicians reason to feel more hopeful about the prognoses of schizophrenia's sufferers, and

116. Rosenheck, *supra* note 114, at 1074 (citing Pamela Mazerski, Associate Commissioner, Social Security Administration, written communication, 2004).

117. Mark Duggan, *Do New Prescription Drugs Pay for Themselves? The Case of Second-Generation Antipsychotics*, 24 J. HEALTH ECON. 1, 11 tbl.2:7 (2005).

118. *Id.* at 2. This includes uses of these drugs to treat not just schizophrenia, but bipolar disorder, dementia, and other conditions. See *infra* Part II.D.3 for discussion of the expanded prescribing of SGAs for FDA indications and “off-label”.

119. Duggan, *supra* note 117, at 2-3.

120. *Id.* at 13.

121. See, e.g., Correll et al., *supra* note 103, at 414.

122. See, e.g., John M. Davis et al., *A Meta-Analysis of the Efficacy of Second-Generation Antipsychotics*, 60 ARCHIVES OF GEN. PSYCHIATRY 553, 553 (2003) (reviewing 124 studies and concluding that four SGAs — clozapine, amisulpride, risperidone, and olanzapine — are more efficacious than FGAs).

123. Commenting on this, one observer noted that a number of the ... studies [comparing FGAs and SGAs] that have been published were developed and sponsored by the pharmaceutical companies whose medications were being evaluated, raising concerns about potential sources of bias in experimental design or interpretation of outcomes.

David A. Lewis, *Atypical Antipsychotic Medications and the Treatment of Schizophrenia*, 159 AM. J. PSYCHIATRY 177 (2002). Two schizophrenia researchers commented that

aggressive marketing by pharmaceutical companies and their pervasive involvement in continuing medical education has contributed to some confusion among clinicians about how available pharmacologic strategies compare and what they can realistically accomplish. Industry-sponsored drug trials are the major source of clinical trial information, and because Phase IV trials are conducted at least in part for marketing purposes, resulting biases can compromise their utility.

Rajiv Tandon & Michael D. Jibson, *Pharmacologic Treatment of Schizophrenia: What the Future Holds*, 6 CNS SPECTRUMS 980, 984 (2001) (citations omitted). As later portions of this article show, these remarks proved prescient.

effective, intensive marketing of SGAs got psychiatrists' attention and helped spur interest in treating schizophrenia. The higher prices of SGAs seemed justified by studies maintaining that prescribing SGAs did not raise (and might even reduce) *overall* costs for patient care compared with the overall costs incurred by patients treated with FGAs.¹²⁴

3. Off-Label Uses

By the early years of the twenty-first century, use of SGAs had expanded rapidly and extended well beyond treating schizophrenia and closely related psychotic disorders.¹²⁵ This made sense: what made SGAs appealing choices for treating patients with schizophrenia also made SGAs attractive for treating both patients who had other conditions for which psychiatrists used FGAs and patients who might have benefited from FGAs were it not for their neuromotor side effects.

The rapid rise in expenditures for SGAs was due, in part, to physicians' prescribing more than one of these drugs at a time¹²⁶ and to prescribing them "off-label."¹²⁷ Off-label use—that is, prescribing a medication or using a medical device outside the scope of its FDA-approved labeling¹²⁸ — is, in

124. See, e.g., Susan H. Hamilton et al., *Clinical and Economic Outcomes of Olanzapine Compared with Haloperidol for Schizophrenia. Results from a Randomised Clinical Trial*, 15 PHARMACOECONOMICS 469, 470 (1999) (higher olanzapine costs were offset by significantly lower inpatient and outpatient costs; study was sponsored by Eli Lilly and Company, which marketed olanzapine); Dennis A. Revicki, *The New Atypical Antipsychotics: A Review of Pharmacoeconomic Studies*, 1 EXPERT OPINION ON PHARMACOTHERAPY 249, 257 (2000) (evidence suggests that clozapine was cost effective treatment for patients who did not respond to FGAs; risperidone and olanzapine may be cost-neutral compared to FGAs). For a review of additional studies available by 2002, see Mossman, *supra* note 15, at 1080-88.

125. See Mossman, *supra* note 15, at 1043-44, nn.49-50 (describing indications as of 2002 for SGAs, but reporting these additional uses: clozapine for treatment-refractory mania, SGAs for acute mania and bipolar disorder, SGAs for schizoaffective disorder, olanzapine for treatment-resistant psychotic mood disorders, risperidone for borderline personality disorder, and quetiapine for mood disorders).

126. The practice is termed "polypharmacy," and though quite common, it has little empirical support. Constantin Tranulis et al., *Benefits and Risks of Antipsychotic Polypharmacy: An Evidence-Based Review of the Literature*, 31 DRUG SAFETY 7, 18 (2008) (reviewing studies of frequency, studies supporting such usage, and concluding that published scientific evidence does not support "[t]he pervasive practice of antipsychotic combination treatment for patients with schizophrenia spectrum disorders").

127. Marisa Elena Domino & Marvin S. Swartz, *Who Are the New Users of Antipsychotic Medications?* 59 PSYCHIATRIC SERVICES 507, 509 (2008) (population prevalence of SGA use increased sevenfold between 1997 and 2005, partly explained by high constant rate of off-label use).

128. Though off-label use most commonly refers to prescribing medications for conditions other than their FDA-approved indications, other meanings include prescribing drugs at unapproved doses, in unapproved formats (e.g., opening and mixing a capsule's contents with applesauce to aid swallowing), outside approved age groups (e.g. to children), longer than approved intervals, or at different dose schedules (e.g., all at bedtime, rather than two or three times a day).

general, a perfectly legal practice¹²⁹ that is very common¹³⁰ and well accepted¹³¹ throughout medicine.¹³² Winning FDA approval for a new drug takes years, and getting approval for additional indications takes more time—if pharmaceutical manufacturers decide to invest the effort and funds required to get a new FDA indication for an already-approved drug.¹³³ But patients have illnesses that need treatment “today,” and their physicians can address these problems only with available drugs. Often, off-label prescribing practices receive confirmation through scientific publications that endorse what physicians have been doing for years.¹³⁴ In recent years, however, off-label use

129. FDA approval permits drugs to be *marketed* in specific ways, but as each edition of the Physicians’ Desk Reference states, “Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling.” *PDR*, *supra* note 93, at Foreword. FDA approval does not “limit or interfere with the authority of a health care practitioner to prescribe” approved drugs or devices “for any condition or disease.” Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 396 (2009). The U.S. Supreme Court has stated that off-label prescribing “is an accepted and necessary corollary of the FDA’s mission to regulate.” *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350 (2001). Judicial endorsements of off-label use also include an appellate decision’s comment that “[b]ecause the pace of medical discovery runs ahead of the FDA’s regulatory machinery, the off-label use of some drugs is frequently considered to be ‘state-of-the-art’ treatment.” *Richardson v. Miller*, 44 S.W.3d 1, 14, n.11 (Tenn. Ct. App. 2000).

130. Sharon Conroy et al., *Survey of Unlicensed and Off Label Drug Use in Paediatric Wards in European Countries*, 320 *BRIT. MED. J.* 79, 80 tbl.1 (thirty-nine percent of prescriptions were off-label); David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 *ARCHIVES OF INTERNAL MED.* 1021, 1023 (2006) (twenty-one percent of prescriptions were off-label).

131. David S. Baldwin and Nick Kosky, *Off-label Prescribing in Psychiatric Practice*, 13 *ADVANCES PSYCHIATRIC TREATMENT* 414, 414 (2007) (acknowledging that “most authorities agree that use of drugs outside the terms of their license is a necessary part of psychiatric practice”).

132. Stuart L. Nightingale, *Off-Label Use of Prescription Drugs*, 68 *AM. FAM. PHYSICIAN* 425, 425 (2003) (“Off-label use is legal and, with important qualifications, generally embraced by physicians and other health care providers, health care institutions, insurers, pharmaceutical companies, and even the FDA.”).

133. According to one estimate, the average cost of drug development is \$802 million (in 2000 dollars). Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 *J. HEALTH ECON.* 151, 151 (2003). The process of research and development “often extends for a decade or more.” *Id.* at 153.

134. For example, sildenafil citrate was originally developed as a potential treatment for angina, but during early clinical trials, observations of its effectiveness for erectile dysfunction led to its being released in March 1998 as *Viagra*®, a treatment for male impotence. Andrew Hopkins et al., *Chemical Tools for Indications Discovery*, in *ANNUAL REPORTS IN MEDICINAL CHEMISTRY* 339, 340 (Annette M. Doherty et al. eds., 2005); Alain Gregoire, *Viagra: On Release: Evidence on the Effectiveness of Sildenafil is Good*, 317 *BRIT. MED. J.* 759 (1998). A prestigious medical journal recently published a study demonstrating the effectiveness of prescribing sildenafil to women with sexual problems induced by antidepressant therapy. H. George Nurnberg et al., *Sildenafil Treatment of Women with Antidepressant-Associated Sexual Dysfunction: A Randomized Controlled Trial*, 300 *JAMA* 395 (2008) (study conducted between 2003 and 2007). Physicians had reported this practice years earlier, however. H. George Nurnberg et al., *Sildenafil for Iatrogenic Serotonergic Antidepressant Medication-Induced Sexual Dysfunction in 4 Patients*, 60 *J. CLINICAL PSYCHIATRY* 33 (1999) (rapid reversal of dysfunction in male and female patients). In June

has received increasing scrutiny because in many instances, such prescribing occurs with little scientific rationale.¹³⁵

In significant part, however, increased prescribing of SGAs was for uses—particularly treatment of mood disorders—that were once off-label but that subsequently received FDA approval.¹³⁶ As of early 2009, approved indications for SGAs included:

- aripiprazole: schizophrenia (adults and in adolescents ages 13-17 years); bipolar disorder (by itself and in combination with mood-stabilizing drugs, for adults and children ages 10-17 years); as an add-on therapy with antidepressants; agitation associated with schizophrenia or bipolar disorder¹³⁷
- clozapine: treatment-resistant schizophrenia; to lower suicide risk in people with schizophrenia or schizoaffective disorder¹³⁸
- olanzapine: schizophrenia; bipolar disorder (as monotherapy, in combination therapy with mood stabilizers, and to prevent relapse); agitation associated with schizophrenia or bipolar disorder;¹³⁹ bipolar depression¹⁴⁰
- quetiapine: schizophrenia, bipolar depression and mania, and adjunctive maintenance treatment in mania¹⁴¹
- risperidone: schizophrenia in adults and adolescents ages 13-17 years; bipolar disorder in adults and children ages 10-17 years; aggres-

2005, sildenafil citrate, marketed as Revatio®, received FDA approval as treatment for pulmonary hypertension. Yael Waknine, *FDA Approvals: Revatio, Xeloda, Alinia*, MEDSCAPE MEDICAL NEWS, June 23, 2005, available at <http://www.medscape.com/viewarticle/507232>.

135. Becky A. Briesacher et al., *The Quality of Antipsychotic Drug Prescribing in Nursing Homes*, 165 ARCHIVES INTERNAL MED. 1280 (2005) (More than one-fourth of nursing home residents received antipsychotic medications; many prescriptions were off-label and/or exceeded dosage guidelines.); Radley, *supra* note 130, at 1025 (Though many off-label drug mentions represented logical extensions of FDA-approved indications, “[n]o more than 30% of the off-label [uses] ... were supported by strong scientific evidence.”).

136. Domino & Swartz, *supra* note 127, at 511.

137. U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION: ABILIFY® 4 (2008), available at <http://www.fda.gov/cder/foi/label/2008/021436s026,021729s012,021713s019,021866s0131bl.pdf>.

138. U.S. FOOD & DRUG ADMIN., PATIENT INFORMATION SHEET: CLOZAPINE (MARKETED AS CLORAZIL) (Sept. 6, 2006), <http://www.fda.gov/cder/drug/InfoSheets/patient/clozapinePIS.htm>.

139. U.S. FOOD & DRUG ADMIN., ZYPREXA®: OLANZAPINE TABLETS 7 (2006), available at <http://www.fda.gov/cder/foi/label/2007/020592s042s043,021086s022s023,021253s0261bl.pdf>

140. U.S. FOOD & DRUG ADMIN., SYMBYAX®: OLANZAPINE AND FLUXETINE HCL CAPSULES 7 (2008), available at <http://www.fda.gov/cder/foi/label/2008/021520s0171bl.pdf> (in Symbyax®, a combination drug with fluoxetine).

141. U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION: SEROQUEL® 4 (2008), available at <http://www.fda.gov/cder/foi/label/2008/020639s025s037s038s0401bl.pdf>.

sion and moodiness in children ages 5-16 years with autistic disorder¹⁴²

- ziprasidone: schizophrenia; agitation in schizophrenia (intramuscular injections); bipolar mania¹⁴³

E. Medical and Scientific Reconsideration

The last few years have witnessed a major reconsideration of the risks, benefits, and costs associated with SGAs, such that psychiatrists are not nearly as confident about their value and superiority as they were at the turn of the 21st century.

1. Risks of SGAs

As we noted earlier, the SGAs seemed to be a significant pharmacological advance because of their apparent capacity to counteract pathological nervous system functioning—that is, to reduce psychosis—without incurring nearly the risk that FGAs posed to other parts of the nervous system in the form of extrapyramidal side effects and TD. By the late 1990s, however, clinicians recognized that SGAs caused other side effects that might, in the long run, be just as significant. Individuals with schizophrenia have a substantially lower life expectancy than average, chiefly because of coronary heart disease.¹⁴⁴ Weight gain is a recognized risk associated with FGA treatment, but the weight gain associated with SGAs appears even greater¹⁴⁵ By 2002, several other reports¹⁴⁶ had emerged showing that, in addition to weight gain,

142. U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION: RISPERDAL ® 3 (2007), available at <http://www.fda.gov/cder/foi/label/2007/020272s46s47,20588s36s37,21444s20s21lbl.pdf>.

143. U.S. FOOD & DRUG ADMIN., GEODON ® (ZIPRASIDONE HCl) CAPSULES 7-8 (2007), available at <http://www.fda.gov/cder/foi/label/2008/021520s017lbl.pdf>.

144. Charles H. Hennekens et al., *Schizophrenia and Increased Risks of Cardiovascular Disease*, 150 AM. HEART J. 1115, 1116-18 (2005) (causes include cigarette smoking, obesity leading to dyslipidemia, diabetes, hypertension, less access to and use of medical care, and not following health regimens).

145. David B. Allison et al., *Antipsychotic-Induced Weight Gain: A Comprehensive Research Synthesis*, 156 AM. J. PSYCHIATRY 1686, 1690 tbl.4 (1999) (reporting more weight gain with clozapine, olanzapine, and risperidone than with haloperidol or placebo; several FGAs associated with weight gain as well, but generally less than with SGAs).

146. See, e.g., Michael J. Sernyak et al., *Association of Diabetes Mellitus with Use of Atypical Neuroleptics in the Treatment of Schizophrenia*, 159 AM. J. PSYCHIATRY 561, 564 fig.1 (2002) (patients who took SGAs were more likely to be treated for diabetes than were patients taking FGAs); Brian B. Sheitman, et al., Letter to the Editor, *Olanzapine-Induced Elevation of Plasma Triglyceride Levels*, 156 AM. J. PSYCHIATRY 1471, 1471-72 (1999); Donna A. Wirshing et al., *The Effects of Novel Antipsychotics on Glucose and Lipid Levels*, 63 J. CLINICAL PSYCHIATRY 856, 863 (2002) (Chart review showed elevated glucose levels and triglyceride levels in patients receiving SGAs, and recommending that physicians “be more aggressive in monitoring glucose and lipid levels.”).

SGAs¹⁴⁷ were associated with abdominal obesity, elevated blood lipids, high blood pressure, and elevated fasting glucose—a “metabolic syndrome”¹⁴⁸ that substantially heighten the risk of cardiovascular disease. In 2004, new guidelines were published for monitoring the weight, blood pressure, blood sugar, blood lipids, and blood pressure of patients taking SGAs.¹⁴⁹

Doctors who treat disturbed elderly patients with dementia have no good pharmacologic options, yet doing nothing and allowing the agitation to continue may put patients and others at risk. SGAs successfully reduce aggression in elderly patients with dementia.¹⁵⁰ Although SGAs have never received approval for this use, doctors have favored SGAs for this purpose because they posed a much lower risk of TD than did FGAs.¹⁵¹ Physicians believed this was a benign practice until studies showed that SGAs were associated with serious adverse events and excess mortality risk.¹⁵² Since then, the FDA has a required inclusion of “black box” warning for all SGAs discouraging the use of SGAs in elderly demented patients with behavioral disturbances.¹⁵³

147. Recent data suggest that clozapine and or olanzapine often induce substantial weight gain, lipid abnormalities, and type 2 diabetes mellitus; risperidone and quetiapine often induce moderate increases in weight; and aripiprazole and ziprasidone induce the least weight gain and relatively little risk adverse metabolic problems. John W. Newcomer, *Second-Generation (Atypical) Antipsychotics and Metabolic Effects: A Comprehensive Literature Review*, 19 CNS DRUGS 1, 1 (Supp. 1 2005).

148. Scott M. Grundy et al., *Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement*, 112 CIRCULATION 2735, 2735-36 (2005).

149. American Diabetes Association et al., *Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes*, 27 DIABETES CARE 596, 599 (2004) (describing monitoring protocol). Psychiatrists appear to have been slow to implement these guidelines. Dan W. Haupt et al., *Prevalence and Predictors of Lipid and Glucose Monitoring in Commercially Insured Patients Treated With Second-Generation Antipsychotic Agents*, 166 AM. J. PSYCHIATRY 345, 349 (2009) (less than thirty percent of psychiatrists had patients undergo lipid or glucose testing before starting a SGA; low rates of subsequent monitoring).

150. Clive Ballard et al., *Atypical Antipsychotics for Aggression and Psychosis in Alzheimer's Disease*, Review, in THE COCHRANE LIBRARY 1, 13 (2006).

151. FGAs had long been used for this purpose. See ROSENBAUM ET AL., *supra* note 21, at 23-24 (mentioning use of haloperidol and fluphenazine after stating preference for risperidone); Lon S. Schneider et al., *Risk of Death with Atypical Antipsychotic Drug Treatment for Dementia: Meta-analysis of Randomized Placebo-Controlled Trials*, 294 JAMA 1934, 1934 (2005) (noting that antipsychotic drugs “have been the mainstay of psychopharmacological treatment for” “elderly patients with dementia [who have] develop[ed] aggression, delusions, and other neuropsychiatric symptoms”).

152. *Id.*

153. U.S. Food and Drug Admin., *FDA Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances*, Apr. 11, 2005, available at <http://www.fda.gov/Cder/drug/advisory/antipsychotics.htm> (citing 1.6-1.7 fold increase in mortality). The FGAs appear just as risky, however. See, e.g., Soko Setoguchi et al., *Potential Causes of Higher Mortality in Elderly Users of Conventional and Atypical Antipsychotic Medications*, 56 J.

2. Doubts about Superiority

Despite the growing evidence about adverse metabolic effects, psychiatrists still felt confident that SGAs, as a group, posed less risk of TD and other neuromotor side effects than did FGAs.¹⁵⁴ This feature of SGAs and the belief that SGAs were more effective than FGAs¹⁵⁵ seemed to justify higher prices through savings on hospitalization costs.¹⁵⁶ Although a few scholars and researchers questioned these views,¹⁵⁷ their views represented a decided minority. Since 2005, however, a series of studies have led increasing numbers of psychiatrists to question whether SGAs are as advantageous as they once thought.

Much of the evidence supporting the superiority of SGAs came from studies sponsored by pharmaceutical manufacturers under restrictive conditions which, though suitable for comparing a test drug to a placebo, did not replicate what happens in real-world psychiatric practice.¹⁵⁸ To address this knowledge gap, the National Institute of Mental Health (NIMH) commissioned and funded the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.¹⁵⁹ This study undertook a double-blind comparison of then-available SGAs and a moderately-dosed FGA (perphenazine) under typical outpatient treatment conditions.¹⁶⁰ To be eligible for the CATIE study,

AM. GERIATRICS SOC'Y 1644, 1648 (2008) (hazard ratio for risk of death during treatment with FGAs was 1.23 compared to treatment with SGAs).

154. Correll et al., *supra* note 103, at 414 (“reduced risk of tardive dyskinesia”).

155. Davis et al., *supra* note 122, at 553 (effect sizes of four SGAs were “greater than those of FGAs”).

156. Hamilton et al., *supra* note 124, at 470.

157. See, e.g. Mossman & Lehrer, *supra* note 113, at 1529-30; Revicki, *supra* note 124, at 429; and John Geddes et al., *Atypical Antipsychotics in the Treatment of Schizophrenia: Systematic Overview and Meta-Regression Analysis*, 321 BRIT. MED. J., 1371, 1371, 1374-76 (2000) (meta-analysis of fifty-two studies suggests that compared to moderately dosed FGAs, SGAs “had no benefits in terms of efficacy or overall tolerability,” though SGAs caused fewer neuromotor side effects).

158. T. Scott Stroup et al., *The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Project: Schizophrenia Trial, Design and Protocol Development*, 29 SCHIZOPHRENIA BULL. 15-16 (2003).

In addition, psychiatrists did not know whether one of the SGAs might be superior to the others. Available industry-sponsored studies almost always showed that the sponsor's drug was superior. See Heres et al., *supra* note 112, at 187-89 (discussing outcomes and possible sources of bias). The CATIE study offered the potential to provide an independent comparison of the SGAs.

159. Stroup et al., *supra* note 158, at 16-17.

160. Patients were randomly assigned to receive olanzapine, quetiapine, risperidone, perphenazine, or (after its introduction in 2002) ziprasidone. These drugs were placed in identical-appearing capsules so that neither patients nor their doctors knew which drug was being administered. Doctors could adjust doses from one to four capsules a day based on their judgments about patients' needs. Jeffrey A. Lieberman et al., *Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia*, 353 N. ENG. J. MED. 1209, 1211 (2005) [hereinafter Lieberman, *Effectiveness*]. In contrast to using high doses of the high-potency FGA haloperidol, the CATIE study chose “perphenazine because of its lower potency and moderate side-effect profile.” *Id.* at 1215.

patients were required to have schizophrenia, but many of the customary exclusion criteria in clinical trials (e.g., substance abuse or medical problems) were not imposed.¹⁶¹ Data for the study, in which patients were followed for up to 18 months, were collected in 2001-04,¹⁶² and publications of results began appearing in 2005.

The chief measure of overall effectiveness used in by the first CATIE publication was time to all-cause discontinuation. Essentially, this criterion asked, “How long did patients continue taking each medication?”¹⁶³ By this measure, olanzapine outperformed the risperidone and quetiapine—but not perphenazine. No medication did very well, though—only a minority of patients remained on their original medication after 18 months. Moreover, olanzapine’s apparent edge in effectiveness was counterbalanced by the drug’s causing the most weight gain and metabolic problems.¹⁶⁴ Most notably, the researchers found *no* differences among the medications in rates of neuromotor side effects—the driving rationale for preferring SGAs.¹⁶⁵ Commenting on these findings, two CATIE researchers stated, “The lack of difference between the new second-generation antipsychotics and perphenazine surprised ... us. However, such surprises are why double-blind randomized clinical trials like CATIE are needed.”¹⁶⁶

Reactions to this initial publication were varied and consistent with expectable interests of their sources. Pharmaceutical companies used selected aspects of the CATIE findings to point out superiorities of their own prod-

161. Stroup et al., *supra* note 158, at 19.

162. Lieberman, *supra* note 160, at 1210.

163. The rationale for this criterion is as follows:

stopping or changing medication is a frequent occurrence and major problem in the treatment of schizophrenia. In addition, this measure integrates patients’ and clinicians’ judgments of efficacy, safety, and tolerability into a global measure of effectiveness that reflects their evaluation of therapeutic benefits in relation to undesirable effects.

Id. at 1211.

164. Seventy-four percent of patients stopped their original study medication in within 18 months. The time to discontinuation was longest for olanzapine, but the difference reached statistical significance only when compared to risperidone and quetiapine. *Id.* at 1209, 1212-16.

165. *Id.* at 1215. See also Del D. Miller et al., *Extrapyramidal Side-Effects of Antipsychotics in a Randomised Trial*, 193 BRIT. J. PSYCHIATRY 279, 279 (2008) (finding no significant differences in neuromotor side effects or TD when comparing SGAs with perphenazine or with each other).

166. Jeffrey A. Lieberman & John K. Hsiao, Letter to the Editor, *Interpreting the Results of the CATIE Study*, 57 PSYCHIATRY SERVICES 139 (2006). The CATIE study’s designers expected that their results would spell the end of FGA usage by providing definitive evidence that SGAs were superior to FGAs. As Dr. Lieberman told an audience at the American Psychiatric Association’s 58th Institute on Psychiatric Services, “I want to emphasize, we didn’t expect the results to turn out this way. We said, ‘Let’s put the final nail in that coffin.’” Karla Harby, *Schizophrenia Drugs Found Similar in Efficacy*, MEDSCAPE MEDICAL NEWS, Oct. 9, 2006, available at <http://www.medscape.com/viewarticle/545738>.

ucts.¹⁶⁷ Patient advocacy groups feared that the CATIE results might be used to restrict access to certain SGAs.¹⁶⁸ The CATIE study's lead author felt that the findings suggested that the medications had significant differences and that treatment should be individualized. Yet "the results of the CATIE study do not appear to justify the current 95 percent market share for second-generation agents. They simply aren't that much better."¹⁶⁹ A *New York Times* editorial concluded that "[t]he nation [had been] wasting billions of dollars on heavily marketed drugs that have never proved themselves in head-to-head competition against cheaper competitors."¹⁷⁰

Since publication of the initial CATIE report, subsequent studies have continued to undermine the view that SGAs are superior to FGAs. All the medications used in the CATIE study appear to improve cognitive functioning equally after two months of treatment;¹⁷¹ after 18 months, CATIE patients taking perphenazine appeared to have benefited the most.¹⁷² SGAs did no better than perphenazine at improving psychosocial functioning¹⁷³ or overall quality of life,¹⁷⁴ but overall treatment expenditures in CATIE patients who received perphenazine were lower because of the medication's lower cost.¹⁷⁵

167. Marvin S. Swartz, *Introduction to the CATIE Special Section*, 59 *PSYCHIATRY SERVICES* 497, 497 (2008) (observing that "too much of the well-deserved debate and discourse on CATIE was thinly veiled industry spin....").

168. Jeffrey A. Lieberman, *What the CATIE Study Means for Clinical Practice*, 57 *PSYCHIATRIC SERVICES* 1075 (2006).

169. *Id.* at 1075.

170. *Comparing Schizophrenia Drugs*, *N.Y. TIMES*, Sep. 21, 2005, at A24, available at 2005 WLNR 14853155.

171. See Richard S. E. Keefe et al., *Neurocognitive Effects of Antipsychotic Medications in Patients with Chronic Schizophrenia in the CATIE Trial*, 64 *ARCHIVES GEN. PSYCHIATRY* 633, 633 (2007).

172. See *id.* at 641. Noting that these results differed from those previously reported, the authors commented that "findings from prior reports may not generalize well to ... everyday clinical practice," and that "previous studies ... used high dosages of [FGAs], ... creating an unfair comparison." *Id.* In support of this conclusion are the results of the European First Episode Schizophrenia Trial (EUFEST), which showed "no overall differences" in the cognitive improvement experienced by patients taking low-dose haliperidol (1-4 mg/day) or SGAs. Michael Davidson et al., *Cognitive Effects of Antipsychotic Drugs in First-Episode Schizophrenia and Schizophreniform Disorder: A Randomized, Open-Label Clinical Trial (EUFEST)*, *AM. J. PSYCHIATRY* 1 <http://ajp.psychiatryonline.org/cgi/content/appi.ajp.2008.08060806v1> (epub ahead of print April 15, 2009).

173. Marvin S. Swartz et al., *Effects of Antipsychotic Medications on Psychosocial Functioning in Patients with Chronic Schizophrenia: Findings From the NIMH CATIE Study*, 164 *AM. J. PSYCHIATRY* 428, 428 (2007) (all groups improved; no differences among treatment groups at 6, 12, or 18 months).

174. Robert A. Rosenheck et al., *Cost-Effectiveness of Second-Generation Antipsychotics and Perphenazine in a Randomized Trial of Treatment for Chronic Schizophrenia*, 163 *AM. J. PSYCHIATRY* 2080, 2087 (2006).

175. *Id.* at 2084 (total monthly health care costs averaged twenty to thirty percent less in perphenazine group).

All the medications lowered the risk of violence, but again, SGAs were not superior to perphenazine.¹⁷⁶

The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS), a non-commercial study funded by the British National Health Service, yielded similar results: patients who received FGAs did no poorer than did recipients of SGAs in terms of quality of life, symptoms, or associated costs; if anything, it was FGA recipients who showed some signs (“a trend”) toward great improvement in symptoms and quality of life.¹⁷⁷ A subsequent CUtLASS publication reported that, as was found in the CATIE study, overall costs were lower but quality of life was *better* in the FGA-treated British patients.¹⁷⁸ That the findings of these studies were valid derived support from a previous study, funded by the U.S. Department of Veterans Affairs, showing no advantage of the olanzapine over moderately-dosed haloperidol.¹⁷⁹

The most recent meta-analysis on this topic suggests that the SGAs are not identical and that some appear superior to other antipsychotic drugs.¹⁸⁰ The authors of this meta-analysis note, however, that most of the studies they reviewed compared SGAs to haloperidol and focused on short-term efficacy under relatively constrained conditions, whereas CATIE and CUtLASS “focused on real-world effectiveness” of SGAs compared to lower potency FGAs.¹⁸¹ Finally, a study of treatment for early-onset psychosis in adolescents, which showed that olanzapine and risperidone were not superior to the FGA molindone, led investigators to “question the nearly exclusive use of second-generation antipsychotics to treat early-onset schizophrenia and schizoaffective disorder.”¹⁸²

Commenting on the findings in the studies they conducted, the chief investigators of the CATIE and CUtLASS studies concluded:

176. Jeffrey W. Swanson et al., *Comparison of Antipsychotic Medication Effects on Reducing Violence in People with Schizophrenia*, 193 BRIT. J. PSYCHIATRY 37, 37 (2008).

177. Peter B. Jones et al., *Randomized Controlled Trial of the Effect on Quality of Life of Second- vs First-Generation Antipsychotic Drugs in Schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)*, 63 ARCHIVES OF GEN. PSYCHIATRY 1079, 1085 (2006). Again, the study design allowed use of moderate doses of a lower potency FGA. *Id.*

178. L. M. Davies et al., *Cost-Effectiveness of First- v. Second-Generation Antipsychotic Drugs: Results from a Randomised Controlled Trial in Schizophrenia Responding Poorly to Previous Therapy*, 191 BRIT. J. PSYCHIATRY 14, 17 (2007).

179. Robert Rosenheck et al., *Effectiveness and Cost of Olanzapine and Haloperidol in the Treatment of Schizophrenia: A Randomized Controlled Trial*, 29 JAMA 2693, 2693 (2003).

180. Stefan Leucht et al., *Second-Generation Versus First-Generation Antipsychotic Drugs for Schizophrenia: A Meta-Analysis*, 373 LANCET 31, 31 (2009) (small-to-medium effect sizes indicate superiority of amisulpride [not available in the U.S.], clozapine, olanzapine, and risperidone).

181. *Id.*, at 40.

182. Linmarie Sikich et al., *Double-Blind Comparison of First- and Second-Generation Antipsychotics in Early-Onset Schizophrenia and Schizo-affective Disorder: Findings From the Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) Study*, 165 AM. J. PSYCHIATRY 1420, 1420 (2008).

[F]irst-generation drugs, if carefully prescribed, are as good as most second-generation drugs in many if not most patients with established schizophrenia. This is good news as it increases the range of choices of antipsychotic drugs. Careful prescribing of first-generation antipsychotics means using lower doses than was often done in the past and avoiding high-potency drugs.¹⁸³

Two researchers in schizophrenia put their conclusions quite succinctly: “Bottom line: the dichotomy between first- and second-generation antipsychotics is not supported by efficacy data (and now, effectiveness data), and only clozapine has documented superiority in treatment-resistant cases.”¹⁸⁴

F. Advertising; Response of Medical Organizations

A growing number of medical authorities believe that “the time has come to abandon the terms first-generation and second-generation antipsychotics, as they do not merit this distinction,”¹⁸⁵ and that psychiatrists were “beguiled” into thinking otherwise.¹⁸⁶ Thus far, however, the impact of these findings has been modest. A study of prescribing practices in New York state public hospitals found that use of perphenazine and clozapine increased following publication of the major CATIE results, suggesting “that CATIE’s findings may not have fallen entirely on deaf ears.” However, increases in uses of these two drugs were modest, and patients receiving of risperidone, olanzapine, quetiapine, and haloperidol far out-numbered those taking perphenazine.¹⁸⁷

A few psychiatrists have attempted to explain the disparity between what was believed a few years ago and what appears now to be the sobering truth. CATIE’s lead investigator has noted that real-world trials of medications almost always show less benefit than do trials designed to satisfy approval requirements of the FDA.¹⁸⁸ But in addition,

[T]he claims of superiority for the SGAs were greatly exaggerated. This may have been encouraged by an overly expectant community

183. Shón Lewis & Jeffrey Lieberman, *CATIE and CUI_LASS: Can We Handle the Truth?* 192 BRIT. J. PSYCHIATRY 161, 163 (2008).

184. William T. Carpenter & Robert W. Buchanan, *Lessons to Take Home From CATIE*, 59 PSYCHIATRY SERVICES 523, 525 (2008).

185. Peter Tyrer & Tim Kendall, *The Spurious Advance of Antipsychotic Drug Therapy*, 373 LANCET 4, 5 (2009).

186. Shankar Vedantam, *In Antipsychotics, Newer Isn’t Better: Drug Find Shocks Researchers*, WASHINGTON POST, Oct. 3, 2006, at A01 (quoting Dr. Peter Jones).

187. Leslie Citrome et al., *Did CATIE Influence Antipsychotic Use?* 59 PSYCHIATRY SERVICES 476, 476 (2008) (after CATIE publications, patients taking perphenazine increased from 1.2% to 2.6%, but Figure 1 shows that nearly 30% of patients still received risperidone, 26% received olanzapine, 22% received quetiapine, and 18% received haloperidol).

188. Jeffrey A. Lieberman, *Comparative Effectiveness of Antipsychotic Drugs*, 63 ARCHIVES GEN. PSYCHIATRY 1069, 1069 (2006) (citing T. Scott Stroup et al., *Clinical Trials for Antipsychotic Drugs: Design Conventions, Dilemmas and Innovations*, 5 NAT. REV. DRUG DISCOVERY 133 (2006)).

of clinicians and patients eager to believe in the power of new medications. At the same time, the aggressive marketing of [SGAs] may have contributed to this enhanced perception of their effectiveness in the absence of empirical evidence.¹⁸⁹

Three psychiatrists with expertise in public policy matters agree that financial incentives played an important role: “the rapid adoption of the second-generation antipsychotics was hastened by the high degree of profitability of these medications, which helped to promote a belief ... that these drugs represented ‘best practice’ treatments.”¹⁹⁰ Two British psychiatrists were more blunt: “The 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.”¹⁹¹

The recognition of marketing’s contribution to the ascendancy of SGAs comes at a time when all medical specialties are recognizing that commercial product promotion can have a pernicious effect on patient care and clinical decision-making. We return to this topic in Part IV, but we first summarize how litigators have responded to the harms and costs of SGAs.

III. LEGAL RESPONSES: HOLDING DRUG COMPANIES RESPONSIBLE

A. Litigation Concerning Olanzapine: An Illustrative Case

Over the past decade, Eli Lilly & Company has borne the brunt of legal actions filed by various parties with grievances about SGAs.¹⁹² In Lilly’s case, the accusations have centered on allegations of failure to disclose side effects and off-label marketing of the highly successful SGA olanzapine, which Lilly markets under the trade name Zyprexa®. Resolution of this litigation continued as we completed this article, and fully chronicling these cases with appropriate depth is thus impossible. Even were all the litigated concluded, however, providing a comprehensive summary would take us far beyond our intended scope.¹⁹³ Here, we only highlight Lilly’s recent legal predicaments, which illustrate the array of legal consequences that pharmaceutical manufacturers can face if they fail to adhere to or knowingly circumvent regulations on the promotions of their products.

189. Lieberman, *supra* note 188, at 1070.

190. Robert Drake et al., *What Explains the Diffusion of Treatments for Mental Illness?* 165 AM. J. PSYCHIATRY 1385, 1388 (2008).

191. Tyrer & Kendall, *supra* note 185, at 4.

192. Various states have also initiated lawsuits against the manufacturers of the SGAs aripiprazole (Abilify®, Bristol-Myers Squibb), risperidone (Risperdal®, Johnson & Johnson), and quetiapine (Seroquel®, AstraZeneca). PsychSearch.net, State Lawsuits – Atypical Antipsychotics, <http://www.psychsearch.net/lawsuits.html> (last visited Feb. 19, 2009).

193. In addition to the substantive state and federal legal claims that we focus on here, the litigation has often raised complex jurisdictional and procedural issues that, for purposes of exposition, we largely ignore.

The successful promotion and sale of effective, safe pharmaceutical products is in drug companies' ultimate self-interest. We can think of no reason why pharmaceutical manufacturers should not realize this. We therefore believe that the most plausible explanations for their behavior—even when that behavior clearly skirts regulations—should emphasize the companies' belief that their products are useful and will help people. Nonetheless, as this section explains, the potential litigation losses for manufacturers who fail to “play by the rules” can run into several billion dollars.¹⁹⁴

Lawsuits have been filed by both state attorney general offices and olanzapine users themselves, asserting that Lilly failed to warn the public of problematic health conditions linked to the use the drug and illegally marketed the drug for off-label uses.

1. States Cases

In March 2008, Lilly settled its first state-initiated, olanzapine-related lawsuit for \$15 million.¹⁹⁵ The suit, filed in April 2006 by the Alaska Attorney General's Office, alleged that Lilly had known about olanzapine's potential to cause high blood sugar, weight gain, diabetes, and pancreatitis, and nonetheless failed to warn both the FDA and the public about such risks.¹⁹⁶ The complaint also stated that Lilly had failed to mention these risks in its nationwide olanzapine marketing campaign and had even instructed its salespeople (or, to use physicians' term, “drug reps”¹⁹⁷) to downplay the drug's side effects.¹⁹⁸ Much like the complaints filed by other states' attorneys general, the Alaska complaint set forth the following counts:

- strict products liability for failure to warn
- strict products liability for design defect
- fraudulent and negligent misrepresentation
- general negligence, and
- violations of the state's unfair trade practices and consumer protection statutes.¹⁹⁹

According to news sources, Alaska believed the suit to be worth some \$200 million dollars.²⁰⁰

194. Alex Berenson, *Lilly Settles With 18,000 Over Zyprexa*, N.Y. TIMES, Jan. 5, 2007, at C1.

195. Jacob Goldstein, *Lilly Settles Alaska Zyprexa Case for \$15 Million*, WALL ST. J. HEALTH BLOG, Mar. 26, 2008, <http://blogs.wsj.com/health/2008/03/26/lilly-settles-alaska-zyprexa-case-for-15-million> (last visited Aug. 10, 2008).

196. Complaint at 3, *Alaska v. Eli Lilly & Co.*, No. 3AN-06-5630 CIV (Alaska Super. Ct. Feb. 28, 2006).

197. Elliott, *supra* note 6. Dr. Elliott is a physician and ethicist at the University of Minnesota.

198. Complaint, *supra* note 196, at 6.

199. *Id.* at 9-14.

200. *See* Goldstein, *supra* note 195.

As of early 2009, other states that had filed suit against Lilly included Connecticut, Louisiana, Mississippi, Montana, New Mexico, Pennsylvania, South Carolina, Utah, Vermont, and West Virginia;²⁰¹ these lawsuits were filed between 2005 and 2008, with Connecticut's being the most recent in March 2008.²⁰² The Connecticut complaint also alleged that Lilly had knowingly misrepresented olanzapine's harmful side effects, including diabetes, weight gain, and cardiovascular problems, thereby causing the Connecticut Medical Assistance Program (CMAP) to incur financial injury and state consumers to suffer medical injury.²⁰³ Unlike the Alaska complaint, the Connecticut complaint was filed in the United States District Court for the Eastern District of New York—the location of the multi-district Zyprexa litigation²⁰⁴ (MDL; also referred to as the "Zyprexa MDL").²⁰⁵ In addition, Connecticut's complaint contained claims for violations of the Racketeering Influenced and Corrupt Organizations Act (RICO)²⁰⁶ against Lilly for unlawful marketing practices.²⁰⁷

201. See PsychSearch.net, *supra* note 192. Although they did not file lawsuits, other states have taken investigative steps against Lilly regarding olanzapine. *Id.* For instance, California, Florida, and Illinois each subpoenaed Lilly for documents relating to the drug. *Id.* Lilly's 2007 SEC annual filing reports that thirty states were "part of a multistate investigative effort being coordinated by an executive committee of attorneys general" that was investigating the company. Eli Lilly & Co., Annual Report (Form 10-K/A) at 35, 75 (Oct. 21, 2008), available at <http://investor.lilly.com/secfiling.cfm?filingID=950137-08-12864>.

202. Complaint at 1, Connecticut v. Eli Lilly & Co., No. CV-08-955 (E.D.N.Y. Mar. 6, 2008).

203. *Id.* at 5.

204. Multidistrict litigation is outlined in Title 28, § 1407 of the United States Code, which explains when such litigation may be appropriate and the procedures that follow once the involved cases have been consolidated:

When civil actions involving one or more common questions of fact are pending in different districts, such actions may be transferred to any district for coordinated or consolidated pretrial proceedings. Such transfers shall be made by the judicial panel on multidistrict litigation . . . upon its determination that transfers for such proceedings will be for the convenience of parties and witnesses and will promote the just and efficient conduct of such actions. Each action so transferred shall be remanded by the panel at or before the conclusion of such pretrial proceedings to the district from which it was transferred unless it shall have been previously terminated: *Provided, however,* That the panel may separate any claim, cross-claim, counter-claim, or third-party claim and remand any of such claims before the remainder of the action is remanded.

28 U.S.C. § 1407(a) (2006).

205. See United States Judicial Panel on Multidistrict Litigation, MDL-1596: In re Zyprexa Products Liability Litigation, http://www.jpml.uscourts.gov/Docket_Information/body_docket_information.html (last visited Apr. 25, 2009). Other states taking part in the MDL have included Louisiana, Montana, New Mexico, Mississippi, and West Virginia. See also Class Action Certification Draft Discussion at 22, In re Zyprexa Products Liability Litigation, No. 04-MD-1596 (E.D.N.Y. July 2, 2008).

206. See 18 U.S.C. § 1962 (2008). RICO provides a private right of action, resulting in treble damages, for those "injured in their business or property" through another's racketeering activities. Michael R. Flaherty, *Cause of Action for Treble Damages for Violation of the Racketeer Influenced and Corrupt Organizations Act*, 11 CAUSES OF ACTION 2D 627 (2008). In addition to proving

2. Recipient-Initiated Lawsuits

Individual recipients of olanzapine—most of whom presumably suffer from significant mental illness—are personally affected by the drug’s side effects. Their claims against Lilly have been similar to those asserted by the states. But until the October 2008 and January 2009 settlements discussed below, there had been much more action by Lilly to settle patients’ claims.

In April 2004, the federal Zyprexa MDL was consolidated in the United States District Court for the Eastern District of New York for common fact and discovery purposes.²⁰⁸ At consolidation, six user-initiated lawsuits from federal districts in California, Kentucky, Louisiana, North Carolina, Ohio, and Tennessee “share[d] allegations concerning the safety of Zyprexa.”²⁰⁹ But more lawsuits were both pending and anticipated even then. As the court’s transfer order explained, “Given the geographic dispersal of current and anticipated constituent actions, no district stands as the focal point for this wide-ranging litigation.”²¹⁰ The Zyprexa MDL has included—and continues to include—claims filed by state attorneys general, injured recipient-plaintiffs, insurance companies, and labor unions.²¹¹ In mid-2005, Lilly agreed to pay \$700 million to more than 7,000 of these plaintiffs.²¹²

a violation of the RICO statute—which includes proving an element of criminal activity—plaintiffs must also prove that they “ha[ve] been injured in [their] business or property by reason of the violation.” *Id.*

207. Complaint, *supra* note 202, at 6-7.

208. Transfer Order at 1, In re Zyprexa Products Liability Litigation, No. 1:04-MD-1596 (E.D.N.Y. 2004). In 2005, an MDL was also created to handle cases by plaintiffs against Merck & Co. related to Vioxx’s heightened risks of heart attacks and strokes. See Alex Berenson, *Analysis See Merck Victory in Vioxx Deal*, N.Y. TIMES, Nov. 10, 2007, at A1, available at 2007 WLNR 22240638. At the time of its consolidation, the Vioxx MDL encompassed 148 separate actions from 41 federal districts. Transfer Order at 1, In re Vioxx Products Liability Litigation, MDL Docket No. 1657 (Feb. 16, 2005) [hereinafter MDL Transfer Order].

209. MDL Transfer Order, *supra* note 208, at 2.

210. *Id.* at 3.

211. The MDL claims against Lilly by insurance companies and labor unions have been based on both state and federal law—the latter alleging specifically that the drug company violated RICO in marketing Zyprexa. Mark Fass, *Narrow Zyprexa Class Certified, Sealed Files Released*, LAW.COM, Sept. 8 2008, available at <http://www.law.com/jsp/article.jsp?id=1202424340649>. In July 2008, District Judge Jack Weinstein proposed class action status for the MDL RICO claims against Lilly, hoping that the threat would spur Lilly to settle, which he himself encouraged, explaining:

A global settlement . . . is desirable. Legal disputes of this nature should be resolved as quickly and comprehensively as possible so that government, the medical profession, and drug manufacturers can get on with their main job—protecting the people’s health effectively at the cheapest practicable cost.

Class Action Certification Draft Discussion at 290, In re Zyprexa Products Liability Litigation, No. 04-MD-1596 (E.D.N.Y. July 2, 2008). In September 2008, Judge Weinstein granted class action status to “third-party payors” involved in the Zyprexa litigation, including labor unions and insurance companies. Fass, *Narrow Zyprexa Class Certified*, Sep. 8 2008. However, Judge Weinstein limited the status strictly to those involving RICO. *Id.*

In addition to the “quasi-class action”²¹³ settlement just described, olanzapine recipients have also filed a number of non-“class action” lawsuits, alleging products liability claims centered on Lilly’s failure to warn about the drug’s harmful side effects. For instance, Lilly settled 18,000 lawsuits for \$500 million in early 2007, bringing the total at that time to “at least \$1.2 billion [paid] to 28,500 people who said they were injured by [the] drug.”²¹⁴ Lilly settled another 900 individual user suits later that year.²¹⁵ But even after that settlement, the drug company still “face[d] product liability lawsuits from about 750 [olanzapine] patients.”²¹⁶

3. Recent Developments

a. October 2008 Settlement

In early October 2008, Lilly announced that it had agreed to settle consumer protection claims with thirty-three states²¹⁷ for \$62 million.²¹⁸ The settlement came in the midst of an investigation by the Illinois and Oregon attorneys general into Lilly’s marketing of olanzapine for non-approved, off-label uses.²¹⁹ The settlement exceeded “the \$58 million that Merck paid to settle similar allegations about” rofecoxib²²⁰—thus becoming the largest set-

212. See *Eli Lilly & Co. to Pay \$700 Million in Product Liability Group Settlement*, MENTAL HEALTH WKLY. DIG., July 25, 2005, at 32. Judge Weinstein approved the settlement in September 2006 for, at that time, 8,362 plaintiffs. Jeff Swiatek, *Judge Approves \$700 Million Zyprexa Deal*, INDIANAPOLIS STAR, Sept. 28, 2006, available at 2006 WLNR 16910731.

213. At the Mass Tort Litigation Blog, Professor Howard M. Erichson has in this way characterized Judge Weinstein’s attitude towards the Zyprexa MDL with regard to settlements, explaining that the Zyprexa MDL’s technically non-class aggregate settlements set it apart from other mass tort cases where settlements were achieved for traditional class actions. Howard M. Erichson, *Zyprexa Settlements: Round Two*, MASS TORT LITIGATION BLOG, Jan. 4, 2007, http://lawprofessors.typepad.com/mass_tort_litigation/2007/01/zyprexa_settlem.html.

214. Berenson, *supra* note 194.

215. *Eli Lilly Settles Lawsuits Over Anti-Psychotic Drug*, SAN JOSE MERCURY NEWS, June 13, 2007, at 2C, available at 2007 WLNR 11093768.

216. Will Connaghan, *Commentary: Watch Out for Side Effects from Advertising*, DAILY RECORD (Kansas City, Mo.) June 15, 2007.

217. This includes the District of Columbia. John O’Brien, *Eli Lilly Case Goes Forward*, LEGAL NEWSLINE, Nov. 21, 2008, available at <http://www.legalnewsline.com/news/217559-eli-lilly-case-goes-forward>.

218. Alex Berenson, *33 States to Get \$62 Million in Zyprexa Case Settlement*, N.Y. TIMES, Oct. 7, 2008, at B7, available at 2008 WLNR 19031435.

219. *Id.*

220. *Id.* Vioxx® is the proprietary name for rofecoxib, a nonsteroidal prescription pain reliever that was withdrawn from the U.S. market in September 2004. MedicineNet.com, *Rofecoxib*, <http://www.medicinenet.com/rofecoxib/article.htm> (last visited Apr. 25, 2009).

tlement of its kind—even though eleven other states chose not to participate.²²¹

In November 2008, Judge Weinstein granted Lilly and the six states participating in the MDL “a month off to hammer out a[settlement] agreement.”²²² According to the judge, who had encouraged settlement in the past, “[i]t would be useful to settle all pending attorney general claims at the same time since the issues in each are much the same.”²²³

b. January 2009 Settlement: Criminal Implication

In early January 2009, news outlets broke the story that Lilly would plead guilty to a misdemeanor charge concerning its marketing of olanzapine,²²⁴ implying an admission of wrongdoing by the drug company. Beside agreeing to a \$515 million criminal fine, Lilly also announced that it would pay \$438 million to the federal government and \$362 million to the states.²²⁵ In all, the settlement totaled \$1.415 billion.

In conjunction with the settlement announcement, Lilly’s CEO, John C. Lechleiter, stressed that the company “‘deeply regret[ted] the past actions covered by the misdemeanor plea,’” and that Lilly “‘take[s] seriously [its] business practices, and . . . realize[s] that [it] ha[s] a tremendous responsibility to . . . patients and health-care professionals.”²²⁶ Notably, the settlement incorporates changes in the company’s business practices: Lilly will have its employees undergo additional training on government regulations, have an independent auditor assess its business operations, and continue an in-house governmental compliance monitoring program.²²⁷

This settlement represents a giant step toward resolving olanzapine-related litigation—and in implementing reforms in promotion methods. In May 2009, settlement sums between Lilly and Georgia and Massachusetts

221. O’Brien, *supra* note 217. The 11 states include Arkansas, Connecticut, Idaho, Louisiana, Mississippi, Montana, New Mexico, Pennsylvania, South Carolina, Utah, and West Virginia. While the suits by Connecticut, Louisiana, Mississippi, Montana, New Mexico, and West Virginia are before Judge Weinstein in the Zyprexa MDL, the suits by the remaining states are pending in state courts. *Id.*

222. *Id.*

223. *Id.* Judge Weinstein further explained that “[i]n view of the applicable statute of limitations, it is unlikely that any new cases can be brought successfully. A global settlement of all cases, including those pending in state courts, is desirable.” *Id.*

224. John Russell, *Eli Lilly to Pay \$1.4 Billion in Zyprexa Probe*, INDIANAPOLIS STAR, Jan. 16, 2009, available at 2009 WLNR 920566. Specifically, the charge concerned the marketing of Zyprexa for the elderly during the period of 1999 to 2001. *Id.*

225. *Id.* These payments are related to the federal government’s investigation, which thirty or so states joined, into Lilly’s promotion of the drug. Lilly, however, would “not admit to . . . civil allegation[s] connected to improperly promoting Zyprexa.” *Id.* Instead, it stated that it would settle for “business reasons.” *Id.*

226. *Id.*

227. *Id.*

were announced.²²⁸ But outstanding lawsuits against the manufacturer remain. The status of the claims by both states and individuals²²⁹ remaining in the MDL, for instance, is still up in the air²³⁰—and the pre-trial phase of the litigation continues to be active with motions,²³¹ discovery conflicts,²³² and expert testimony debates.²³³

4. Concluding Thoughts

In aggregate, states' and recipients' claims have made olanzapine-related litigation a prominent legal event over the past few years. For Lilly, the litigation has been both financially costly and has repeatedly generated negative publicity about the company in popular press accounts and in legal, medical, and corporate publications.

B. Antipsychotic Drug Litigation: Areas of Law

Having summarized the outcomes of complaints filed against Lilly as of early 2009, we next provide a summary of potential and actual claims against an SGA manufacturer.

1. Products Liability

The products liability claims made against Lilly and olanzapine have been primarily based on the strict liability theories of design and warning defects. The doctrine of "strict" products liability involving defects developed in the mid-twentieth century, with the aid of the *Greenman v. Yuba Power Products*,

228. See Martin Berman-Gorvine, *Eli Lilly Pays \$15 Million to Settle Zyprexa Litigation in Georgia*, 8 DRUG INDUS. DAILY 87, May 5, 2009, available at 2009 WLNR 8546942; Julie M. Donnelly, *Mass. Gets \$22.5M in Eli Lilly Settlement*, BOSTON BUS. J., May 18, 2009, available at <http://boston.bizjournals.com/boston/stories/2009/05/18/daily3.html> (last visited June 1, 2009).

229. Claims by individual recipients of olanzapine also remain in the MDL. See e.g., In re Zyprexa Products Liability Litigation, 2009 WL 1044508 (E.D.N.Y. Apr. 15, 2009) (granting summary judgment for defendant hospital based on fraudulent joinder in an action brought by decedent's estate against the hospital and Lilly).

230. See John O'Brien, *Eli Lilly Finalizing \$1.4 Billion Settlement*, LEGAL NEWSLINE, Jan. 15, 2009, available at <http://www.legalnewsline.com/news/218553-eli-lilly-finalizing-1.4-billion-settlement> (noting the state lawsuits still outstanding against Lilly); see also In re Zyprexa Products Liability Litigation, 2009 WL 1173069 (E.D.N.Y. May 1, 2009) (citing the addition of lawsuits by Idaho and Minnesota to the MDL).

231. See e.g., In re Zyprexa Products Liability Litigation, 2009 WL 691942 (E.D.N.Y. Mar. 11, 2009) (denying New Mexico's motion to remand its action to state court).

232. See In re Zyprexa Products Liability Litigation, 2009 WL 1310890 (E.D.N.Y. May 8, 2009) (denying Connecticut's motion to compel Lilly's production of certain documents).

233. See In re Zyprexa Products Liability Litigation, 2009 WL 1322292 (E.D.N.Y. May 12, 2009) (denying plaintiff's motion to exclude testimony of Lilly's expert).

*Inc.*²³⁴ decision and the American Law Institute's (ALI) *Restatement (Second) of Torts* Section 402A.²³⁵

a. Design Defect

Most states have adopted Section 402A.²³⁶ Under that section, product manufacturers are liable for injuries caused by products found to be "in a defective condition unreasonably dangerous to the user or consumer..."²³⁷ A claim based on design defect of a product alleges that the *entire* line of that product is defective.²³⁸ However, the courts have diverged when it comes to addressing the issue of whether a product is "unreasonably dangerous" because of its design.²³⁹ Some courts, for example, employ a consumer expectations test. "[F]or a plaintiff to recover [using that test], the defect in a product which causes his injuries must not be one which the plaintiff, as an ordinary consumer, would know to be unreasonably dangerous to him."²⁴⁰ Other courts employ a "risk-utility" test, which asks whether or not "a reasonable

234. 377 P.2d 897 (Cal. 1963). In *Greenman*, Justice Traynor found a combination power tool manufacturer strictly liable for a defect in the product that injured the plaintiff. *Id.* at 901. In abandoning contract theories in favor of strict liability, Justice Traynor explained that "rules defining and governing warranties that were developed to meet the needs of commercial transactions cannot properly be invoked to govern the manufacturer's liability to those injured by their defective products unless those rules also serve the purposes for which such liability is imposed." *Id.*

235. Under the RESTATEMENT (SECOND) OF TORTS, Special Liability of Seller of Product for Physical Harm to User or Consumer is

(1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if

(a) the seller is engaged in the business of selling such a product, and

(b) it is expected to and does reach the user or consumer without substantial change in the condition in which it is sold.

(2) The rule stated in Subsection (1) applies although

(a) the seller has exercised all possible care in the preparation and sale of his product, and

(b) the user or consumer has not bought the product from or entered into any contractual relation with the seller.

Restatement (Second) of Torts § 402A (1965).

236. See Matthew R. Sorenson, Comment, *A Reasonable Alternative? Should Wyoming Adopt the Restatement (Third) of Torts: Products Liability?*, 3 WYO. L. REV. 257, 262 (2003).

237. *Id.*

238. See e.g., J. Stanley Mcquade, *Products Liability – Emerging Consensus and Persisting Problems: An Analytical Review Presenting Some Options*, 25 CAMPBELL L. REV. 1, 47 (2002).

239. Another approach has also surfaced following Section 402A in design defect cases "because [the section] gave no guidance as to what to do in a design defect case": a combination of both the consumer expectations and risk-utility tests. *Id.* at 264.

240. *Sperry-New Holland v. Prestage*, 617 So. 2d 248, 254 (Miss. 1993) (Mississippi Supreme Court explicitly abandons the consumer expectations test in strict products liability cases in favor of the risk-utility test).

person would conclude that the danger-in-fact, whether foreseeable or not, outweighs the utility of the product.”²⁴¹

With regard to prescription drugs specifically, Section 402A’s comment k states, “There are some products which . . . are quite incapable of being made safe for their intended and ordinary use,” and notes this designation is “especially common in the field of drugs.”²⁴² Under comment k, products in this category, encompassing “many other drugs, vaccines, and the like,” are deemed not defective and not unreasonably dangerous when “properly prepared, and accompanied by proper directions and warning.”²⁴³ Courts have taken varying views on comment k’s application to prescription drugs.²⁴⁴

In the 1990s, the ALI took a different approach to strict products liability.²⁴⁵ With the *Restatement (Third) of Torts: Products Liability*, the ALI not only “ma[de] a tripartite-type division” between manufacturing, design, and warning defects, but also adopted the risk-utility test outright.²⁴⁶ Notable for our

241. *Id.* The risk-utility test has been equated with the formula for determining when negligence should be implied that Judge Learned Hand created in *United States v. Carroll Towing Co.*, 159 F.2d 169, 173 (2d Cir. 1947). See David G. Owen, *Design Defects*, 73 MO. L. REV. 291, 312-314 (2008). Additionally, many courts invoke the so-called “Wade Factors” when assessing risk-utility in a design defect case. See *id.* at 315-322 (listing the factors and describing their history). See also David G. Owen, John E. Montgomery, & Mary J. Davis, *PRODUCTS LIABILITY AND SAFETY* 226-299 (5th ed. 2007).

242. See RESTATEMENT (SECOND) OF TORTS §402A, cmt. k (1965).

243. *Id.*

244. See George H. King, Case Note, *A Prescription for Applying Strict Liability: Not All Drugs Deserve Comment K Immunization*, *Brown v. Superior Court*, 21 ARIZ. ST. L.J. 809 (1989). While “[s]ome courts have held that the decision of the FDA to approve a drug or device and make it available only by prescription [under comment k] make it unavoidably dangerous as a matter of law,” *id.* at 817, others have rejected this position—and may not consider comment k to include all prescription drugs. *Id.* at 818-19.

245. Sorenson, *supra* note 236 at 266.

246. *Id.* In addition to the risk-utility test described *supra* note 235, the RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY requires that a plaintiff demonstrate the existence of a reasonable alternative design for the particular product. See RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY §2(b), cmt. e-f (1998). As comment b points out, “[Section] 2(b) . . . reflects the substantial body of case law suggesting that reasonable alternative design is the predominant, yet not exclusive, method for establishing defective design.” *Id.* at cmt. b.

In the RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY, Section 402A’s “unreasonably dangerous” standard has evolved to become a “not reasonably safe” standard in design and warning defect cases. See RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY §2(b)-(c) (1998); Dominick Vetri, *Order Out of Chaos: Products Liability Design-Defect Law*, 43 U. RICH. L. REV. 1373, 1406 (noting that this “language . . . evokes a negligence standard without using the word ‘negligence’”).

A products liability lawsuit, particularly one employing a risk-utility test where a reasonable alternative design is required, will often involve (and potentially hinge on) expert testimony. See generally Richard L. Cupp, Jr., *Believing in Products Liability: Reflections on Daubert, Doctrinal Evolution, and David Owen’s Products Liability Law*, 40 U.C. DAVIS L. REV. 511 (2006). As a result, the evidentiary standards for expert testimony set forth in *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579 (1993)—or a state’s interpretations of those or other factors—will become a crucial element of the underlying tort case itself. See *id.* at 523-24.

purposes, however, is a specific section in the *Restatement (Third) of Torts: Products Liability* concerning drugs and drug manufacturers,²⁴⁷ which articulates a steeper burden for plaintiffs alleging design defect(s) of a prescription drug:

A prescription drug or medical device is not reasonably safe due to defective design if the foreseeable risks of harm posed by the drug or medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health-care providers, knowing of such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients.²⁴⁸

But while Section 6 of the *Restatement (Third) of Torts: Products Liability* favors drug manufacturers, the group ultimately desires even greater protection. In *Wyeth v. Levine*,²⁴⁹ for example, Wyeth Pharmaceuticals argued for the preemption of tort liability for manufacturers whose medications or devices have been deemed marketable by the FDA.²⁵⁰ However, the Supreme Court, in an opinion by Justice Stevens, ultimately rejected this position: “We conclude that it is not impossible for Wyeth to comply with its state and federal law obligations and that Levine’s common-law claims do not stand as an obstacle to the accomplishment of Congress’ purposes in the [Federal Food, Drug, and Cosmetic Act (FDCA)].”²⁵¹ Specifically, the history of the FDCA showed that, contrary to Wyeth’s claims, “Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.”²⁵² Thus, state tort-based cases remain an available avenue for plaintiffs to seek recompense for drug-induced injuries.

b. Warning Defect

Under Section 402A’s comment j., “In order to prevent [a] product from being unreasonably dangerous, the seller may be required to give directions or warning, on the container, as to its use.”²⁵³ A product may be deemed defective, then, when an injured plaintiff can show that its warning label or instructions were inadequate in some way²⁵⁴ or absent.²⁵⁵ The elements involved in a warning defect case include

247. RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY §6 (1998).

248. *Id.* at §6(c).

249. 129 S.Ct. 1187 (2009).

250. Nan Aron & John Philo, *Drugmakers Seek Lawsuit Immunity*, DETROIT FREE PRESS, Feb. 20, 2009, available at <http://www.freep.com/article/20090220/OPINION05/902200328/1068/rss06>.

251. *Wyeth v. Levine*, 129 S.Ct. 1187, 1204; see also Jacob Goldstein, *Supreme Court Rules in Wyeth v. Levine*, WALL ST. J. HEALTH BLOG, Mar. 4, 2009, <http://blogs.wsj.com/health/2009/03/04/supreme-court-rules-in-wyeth-v-levine> (last visited June 1, 2009).

252. *Wyeth*, 129 S.Ct. at 1200.

253. RESTATEMENT (SECOND) OF TORTS §402A, cmt. j (1965).

254. See e.g., RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY §2(c). However, a plaintiff’s manufacturing or design defect claim will not be defeated simply by a manufacturer

that the defendant manufacturer . . . knew or should have known of the dangers related to the product's intended use; (2) the product's user/consumer was reasonably unaware of those dangers; (3) the defendant manufacturer . . . failed to exercise reasonable care to notify the user/consumer of the products unsafe condition or facts which make the product prone to be dangerous; and (4) the risk and degree of harm was large enough to justify that a warning should have been provided.²⁵⁶

The success of a warning defect case is tied to the element of proximate cause.²⁵⁷ Plaintiffs in such cases must show that the warning(s) they argue for would have prevented the injuries sustained.²⁵⁸ As described above, there still remains the matter of how Section 402A, comment k applies in a prescription drug situation.²⁵⁹

Interestingly, the *Restatement (Third) of Torts: Products Liability* Section 6(d) carves out a specific duty for manufacturers of “[a] prescription drug or medical device” to properly instruct or warn prescribers²⁶⁰ (to help them make the best decisions for their patients²⁶¹) and patients (for “drugs that are dispensed . . . without the personal intervention or evaluation of a health-care provider”²⁶²) of “foreseeable risks” associated with use.²⁶³ The section also notes that a claim of warning defect “is the major basis of liability for manufacturers of prescription drugs and medical devices.”²⁶⁴ In terms of developing adequate warning labels for their products under this provision, then, drug manu-

supplying a warning. J. Scott Dutcher, Comment, *Caution: This Superman Suit Will Not Enable You To Fly—Are Consumer Product Warning Labels Out of Control?*, 38 *Az. St. L. J.* 633, 635 (2006). Additionally, although “strict” liability-based, warning defects claims have been equated with negligence claims. *See id.* at 635, n.11.

255. Dutcher, *supra* note 254 at 637.

256. *Id.* at 636.

257. *See id.*

258. *See id.* As Dutcher explains, “Many common law courts have dropped the requirement that had there been a proper warning for the product, the user [plaintiff] would have heeded it, because courts assume that all plaintiffs would always testify that they would have heeded the warning.” *Id.* at n.14.

259. *See supra* note 244 and accompanying text.

260. *RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY* §6(d) (1998).

261. *See id.* at cmt. d.

262. *Id.* at cmt. e.

263. *Id.* at §6(d). The section reads in full,

(d) A prescription drug or medical device is not reasonably safe due to inadequate instructions or warnings if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to:

(1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings; or

(2) the patient when the manufacturer knows or has reason to know what health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings.

Id. at §6(d).

264. *Id.* at cmt. d.

facturers ultimately must seek to meet the informational needs of both doctors and patients.

Concerning the products liability claims alleged against Lilly, it cannot be denied that olanzapine has helped many thousands of people with treating schizophrenia, bipolar disorder, and other mental illnesses.²⁶⁵ As one Lilly-employed psychiatrist explained,

While the potential side effects for any medication must be taken into consideration when evaluating treatment options, it is equally important not to lose sight of the benefits. More than 22 million people have taken Zyprexa. For many, it's helped them obtain employment, maintain housing, and re-establish relationships.²⁶⁶

Like olanzapine, SGAs have helped a multitude of patients around the world. The SGAs clearly have drawbacks, but so do the alternatives (FGAs, or no drug treatment at all). As we have seen, even those psychiatrists who regard FGAs and SGAs as equivalent overall acknowledge that for individual patients one type of drug may be far more useful and acceptable than others. It is therefore hard to conclude that SGAs are defective products *simpliciter*, especially under a risk-utility theory or under Section 6 of the *Restatement (Third) of Products Liability*.

2. Corporate Law Implications: SEA §10(b) and SEC Rule 10b-5

In addition to recipients and purchasers of SGAs, shareholders in pharmaceutical companies are potentially affected by extensive and costly litigation. In 2007, Lilly shareholders sued the corporation in the Eastern District of New York for its behavior regarding olanzapine.²⁶⁷ The shareholders alleged violations of the Securities Exchange Act of 1934 (SEA) §10(b),²⁶⁸ and the Securities and Exchange Commission's Rule 10b-5, which the SEC created to enforce §10(b);²⁶⁹ these provisions relate to shareholder communication.²⁷⁰ Under Rule 10b-5, it is "unlawful for any person, directly or indirectly,"²⁷¹ to employ a mechanism to defraud, make untrue statements of material facts, omit material facts that would make a statement no longer mis-

265. Other possible defenses in a strict products liability case could include unforeseeable misuse of the product by a plaintiff, alterations to the product, or assumption of the risk.

266. Sara Corya, Letter to the Editor, *Drug's Benefits Should Not Be Overlooked*, ST. PETERSBURG TIMES, Dec. 23, 2007, at 2P, available at 2007 WLNR 25325060.

267. *Lawsuit Filed Against Eli Lilly by Grant & Eisenhofer P.A.*, OBESITY, FITNESS & WELLNESS WEEK, Apr. 21, 2007, at 307, available at 2007 WLNR 7008003 [hereinafter *Grant*].

268. 15 U.S.C. § 78j (2009).

269. See 17 C.F.R. §240.10b-5 (1951); see also 69A AM. JUR. 2D *Securities Regulation -- Federal* § 1514 (2008) (explaining the ability of the SEC to adopt rules to carry out the intent of certain federal securities laws).

270. The lawsuit also made allegations under SEA §20(a), which discusses the availability of joint and several liability for SEA violations. See *Grant*, *supra* note 255.

271. 17 C.F.R. §240.10b-5.

leading, or engage in an act that “would operate as fraud or deceit upon any person....”²⁷² Nonetheless, Rule 10b-5 is only applicable to shareholder communications that were made “in connection with the purchase or sale of any security.”²⁷³ The shareholder class action, as a result, was limited to those persons who had purchased Lilly stock between March 28, 2002 and December 22, 2006.²⁷⁴

The crux of this lawsuit was a claim that Lilly misrepresented olanzapine’s side effects to shareholders through its marketing campaigns.²⁷⁵ The suit also claimed that Lilly marketed olanzapine for uses that were not FDA approved in violation of FDA marketing regulations.²⁷⁶ Approximately a year after it was filed, Judge Weinstein dismissed the shareholder suit for exceeding the SEA’s statute of limitations.²⁷⁷ His dismissal explained that “[f]or years before the statute of limitations barred this suit, the red triangular flags of an incipient hurricane had been figuratively hoisted over Lilly and Zyprexa,” and so “[t]he reasonable investor c[ould not] blink away what the market [had] see[n].”²⁷⁸

Interestingly, a similar issue continues to survive in still-ongoing rofecoxib litigation. Though Merck has settled a number of claims related to the side effects of its prescription pain reliever,²⁷⁹ the Third Circuit Court of Appeals reversed the dismissal of a shareholder lawsuit against the company related to the medication in September 2008, four years after the company took the drug off the U.S. market.²⁸⁰ The lawsuit, which contended that Merck misled and omitted information related to rofecoxib-associated risks of heart attacks and strokes, had previously been dismissed by the district court for exceeding the statute of limitations.²⁸¹ According to the Third Circuit, the plaintiff-shareholder class made a timely filing of its lawsuit, because “amid early signs of trouble with Vioxx, Merck was still reassuring investors about the safety of [the drug] and financial analysts were projecting growth in sales.”²⁸²

272. *Id.*

273. *Id.*

274. *See Gram, supra* note 267.

275. *Id.*

276. *See id.*

277. *See Eli Lilly Wins Dismissal of Zyprexa Shareholders Suits*, PHARMA BUS. DAILY BULL., May 1, 2008, available at 2008 WLNR 8073598.

278. *Id.*

279. *Court Reinstates Merck Vioxx Shareholder Lawsuit*, INT’L. HERALD TRIBUNE, Sep. 9, 2008, available at <http://www.iht.com/articles/ap/2008/09/09/business/NA-US-Merck-Vioxx-Lawsuit.php>.

280. *Id.*

281. *Id.*; *see Berenson, Merck Victory, supra* note 208.

282. *Court Reinstates, supra* note 279. In late May 2009, the Supreme Court granted certiorari to hear Merck’s appeal in this case. *Merck & Co. v. Reynolds*, No. 08-905, 2009 U.S. LEXIS 3913 (May 26, 2009). At issue is when the statute of limitations begins to run in this type of securities lawsuit. *See Ashby Jones, On Vioxx, Storm Warnings and the Supreme Court*, WALL ST. J. LAW BLOG, May 27, 2009,

a. Elements of a Rule 10b-5 Claim

If not for dismissal under the statute of limitations, Lilly shareholders meeting Rule 10b-5's standing requirement (being either purchasers or sellers of Lilly stock)²⁸³ in the lawsuit referenced above would have additionally needed to show elements of materiality, *scienter*, reliance, economic loss, and loss causation in order for their cause of action to survive.²⁸⁴ Under the Private Securities Litigation Reform Act of 1995 (PSLRA), class action plaintiffs invoking Rule 10b-5 must plead their cases "with particularity."²⁸⁵ Materiality can be illustrated via the importance of the information at issue. In *TSC Industries, Inc. v. Northway*,²⁸⁶ the U.S. Supreme Court explained that "[a]n omitted fact is material if there is a substantial likelihood that a reasonable shareholder would consider it important in deciding how to vote."²⁸⁷ Olanzapine has been

<http://blogs.wsj.com/law/2009/05/27/on-vioxx-storm-warnings-and-the-supreme-court/> (last visited Jun. 1, 2009); see also Jacob Goldstein, *Supremes Will Hear Merck Appeal in Vioxx Shareholder Lawsuit*, WALL ST. J. HEALTH BLOG, May 27, 2009, <http://blogs.wsj.com/health/2009/05/27/supremes-will-hear-merck-appeal-in-vioxx-shareholder-lawsuit/> (last visited Jun. 1, 2009). As Goldstein explains, a ruling in this case "could clarify the rules for how much information is enough to start the clock running, which could have widespread implications for the statute of limitations for filing securities-fraud claims." *Id.*

283. Regarding the requirement of "a connection with the purchase or sale of a security," see *Dura Pharmaceuticals, Inc. v. Broudo*, 544 U.S. 336, 341 (2005) (citing *Blue Chip Stamps v. Manor Drug Stores*, 421 U.S. 723, 730-31 (1975)). In *Blue Chip*, the Supreme Court noted that "virtually all lower federal courts . . . have reaffirmed [the] conclusion that the plaintiff class for purposes of a 10(b) and Rule 10b-5 private damages actions is limited to purchasers and sellers of securities." 421 U.S. at 731.

284. See *Dura*, 544 U.S. at 341-42. Another interpretation of the elements is as follows: While the elements of an action under §10(b) of the [SEA] and SEC Rule 10b-5 the-reunder have been variously stated by the courts, it is generally agreed that there must be proven: (1) use of the means or instrumentalities of interstate commerce; (2) to implement a deceptive or manipulative practice; (3) with the requisite *scienter*; (4) in connection with; (5) the offer or sale; (6) of a security; (7) causing; (8) damages. 69A AM. JUR. 2D *Securities Regulation — Federal* § 1466 (2009).

285. 15 U.S.C. § 78u-4(b)(1) (2009). The PSLRA altered the pleadings requirements for securities class actions. See Jonathan C. Dickey, *Current Trends in Federal Securities Litigation*, 101 A.L.I.-A.B.A. 725, 731 (2007). According to the PSLRA, where a material omission or false statement has been alleged, "[T]he complaint shall specify each statement alleged to have been misleading, the reason or reasons why the statement is misleading, and, if an allegation regarding the statement or omission is made on information and belief, the complaint shall state with particularity all facts on which that belief is formed." 15 U.S.C. §78u-4(b)(1). A similar pleading requirement exists for causes of action which hinge "on proof that the defendant acted with a particular state of mind." *Id.* at §78u-4(b)(2). For more on issues related to interpreting the PSLRA's requirements, including pleading the elements of *scienter* and loss causation for a Rule 10b-5 claim discussed in this section, see Dickey, *supra*.

286. 426 U.S. 438 (1976).

287. *Id.* at 449. Although *TSC* actually revolved around an SEC Rule 14a-9 issue, the materiality standard under both provisions is the same.

Lilly's number one selling drug,²⁸⁸ and information relating to harmful side effects arguably could have been something its shareholders would have found important.

To illustrate reliance (also known as transaction causation) in a securities class action, the “fraud on the market” theory—where “reliance is presumed when the statements at issue become public”—is typically invoked.²⁸⁹ Lilly's marketing campaigns for olanzapine, thus, could have been employed to show impact on the plaintiff-shareholders. As for Rule 10b-5's *scienter* requirement, plaintiffs in general must show something greater than negligence, such as recklessness.²⁹⁰

Finally, Rule 10b-5 plaintiffs must allege and ultimately show an economic loss of some sort,²⁹¹ as well as loss causation, which mirrors the “proximate cause” requirement seen in basic tort law.²⁹² Pleading loss causation is a sticky issue for courts in securities litigation,²⁹³ but put most simply, there must be “a causal connection between the material misrepresentation [alleged] and the loss.”²⁹⁴

3. Claims Under Federal Off-Label Prohibitions

During the rofecoxib litigation, the FDA came under heavy fire for failing to withdraw the drug more quickly after its harmful cardiovascular side effects came to light.²⁹⁵ FDA-related issues concerning olanzapine and other SGAs arose after litigation began and have focused on promotion of these drugs for unapproved, off-label uses—most notably, in the case of olanzapine, for depression.

Under the now-expired Food and Drug Administration Modernization Act²⁹⁶ (FDAMA), a 1997 series of amendments to the Food, Drug & Cosmetic Act (FDCA),²⁹⁷ a drug manufacturer could disseminate information con-

288. *Report: Eli Lilly Hid Top Drug's Risks*, CNNMONEY.COM, Dec. 16, 2006, available at http://money.cnn.com/2006/12/16/news/companies/elililly_zyprexa/index.htm.

289. *Stoneridge Inv. Partners, LLC v. Scientific-Atlanta*, 128 S.Ct. 761, 769 (2008); see also *Dura Pharmaceuticals, Inc. v. Broudo*, 544 U.S. at 341-42.

290. See *Dura*, 544 U.S. at 341-42. With regard to the PSLRA and *scienter*, as Dickey notes, “the majority of Circuits have held that the court must consider *all* reasonable inferences to be drawn from the allegations, including inferences unfavorable to the plaintiffs.” Dickey, *supra* note 273, at 741.

291. See *Dura*, 544 U.S. at 342.

292. See *id.*

293. See Dickey, *supra* note 285, at 766-80.

294. *Id.*

295. See Janis Kelly, *Harsh Criticism Lobbed at FDA in Senate Vioxx Hearing*, MEDSCAPE MED. NEWS, Nov. 23, 2004, <http://www.medscape.com/viewarticle/538021>.

296. See 21 U.S.C. § 301 *et seq.* (1997).

297. James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 297 (2003). In brief, the FDCA performs the following statutory function:

cerning a drug's off-label uses²⁹⁸ to a limited group: health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, or a Federal or State Government agency.²⁹⁹ Before the FDAMA, the FDCA prohibited drug manufacturers from engaging to even this extent in off-label promotion.³⁰⁰ The FDAMA expired in 2006, however.³⁰¹ As Professor Ausness has commented, in the wake of the FDAMA's expiration, the FDA has provided "a draft guidance document entitled 'Good Reprint Practices.'"³⁰² This document "identifies how drug manufacturers should distribute scientific or medical journal reprints, articles, or reference works" concerning off-label uses; ultimately, "the FDA retains its power to determine whether distribution of an article or publication constitutes promotion of an unapproved 'new use' or whether such a product may be considered misbranded or adulterated under the [FDCA]."³⁰³ Of course, physicians are not bound by off-label restrictions³⁰⁴ and "may use FDA-licensed drugs or medical devices in any way they believe will benefit their patients and are not limited to approved uses."³⁰⁵

Turning to the state complaints still pending against Lilly, those in the MDL contend that the drug company knowingly marketed olanzapine for off-label uses in violation of federal law. Montana,³⁰⁶ for instance, alleged that "Lilly created a 280-person sales force to promote Zyprexa exclusively for off-label uses, specifically for Long Term Care ("LTC") facilities to maximize off-label use of Zyprexa sales in elderly population,"³⁰⁷ that "Lilly management participated, encouraged, and authorized the unlawful payment of illegal kick-

[A]fter introductory chapters defining the terms used and listing general prohibitions and enforcement methods, deals successively with foods, drugs, and cosmetics. It defines adulteration and misbranding for each, and meets peculiar problems in each area by special regulatory provisions such as definition and standardization of foods and pre-shipment control of new and untested drugs. It then prescribes the administrative procedure to be employed, and finally sets forth specific provisions governing imports and exports.

Harvard Law Review Association, *Developments in the Law – The Federal Food, Drug, and Cosmetic Act*, 67 HARV. L. REV. 632, 635 (1954).

298. See O'Reilly, *supra* note 297, at 296.

299. 21 U.S.C. §360aaa(a)(1)-(5) (1997); see also 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, 1259-60, and accompanying footnotes (2008).

300. See Ausness, *supra* note 299, at 1260-61.

301. See *id.*

302. *Id.* at 1261.

303. *Id.*

304. See *id.* at 1259.

305. *Id.*

306. Although its complaint was originally filed in state court, Montana is now part of the Zyprexa MDL pending in the District Court for the Eastern District of New York. See O'Brien, *supra* note 217.

307. Complaint at 9, *Montana v. Eli Lilly & Co.*, No. ADV-2007-188 (Mont. Dist. Ct. Mar. 9, 2007).

backs to physicians in order to continue generating sales of Zyprexa,”³⁰⁸ and that “Lilly marketed Zyprexa off-label because the drug’s on-label uses were far too narrow to achieve the blockbuster revenues Lilly had planned for the drug.”³⁰⁹ Connecticut’s complaint alleged that “to gain additional sales and to compete with other antipsychotics[,] ... Lilly undertook a scheme to market and promote Zyprexa for off-label purposes,”³¹⁰ including for unapproved uses in the treatment of children and elderly persons.³¹¹

The allegations of off-label marketing against Lilly, if ever proved, could result in both civil and criminal penalties against the corporation under the FDCA.³¹² Civil and criminal penalties could similarly arise under RICO for off-label marketing if the requisite “predicate acts” of racketeering were established.³¹³

4. *The Quest for Solutions*

A variety of potential legal claims serve as potential deterrents to prevent pharmaceutical companies from marketing faulty products or promoting those products for unapproved uses. In the case of litigation against the manufacturer of olanzapine, litigation has resulted in compensation to recipient-victims, civil and criminal financial penalties, and a promise by Lilly to desist from certain promotion practices. Although the payouts by Lilly have been extraordinary, drug manufacturers regard a certain amount of product liability litigation as “normal to our business,”³¹⁴ as a risk against which they may insure themselves, or as something they may factor into drug prices.³¹⁵ More importantly, however, litigation has had little impact on drug sales and physicians’ prescribing practices, and therefore seems an imperfect, at-best-incomplete response to collective medical judgment errors reflected in physicians’ over-enthusiastic adoption of SGAs. In the next Part, we examine other factors that illustrate how medical judgment occurs.

308. *Id.* at 10.

309. *Id.*

310. Complaint, *supra* note 202, at 32.

311. *Id.* at 35-37.

312. *See* 21 U.S.C. § 333 (2008).

313. *See* Ausness, *supra* note 299, at 1264-65.

314. Eli Lilly SEC filing, *supra* note 203, at 16.

315. *See id.* at 12 (describing “difficulties in obtaining product liability insurance due to a very restrictive insurance market” and expectation “that we will continue to be largely self-insured for future product liability losses”). Lilly’s capacity and willingness to pay large olanzapine-related claims may be a reflection of the fact, reported in the company’s latest SEC filing, that “Zyprexa sales of \$4.76 billion represented [twenty-six] percent of our revenues in 2007.” *Id.* at 11.

IV. RESPONSIBILITY AND VULNERABILITY OF PHYSICIANS

A. Drug Company Blandishments

The promotion techniques used by drug reps and pharmaceutical companies have received substantial publicity over the past few years.³¹⁶ Pharmaceutical companies also have employed physicians in various promotional capacities, including efforts to encourage forms of off-label prescribing that those physicians believe are effective. Physicians are often needed to assist pharmaceutical companies in the development of their products,³¹⁷ but they have served as spokespersons for products, too. Accepting this role—often by becoming a member of a company’s “speaker’s bureau”³¹⁸—and accepting payments from pharmaceutical companies is not illegal for physicians,³¹⁹ but these “entanglements” are actually “common in the medical industry”³²⁰ and appear to have compromised medical education.

The incentivizing of psychiatrists gained media attention in 2008 when Iowa Senator Charles Grassley began investigating payments made by pharmaceutical companies to psychiatrists.³²¹ The Grassley investigation revealed the previously undisclosed sum of \$500,000 given by drug manufacturer GlaxoSmithKline to the chair of Emory University’s psychiatry department for speaking engagements that promoted the company’s products.³²² Along with the federal probe, states have also investigated the tactic. A report released by the Vermont Attorney General’s Office found that psychiatrists

316. Elliott, *supra* note 6; Jerome E. Groopman, HOW DOCTORS THINK 203-12, 289-90 (2007) (describing promotion techniques and citing five articles from the New York Times).

317. Emily Ramshaw, *Some Texas Foster Kids’ Doctors Have Drug Firm Ties*, Dallas Morning News, Aug. 17, 2008, available at <http://www.dallasnews.com/sharedcontent/dws/dn/latestnews/stories/081708dnmetdrugdocs.45052b6.html>.

318. Full disclosure: the first author, who claims no moral superiority over his colleagues, acknowledges having been on drug makers’ speakers bureaus.

319. Ramshaw, *supra* note 317.

320. *Id.*

321. John Gever, *Senator Demands Records of Psychiatric Association-Drug Industry Fiscal Ties*, MedPage Today, Jul. 14, 2008, available at <http://www.medpagetoday.com/Psychiatry/GeneralPsychiatry/10117>; see also Ramshaw, *supra* note 317 (describing a Minnesota investigation that revealed a third of its psychiatrists had taken money from drug companies).

322. Marcia Angell, *Drug Companies & Doctors: A Story of Corruption*, N.Y. Rev. Books, Jan. 15, 2009, available at <http://www.nybooks.com/articles/22237>. Two other instances mentioned by Dr. Angell: (1) Drug companies paid psychiatrist Joseph L. Biederman \$1.6 million in consulting and speaking fees between 2000 and 2007 to advocate treatments for childhood bipolar disorder when studies demonstrating drugs’ effectiveness were lacking. (2) Psychiatrist Alan F. Schatzberg controlled more than \$6 million worth of stock in a company he co-founded that was testing a drug to treat psychotic depression; Dr. Schatzberg was also the principal investigator on a National Institute of Mental Health grant that included research on the drug. *Id.*

received twenty percent of all pharmaceutical money paid to its state's physicians.³²³

Medical schools were once relatively insulated from the influence and lure of pharmaceutical money. But as other sources of funding for research and education have dried up, financial entanglements have tied many academic doctors to drug companies.³²⁴ By and large, academic recipients of drug companies' largesse do not see their relationships with industry as influencing their professional activities or biasing their training, particularly if the gifts are small.³²⁵ Apparently, drug companies are savvy, and know that small gifts influence behavior even when the gifts are not linked to explicit requests.³²⁶

The ethical problems stemming from physicians' acceptance of money and favors have been recognized for several years,³²⁷ but recently, the volume of gifts and money spent on advertising to practicing physicians has increased substantially.³²⁸ Drug companies also do promotions for resident and medical students who are beginning and future prescribers of companies' products.³²⁹ Until just recently, however, regulations on such promotions had not been implemented by either the federal government or the pharmaceutical companies themselves.³³⁰

1. *The Breadth of Inducements*

The American Medical Association's *Ethical Guidelines for Gifts to Physicians from Industry* describes "modest items"—including office supplies, teaching

323. Gever, *supra* note 321.

324. Eric G. Campbell et al., *Institutional Academic-Industry Relationships*, 298 JAMA 1779, 1781-82 (2007) (Sixty percent of department chairs had some personal relationship with the pharmaceutical industry [e.g., serving as a consultant, paid speaker, or member of the board of directors]; sixty-seven percent of academic departments had relationships with drug companies; many also received moneys for training residents and continuing medical education).

325. *Id.* at 1785.

326. Jason Dana & George Loewenstein, *A Social Science Perspective on Gifts to Physicians from Industry*, 290 JAMA 252, 253 (2003) (citing studies and providing examples).

327. See Alexander C. Tsai, *Policies to Regulate Gifts to Physicians from Industry*, 290 JAMA 1776, 1776 (2003) (noting that Congressional hearings were held on the topic of drug company marketing in both the early 1970s and 1990s).

328. Marc-André Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, 5 PLoS Med. 29, 29 (2008) (describing hearings in the 1950s, and describing new activities, such as medical meetings and "seeding trials").

329. See, e.g., Michael Eisman, *Letter to Editor, Medical Student Exposure to Drug Company Interactions*, 295 JAMA 281 (2006).

330. See Tsai, *supra* note 327. As Tsai explains, the American Medical Association enacted "voluntary ethical guidelines on pharmaceutical gifts" in 1990. *Id.* But while these guidelines were endorsed by the now-titled Pharmaceutical Research and Manufacturers of America (PhRMA), "[A]n abatement of marketing abuses ... was short-lived. Within a few years, commercial detailers and physicians continued to exhibit behavior inconsistent with the guidelines." *Id.* As discussed below, however, some state legislatures have taken action to address the problem themselves. *Id.*

materials, and meals provided during research meetings—as “acceptable” under the group’s guidelines on gifts to physicians.³³¹ On the other hand, “lavish dinners, free trips, offers of cash and other inducements . . . are clearly not in compliance.”³³²

Physicians, including physicians in training, have regarded themselves as immune from advertising, insisting that drug companies’ trinkets (pens, notepads, etc.) and other favors do not influence the treatment of their patients. Doctors maintain (and sincerely believe) that because they are not paid per prescription, their decisions to prescribe only reflect what is best for their patients.³³³ Empirical evidence has shown otherwise,³³⁴ however, including contexts where psychiatrists have done the prescribing. Figures from Minnesota, for instance, revealed that psychiatrists who received more than \$5,000 from SGA manufacturers wrote more prescriptions of the drugs for children than did other psychiatrists.³³⁵ As Dr. Jerome P. Kassirer, a professor at the Tufts University School of Medicine, commented in an article from ABCNews: “One important question: why would the drug industry spend so much money advertising if they didn’t think they were influencing physicians? The notion that this is all for physician education is nonsense.”³³⁶

331. Ethical Guidelines for Gifts to Physicians from Industry: Frequently Asked Questions, AMA-ASSN, available at <http://www.ama-assn.org/ama/pub/category/13394.html> (last visited June 1, 2009).

332. *Id.*

333. Daniella A. Zipkin & Mark A. Steinman, *Interactions Between Pharmaceutical Representatives and Doctors in Training: A Thematic Review*, 20 J. GEN. INTERNAL MED. 777, 777 (2005); Mark A. Steinman et al., *Of Principles and Pens: Attitudes and Practices of Medicine Housestaff Toward Pharmaceutical Industry Promotions*, 110 AM. J. MED. 551, 551 (2001).

334. Former drug company sales representatives have also spoken out about tactics they say they were told to use by their employers. Shahram Ahari, a former sales representative for Lilly, gained exposure through a YouTube video addressing the marketing of Zyprexa. (The video is available at <http://www.youtube.com/watch?v=nj0LZZzrcrs>.) When he testified before the Senate Aging Committee in March 2008, Ahari explained not only downplaying side effects of drugs, but gift giving as well. See Marcus Baram, *Ex-Drug Sales Rep Tells All*, ABCNEWS.com, available at <http://abcnews.go.com/Health/Story?id=4438095&page=1>. Ahari’s Letter to Congress commented about the purpose behind gifts to physicians specifically noting that

[w]hether [it is] pens, pads, clip boards, or anatomical models, companies take great pains to make their gifts vibrantly colored and clearly logo’ed. The strategy behind these gifts is to draw attention to the pharmaceutical products and to serve as reminders of the company’s generosity. These reminders generate a conscious or subconscious desire to return the “favor.” Referred to as “reciprocity” (a well known term in psychology and marketing), this desire is cultivated by drug reps with whom doctors have a social bond.

Letter from Shahram Ahari to the U.S. Congress (<http://aging.senate.gov/events/hr190sa.pdf>).

335. *Id.*

336. Baram, *supra* note 334.

Gift-giving by pharmaceutical companies affects future medical professionals as well. A 2005 study published in the *Journal of American Medical Association* concluded that medical students were “at risk for unrecognized influenced by marketing efforts.”³³⁷ In reaching that conclusion, the study revealed an average of one sponsored activity attended or one gift received per week, per student.³³⁸ Additionally, the study found that:

Most students perceive that they are entitled to gifts. Many simultaneously think that sponsored educational events are likely to be biased, but are helpful. Most think that their prescribing is not likely to be influenced by these interactions and that their colleagues are more likely to be influenced.³³⁹

In response to such findings, a 2006 article from JAMA recommended that medical schools and teaching hospitals implement a ban on individual doctors’ accepting *any* meals, gifts, books, or other favors from pharmaceutical companies,³⁴⁰ echoing the ban on all gifts and marketing by pharmaceutical companies to medical students that the American Medical Students Association had recommended in 2002.³⁴¹ A few institutions are implementing such bans.³⁴²

2. Other Restrictions on Advertising

Some states have decided to track or halt the efforts of pharmaceutical companies when it comes to providing incentives to physicians.³⁴³ In 2002, Vermont became the first state to do so,³⁴⁴ passing a bill that required pharmaceutical companies to report such items as travel expenses and other pay-

337. Federick S. Sierles et al., *Medical Students’ Exposure to and Attitudes About Drug Company Interactions: A National Survey*, 294 JAMA 1034, 1040 (2005). The study tracked third-year medical students at eight schools: Case Western Reserve University, George Washington University, the Mayo Clinic College of Medicine, Ohio State University, Rosalind Franklin University, State University of New York Upstate Medical University, University of California at San Francisco, and University of Nebraska. *Id.* at 1035.

338. *Id.* at 1038. The survey included everything from free lunches and dinners, to snacks, to utensils, to sponsored ground rounds, to workshops, to waived registration fees paid by drug companies. *Id.* at 1036.

339. *Id.* at 1040.

340. Troyen A. Brennan et al., *Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers*, 295 JAMA 429, 429 (2006).

341. See *American Medical Student Association Applauds Pharmaceutical Industry for Voluntary Ban; Continues to Call for Federal Regulation*, AMSA.ORG, Jan. 2, 2009, available at <http://www.amsa.org/news/release2.cfx?id=365>.

342. See, e.g., Aaron Nicodemus, *Doctors Reject Drug-Pusher Favors*, WORCESTER TELEGRAM & GAZETTE, Jan. 18, 2009, available at <http://www.telegram.com/article/20090118/NEWS/901180384/1008/NEWSREWIND> (at the University of Massachusetts Medical School, “gifts of any value—right down to the pens—are banned”).

343. See Tsai, *supra* note 327, at 1776.

344. *Id.*

ments to physicians.³⁴⁵ Items of *de minimis* value, less than \$25, were excused from the reporting requirement.³⁴⁶ In 2009, the Vermont legislature passed a stricter version of the law that bans *all* gifts and requires that pharmaceutical companies report *all* payments to physicians.³⁴⁷ Under a newly-enacted Massachusetts law, set to go into effect on July 1, 2009, pharmaceutical companies will not only be required to report the sums paid to physicians, but will also be banned or severely restricted from giving “most gifts and dinners.”³⁴⁸ Interestingly, some commentators have viewed state legislation as mere redundancy in “an industry that is already adequately regulated by the FDA and the U.S. Department of Justice, which ‘enforces fraud, abuse, and anti-kickback laws.’”³⁴⁹ Looking at aspects of the litigation on olanzapine, however, raises questions about whether the federal government does in fact adequately regulate physician inducements.

Pharmaceutical companies, through the Pharmaceutical Research and Manufacturers of America, responded to adverse publicity about advertising with new guidelines that became effective January 1, 2009.³⁵⁰ The guidelines, which approximately 40 pharmaceutical companies have agreed to follow,³⁵¹ limit the distribution of office items (such as pens, mugs, and staplers), and prohibit drug company sales reps from paying for physicians’ and other health care professionals’ meals.³⁵² Because of the newness of these guidelines, their effect of their impact on doctors’ prescribing and their willingness to prescribe new drugs is not yet known.

3. Non-Marketing Factors

Doctors are as susceptible as other human beings to marketing techniques (though they have been slow and reluctant to recognize this).³⁵³ Physicians have a fiduciary duty to insulate themselves from the effect such techniques have on their practice decisions, and medical organizations have finally

345. Gever, *supra* note 321. Minnesota has a similar statute. See Peggy Peck, *State Oversight of Industry Gifts to Physicians All Bark*, MEDPAGE TODAY, Mar. 20, 2008, <http://www.medpagetoday.com/PublicHealthPolicy/HealthPolicy/5291> (last visited Jan. 23, 2009).

346. Gever, *supra* note 321.

347. Natasha Singer, *Doctors Gifts To Be Public In Vermont*, N.Y. TIMES, May 19, 2009, at B1, available at 2009 WLNR 9573599. The law even “ban[s] all free meals” to physicians. *Id.*

348. Nicodemus, *supra* note 342.

349. Peck, *supra* note 345.

350. See Editorial, *No Mugs, But What About Those Fees?*, N.Y. TIMES, Jan. 4, 2009, at A20, available at <http://www.nytimes.com/2009/01/05/opinion/05mon1.html>.

351. *Id.*

352. *Id.* The ban does *not* affect meals given to health care professionals while sales representatives are “pitching their products,” or from drug companies paying for CMEs. *Id.*

353. See generally Dana & Loewenstein, *supra* note 326, at 253-254 (citing studies and providing examples).

taken steps to fulfill this obligation.³⁵⁴ Having finally acknowledged their susceptibility to drug advertising, it seems sensible that physicians should take steps to limit (or ban) their exposure to favors, meals, trinkets, and other blandishments from pharmaceutical manufacturers. Physicians should base prescribing decisions primarily on scientifically grounded beliefs about what will conduce to patients' welfare, not on how well they like particular drug reps or on what they have heard while consuming expensive restaurant meals.³⁵⁵

However, aggressive (and occasionally overly aggressive) promotion is far from the only reason that psychiatrists so rapidly and enthusiastically switched to prescribing SGAs between 1995 and 2000. Here, we describe other factors that contributed to the rapid FGA-to-SGA prescribing transition.

a. Avoiding Malpractice Liability

One distinctive advantage of the SGAs—an advantage that recent studies still support—is their lower propensity to cause TD. Although it is difficult to find documentary evidence of this, a desire to avoid putting patients at unnecessary risk of developing TD was a major factor in many psychiatrists' preference for the SGAs. This was partly an ethical decision (fulfilling the Hippocratic dictum to “do no harm”) and partly a reflection of litigation fear.³⁵⁶ Though some professional groups regard negligence suits as a mere “cost of doing business,” physicians do not.³⁵⁷ Actual lawsuits involving TD have been relatively uncommon, but psychiatrists knew about them and were intensely concerned about them even when the only drugs available to treat psychotic patients were FGAs.³⁵⁸ When the arrival of SGAs gave doctors an

354. See David J. Rothman & Susan Chimonas, *New Developments in Managing Physician-Industry Relationships*, 300 JAMA 1067, 1067 (2008) (noting that recently, “policies governing the relationship between physicians and pharmaceutical and device companies have undergone remarkable changes,” including recommendations from the Association of American Medical Colleges to prohibit all gifts and prohibit food provided by industry).

355. Brennan et al., *supra* note 340, at 430 (arguing that academic medical centers should lead the way in eliminating drug advertising in which “physicians have motives or are in situations for which reasonable observers could conclude that the moral requirements of the physician’s roles are or will be compromised”).

356. See, e.g., Mossman & Lehrer, *supra* note 113, at 1531 (quoting other physician’s discussion of potential liability).

357. The professional socialization of physicians instills an ideal of error-free practice and a belief that good physicians are virtually infallible. See David Hilfiker, *Facing Our Mistakes*, 310 NEW ENG. J. MED. 118, 121 (1984). Legalistic and self-critical thinking has led physicians to believe that medical error only occurs because of negligence. Physicians often personalize this even further, concluding (consciously or unconsciously) that medical errors reflect underlying character flaws. See Lucian L. Leape, *Error in Medicine*, 272 JAMA 1851, 1852 (1994).

358. Perhaps the best known case is *Clites v. State*, 322 N.W.2d 917 (Iowa App. 1982). Tim Clites’s development of TD was compounded by poor monitoring, *id.* at 921, and lack of con-

alternative to prescribing FGAs, many psychiatrists felt that to prescribe an FGA was to invite a lawsuit.³⁵⁹ Suicide and violence by patients are major liability concerns for psychiatrists, so literature supporting the superior effectiveness of SGAs at reducing violence risk provided yet another reason for prescribing the newer drugs and avoiding the older ones.³⁶⁰

b. Physicians' Mental Limits

Problems with SGAs and limitations of studies supporting their superiority were becoming apparent in the late 1990s—the very point at which psychiatrists were switching to the newer drugs. Why did this anti-SGA information have so little impact on what psychiatrists were doing? The short answer is that physicians have cognitive limitations.

Practicing physicians can devote only so much time to assessing and weighing of probabilistic information. Like all other human beings, doctors use “fast and frugal” heuristics to make decisions.³⁶¹ Because most physicians cannot make their own informed judgments about drugs' relative advantages, the pharmaceutical reps who visit physicians' offices often become the key sources of information about medications. Doctors often fail to recognize that the goal of these salesmen are to promote their companies' interests³⁶² or, if doctors realize that reps' information is biased, they mistakenly believe they are immune to marketing techniques.³⁶³

Physicians can examine only a tiny sliver of the findings and minutiae published in journals concerning just their own specialty, and most read only

sent, *id.* at 922, but these details often escaped clinicians' notice. By the mid-1980s, more than a decade after the recognition of TD, just ten TD-related lawsuits had been identified. Phil Brown & Steven C. Funk, *Tardive Dyskinesia: Barriers to the Professional Recognition of an Iatrogenic Disease*, 27 J. HEALTH SOC. BEHAVIOR 116, 124 (1986) (citing these cases). Nonetheless, psychiatrists warned their colleagues of dire consequences from future TD-related litigation. See C. Thomas Gualtieri & Robert L. Sprague, *Preventing Tardive Dyskinesia and Preventing Tardive Dyskinesia Legislation*, 20 PSYCHOPHARMACOLOGY BULL. 346 (1984).

359. See Mossman & Lehrer, *supra* note 113, at 1531-33 (medical journal's discussion of malpractice and various other theories under which FGA prescribing might generate litigation); see also Mossman, *supra* note 15, at 1092-1125 (lengthy exploration of potential sources of liability).

360. See Mossman & Lehrer, *supra* note 113, at 1533; see also Mossman, *supra* note 15, at 1104-06. Several medical publications now support a connection between SGA therapy and violence reduction. See, e.g., Jeffrey W. Swanson et al., *Effectiveness of Atypical Antipsychotic Medications in Reducing Violent Behavior Among Persons With Schizophrenia in Community-Based Treatment*, 30 SCHIZOPHRENIA Bull. 3 (2004) (finding that SGAs “significantly reduce the risk of violent behavior” but FGAs do not, and recommending that SGAs “be considered as an important component of violence risk management”).

361. Glyn Elwyn et al., *Decision Analysis in Patient Care*, 358 LANCET 571, 573-74 (2001).

362. Howard Brody, *The Company We Keep: Why Physicians Should Refuse to See Pharmaceutical Representatives*, 3 ANNALS FAM. MED. 82, 83 (2005).

363. Melinda L. Randall et al., *Attitudes and Behaviors of Psychiatry Residents toward Pharmaceutical Representatives before and after an Educational Intervention*, 29 ACAD. PSYCHIATRY 33, 35-36 (2005).

summaries of most articles that they hear about.³⁶⁴ If one looks only at the abstracts of studies on SGAs from the 1990s, those studies really seem to show that SGAs are better than FGAs.³⁶⁵ In general, prior to the CATIE study, most psychiatrists had little basis for thinking that these advantages did not translate into real-world benefits. The research details that might have alerted psychiatrists to SGA limitations—for example, using a high-potency FGA (usually haloperidol) as the comparator drug and dosing it high enough to induce many side effects,³⁶⁶ or selecting nonrepresentative patients as subjects for studies³⁶⁷—were easy to miss.

The problems caused by FGAs versus SGAs differ importantly in their obviousness, timing, and salience. Many persons who take high-potency FGAs look drugged and slowed down by neuromotor side effects that quickly occur, but the movements of people who take SGAs usually are not effected much.³⁶⁸ By contrast, weight gain induced by SGAs accumulates over weeks

364. See Teresa Jones et al., *What British Psychiatrists Read: Questionnaire Survey of Journal Usage Among Clinicians*, 185 BRIT. J. PSYCHIATRY 251, 253 (2004) (only two journals read by most psychiatrists); Sanjay Saint et al., *Journal Reading Habits of Internists*, 15 J. GEN. INTERNAL MED. 881, 881 (2000) (internists “rely heavily on abstracts”); David T. Burke et al., *Reading Habits of Practicing Psychiatrists*, 81 AM. J. PHYS. MED. & REHABILITATION 779, 779 (2002) (“most psychiatrists only scan the table of contents and read the most important abstracts”).

365. See, e.g., Richard L. Borison et al., *JCI 204,636, an Atypical Antipsychotic: Efficacy and Safety in a Multicenter, Placebo-Controlled Trial in Patients with Schizophrenia*, 16 J. CLINICAL PSYCHOPHARMACOLOGY 158, 158 (1996) (“treatment with [quetiapine] did not induce” extrapyramidal side effects); Chouinard et al., *supra* note 23, at 38 (risperidone at least as effective as haloperidol with far lower incidence of EPS); Donald C. Goff et al., *An Exploratory Haloperidol-Controlled Dose-Finding Study of Ziprasidone in Hospitalized Patients with Schizophrenia or Schizoaffective Disorder*, 18 J. CLINICAL PSYCHOPHARMACOLOGY 296, 304 (1998) (ziprasidone at least as effective as haloperidol with far lower incidence of EPS); and Gary D. Tollefson et al., *Olanzapine Versus Haloperidol in the Treatment of Schizophrenia and Schizoaffective and Schizophreniform Disorders: Results of an International Collaborative Trial*, 154 AM. J. PSYCHIATRY 466, 473 (1997) (olanzapine at least as effective as haloperidol with far lower incidence of EPS).

366. See *supra* note 103 and accompanying text.

367. To avoid confounding variables that would make results difficult to interpret statistically, studies of new medications typically exclude patients with various medical problems, co-existing psychiatric problems, and substance use disorders. See, e.g., Borison et al., *supra* note 365, at 344 (exclusion criteria included patients with “any other psychiatric disorder, ... [s]uicidal ideation within a year of trial entry, mental retardation, convulsive disorders, history of severe head trauma or suspected organic brain disease, ... risk of pregnancy, ... clinically significant laboratory findings or abnormal electrocardiograms”). In real-world psychiatry, however, such patients make up the vast majority of persons who receive treatment for severe mental illnesses. See *supra* note 188, at 1069 (noting that drug approval studies are “conducted at least partially in a hospital setting, involve only a selected subsample of the population for which the drug will eventually be indicated, and exclude patients with psychiatric and medical comorbidities”).

368. See *supra* note 103 and accompanying text (discussing SGAs’ lower incidence of neuromotor side effects).

or months,³⁶⁹ and any glucose and lipid abnormalities are usually evident only in laboratory results of blood tests. At a time when the entire American population was becoming fatter,³⁷⁰ observing weight gain in a person whose mental state was improving may not have seemed unusual or troubling. In sum, the limitations of FGAs are gross and immediately apparent, while the problems with SGAs are subtle and slower to materialize. Individual physicians have very limited ability to discern large population trends such as a higher incidence of obesity and metabolic syndrome in certain patients. Movement abnormalities in an individual patient are, by contrast, easy to spot and worry about.³⁷¹

From the standpoint of a practitioner with limited time and resources, SGAs are huge time-savers. Prescribing high-potency FGAs so that they do not produce troubling side effects often requires careful dose adjustment and frequent monitoring of a patient's response.³⁷² By contrast, the SGAs were marketed with relatively clear dosage guidelines,³⁷³ and the margin of error between a dose that quells psychosis and the dose that causes neuromotor side effects is much wider.³⁷⁴ As the effectiveness of SGAs for other conditions (e.g., mood disorders) was recognized, psychiatrists could prescribe them instead of older mood stabilizers (e.g., lithium and valproate), which also require careful dose adjustments.³⁷⁵ SGAs thus are an easy-to-prescribe, one-

369. David B. Allison et al., *Antipsychotic-Induced Weight Gain: A Comprehensive Research Synthesis*, 156 AM. J. PSYCHIATRY 1686, 1692 (1999) (weight gains with SGAs of 1-4 kg over 10 weeks).

370. See Centers for Disease Control and Prevention, U.S. Obesity Trends 1985–2007, <http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/index.htm> (last visited Feb. 10, 2009) (animated map showing no state with obesity rates above fifteen percent in 1985 and only one state (Colorado) with obesity rate below twenty percent in 2007; obesity rates above twenty-five percent in most states).

371. See Michael J. Sernyak & Robert A. Rosenheck, *Antipsychotic Use in the Treatment of Outpatients With Schizophrenia in the VA From Fiscal Years 1999 to 2006*, 59 PSYCHIATRY SERVICES 567, 569 (2008) (concluding that “antipsychotic prescribing patterns over an eight-year period suggests that concerns about side effects are the strongest driver of differences in medication use”).

372. See, e.g., McEvoy et al., *supra* note 103, at 741 (discussing every-other-day assessment of patients); Douglas Mossman, *A Decision Analysis Approach to Neuroleptic Dosing: Insights from a Mathematical Model*, 58 J. CLINICAL PSYCHIATRY 66, 69-70 (1997) (discussing ranges of FGA doses and balancing of benefits with side effects). See also Peter J. Weiden et al., *Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap*, 68 J. CLINICAL PSYCHIATRY 4, 13-19 (Supp. 7 2007) (discussing narrow range of doses that are effective with inducing neuromotor side effects).

373. Heres et al., *supra* note 112, at 190 (noting that the SGAs were “a major step forward. For the first time antipsychotic drugs with clearly defined dose ranges were made available, while the optimum dose, even of the standard conventional antipsychotic haloperidol, is still in doubt”).

374. Michael D. Jibson & Rajiv Tandon, *New Atypical Antipsychotic Medications*, 32 J. PSYCHIATRIC RES. 215, 223 (1998) (graphic summary of SGA advantages over FGAs).

375. See THE AMERICAN PSYCHIATRIC PUBLISHING TEXTBOOK OF MOOD DISORDERS 471 (Dan J. Stein et al. eds., 2005) (discussing need for plasma levels and noting that lithium's the-

drug-fits-all solution for a large fraction of the severely ill patients whom many psychiatrists treat.

Finally, the high cost of new drugs—a drawback of which doctors and payors *were* immediately aware—was not a factor blocking the adoption of SGAs. In most U.S. healthcare settings, neither the prescribing doctor nor the patient who takes (and benefits from) a particular drug has any personal incentive to control pharmaceutical costs.³⁷⁶ However, doctors do have ever-present incentives to avert liability, and patients have incentives to avoid side effects that they experience immediately.

For all these reasons, SGAs seemed much more attractive choices with apparently little disadvantage.

c. Outside Influences

Entities that pay for new and expensive treatments are logical sources of opposition to adopting those treatments, especially if those treatments do not clearly offset higher costs. In the early to mid-1990s, some agencies responsible for paying pharmaceutical bills attempted to limit costs by putting limits on use of SGAs. In some cases, court decisions barred large-scale efforts to do this consistently.³⁷⁷ Even after the results of CATIE, few formulary restrictions limit use of SGAs,³⁷⁸ though some state mental health directors suggest that these might be justified.³⁷⁹ Formulary restrictions have been opposed by advocacy groups, such as the National Association for the Mentally Ill,³⁸⁰ who appear to accept what pharmaceutical companies and prescribing psychiatrists believe about the advantages of SGAs.³⁸¹ State legislatures and state

rapeutic range is 0.8-1.2 mEq/L, with toxicity at 1.5 mEq/L); *see also* THE MEDICAL BASIS OF PSYCHIATRY 609 (S. Hossein Fatemi & Paula J. Clayton eds., 2008) (valproate dose ranges from 750 to 6,000 mg/day and requires monitoring of blood levels).

376. Duggan, *supra* note 117, at 2 (“[B]ecause Medicaid recipients typically do not share in the cost of their prescription drugs, the program distorts medical care purchase decisions.”).

377. *See supra* note 94 (discussing *Visser v. Taylor*, 756 F. Supp. 501 (D. Kan. 1990) and *Alexander L. v. Cuomo*, 588 N.Y.S.2d 85 (N.Y. Sup. Ct. 1991)).

378. *See, e.g.*, Chi-Chuan Wang et al., *Coverage of Atypical Antipsychotics Among Medicare Drug Plans in the State of Washington for Fiscal Year 2007*, 10 Prim. Care Companion J. CLINICAL PSYCHIATRY 313, 314 (2008) (almost all Medicare plans cover all SGAs).

379. *See* Joseph J. Parks et al., *Impact of the CATIE Findings on State Mental Health Policy*, 59 PSYCHIATRIC SERVICES 534, 535, 536 (2008) (three medical directors who previously endorsed SGAs now feel that “neither complete open access for all patients at all times nor a uniform fail-first trial of a first-generation drug are optimal approaches.”).

380. *See, e.g.*, *Dr. Fred Frese Testifies before House Veteran’s Affairs Committee*, NAMI E-News, June 20, 2001, <http://www.namisc.org/newsletters/Sept01/veteran.htm> (last visited Feb. 10, 2009) (quoting testimony of NAMI board member (who is also a psychologist with mental illness) opposing VA formulary restrictions).

381. Pharmaceutical companies have made substantial donations to NAMI. Thus, it was not just physician recipients of drug company blandishments who were convinced that SGAs were superior treatments; patients and their advocates believed this too.

mental health departments have also exempted SGAs from the sorts of cost controls placed on other medications.³⁸²

d. Lack of Good Information

A final factor in the collective judgment error concerning SGAs is the sub-optimal quality of information that physicians receive about medications. Drug development has become very costly, but pharmaceutical companies spend twice as much on drug advertising as they do on research—\$57.5 billion by one recent estimate.³⁸³ As anyone who has attended a large medical meeting knows, the most interesting “educational” events—and the ones offering meals and gifts—are those sponsored by pharmaceutical firms, at which the topics and speakers can be selected in ways that highlight advantages of products produced by those firms.³⁸⁴ Similarly, a glance at any medical journal quickly reveals that the most vivid, esthetically appealing pages are not those that contain scientific articles, but those that contain advertisements paid for by commercial concerns.

Though physicians may underestimate their invulnerability to advertising, they certainly know when they are attending commercially sponsored events or reading promotional materials. In recent years, however, pharmaceutical companies have used activities that physicians have usually regarded as independent of commercial influence to promote products, especially off-label uses. Pharmaceutical enterprises have created physician advisory boards and have organized gatherings of “consultants” (physicians identified as professionally influential), knowing that the doctors attending these functions will later discuss the companies’ products favorably with their colleagues. Companies have sponsored continuing medical education events where “thought leaders” (again, prominent physicians) spread the word about their products; often, a purpose of these events is to promulgate off-label uses of drugs, something physician speakers may do even when drug manufacturers may not.³⁸⁵ Drug companies have also hired communication companies that get

382. See Chris Koyanagi et al., *Medicaid Policies To Contain Psychiatric Drug Costs*, 24 HEALTH AFFAIRS 536, 540 (2005) (noting that although many Medicaid programs put limits on some medications, many “states have legislated exemptions from those policies for certain medications, particularly antipsychotics and antidepressants”); David Bergman et al., *State Efforts to Manage The Behavioral Health Pharmaceutical Benefit*, NAT’L ACAD. STATE HEALTH POL’Y, Mar. 2006, at ISSUE BRIEF 1, 3 (noting that “no state used the fail-first strategy” to limit costs).

383. See Gagnon & Lexchin, *supra* note 316, at 30, 32.

384. This problem is not restricted to psychiatry. For just two of many recent descriptions, see Arnold S. Relman, *Industry Support of Medical Education*, 300 JAMA 1071 (2008), and Brennan, *supra* note 328, at 429 (2006). This is not a recent problem. See, e.g., Anthony G. Salem, *Medical Education and the Pharmaceutical Industry*, 5 J. GEN. INTERNAL MED. 91, 91-92 (1990), and older sources cited therein.

385. See, e.g., Michael A. Steinman et al., *Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents*, 145 ANNALS OF INTERNAL MED. 284, 286-290 (2006) (describing use of advisory boards, consultants meetings, medical education events, recruitment

articles published in medical journals.³⁸⁶ Many research studies that appear to have been proposed and designed by academic, independent researchers show evidence of “ghost authorship” by commercial concerns.³⁸⁷

Even peer-reviewed, double-blind studies published in prestigious medical journals can spread faulty information about off-label drug uses when sponsors of these studies structure them or use statistical analyses to cast their products in a favorable light. The former editors of the *British Medical Journal* and the *Lancet* believe that these publications have unwittingly functioned as “an extension of the marketing arm”³⁸⁸ or “information-laundering operations” for drug companies’ indirect promotions of off-label drug uses.³⁸⁹ Also, medical journals prefer to publish results showing that medications are effective, and manufacturers often decide not to submit for publication the results of studies showing lack of effectiveness. This means that even for psychotropic medications used for their FDA-approved indications, published results make drugs seem more effective than one would conclude if one knew the results of all studies.³⁹⁰

Conducting studies of medication is an expensive enterprise. Proving efficacy and safety of a drug under FDA guidelines usually requires experiments that involve thousands of volunteer subjects. For each of these subjects, proper monitoring may require dozens of hours of clinicians’ time and extensive laboratory testing. The result, according to one widely cited estimate, is that companies’ out-of-pocket costs are more than \$800 million per FDA-

of local champions to communicate favorable product messages to fellow physicians, and noting that by using these “techniques . . . commercial interests can intrude into the practice of medicine in both visible and hidden ways”).

386. These practices are described in Sergio Sismondo, *Ghost Management: How Much of the Medical Literature Is Shaped Behind the Scenes by the Pharmaceutical Industry?* 4 PLOS MED 1429, 1431 (2007) (noting that “medical journals have real effects upon physician prescribing behavior, which is why pharmaceutical companies invest so much in their publication”).

387. See Peter C. Götzsche et al., *Ghost Authorship in Industry-Initiated Randomised Trials*, 4 PLOS MED. 47, 48-49 (2007) (finding evidence of ghost authorship in 75% of trials, further evidence if acknowledgments are included, particularly among the statisticians who had primary responsibility for mathematical analyses).

388. Richard Smith, *Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies*, 2 PLOS MED. 364, 365 (2005).

389. Richard Horton, *The Dawn of McScience*, N.Y. REV. BOOKS, Mar. 11, 2004, at 7, 9. The former editor of the *New England Journal of Medicine* echoes these sentiments:

It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of *The New England Journal of Medicine*.

Angell, *supra* note 5.

390. See Erick H. Turner et al., *Selective Publication of Antidepressant Trials and its Influence on Apparent Efficacy*, 358 NEW ENG. J. MED. 252 (2008) (medical publications made it appear that ninety-four of antidepressant trials were positive, whereas only fifty-one percent of all trials were).

approved drug.³⁹¹ Because relatively little money for drug studies is available from non-commercial sources, most drug studies are initiated and designed by pharmaceutical manufacturers whose understandable and perfectly reasonable goal is to improve sales of their products. Criteria for receiving FDA approval require a showing that a compound is safe and superior to placebo for treating a particular disorder.³⁹² What doctors often need to know, however, is whether a new (and usually more expensive) drug is not only effective, but *better* than an older (an often less expensive) already existing drug, and if so, how much better. Pharmaceutical companies currently have no obligation to conduct such costly comparison studies, and even if they wished to do so, their efforts must first be focused on meeting high-cost requirements of FDA trials. Moreover, manufacturers often have only disincentives to conduct comparison studies of their products because of the threat to sales that such adverse results might pose.

B. Concluding Thoughts

If the FGA-to-SGA prescribing transition described in Part II indeed reflects a collective judgment error by psychiatrists, it was a judgment error produced by a confluence of forces: physicians' fears of liability, unopposed power of industry to structure scientific knowledge, promotional excesses, advocacy groups' clamor for better treatment of devastating illnesses, and individual physicians' limited power to perceive trends and evaluate scientific data. Limiting pharmaceutical promotional activities, restricting gifts to physicians, and punishing companies for improper (off-label) promotion are all appropriate steps. As we have seen, however, these measures do not address the huge information-dispensing advantage held by pharmaceutical companies and the collective judgment errors exemplified by psychiatrists' over-eagerness to jettison older antipsychotic drugs.

V. THE NEED FOR BETTER INFORMATION

A. Problems with Past Responses

In describing the legal system's responses to the costs and imperfections of SGAs, Part III has discussed what are, in essence, efforts to control future behavior by punishing undesirable past behavior. These remedies are founded on an implicit conception of pharmaceutical companies' legal transgressions as bad decisions by many persons who, left to their own devices, would not accept and respond properly to their social responsibilities. This implicit conception also regards punishment—either in the form of tort-based compensa-

391. See Ross Tonkens, *An Overview of the Drug Development Process*, PHYSICIAN EXECUTIVE, May-June 2005, at 48, 49-50 (May-Jun. 2005); DiMasi, *supra* note 133, at 166.

392. DiMasi, *supra* note 133, at 155-56; Tonkens, *supra* note 378 at 50.

tion for victims or in monetary penalties for violating regulations—as the appropriate response to bad decisions.

We see three problems with this response. First (and most obviously, though not trivially), penalties *follow* disapproved-of behavior; they occur after the *harm* is done. An often promulgated justification of tort penalties is that they prevent harm: individuals, knowing the potential adverse consequences of certain course of action, will do what is desirable or at least not do what is harmful. The problem with this idea, however, is that to the extent that persons rationally weigh consequences of potential courses of action, punishments only create motivations to avoid punishment.³⁹³ If we can avoid punishment by means other than doing what is desired, and if avoidance is less costly or less onerous than doing what is desired because we continue to receive the rewards of undesirable behavior, then avoidance plus engaging in the disapproved-of behavior may seem like the best choice.³⁹⁴

In the case of drug manufacturing and promotion, legal sanctions compensate plaintiffs or states for wrongdoing if the wrongdoing is detected and the litigation is successful. However, legal sanctions create incentives to avoid adverse consequences rather than to engage in desirable conduct.³⁹⁵ As experience with medical malpractice litigation suggests, lawsuits create incentives to avoid lawsuits. Lawsuits may also promote better practices and avoid harms,³⁹⁶ but they do this only imperfectly. The threat of litigation may make practitioners improve their performance and act more safely. However, the punitive and adversarial approaches of tort law are the opposite of the systems-oriented, cooperative strategies that leaders of the patient-safety movement believe are conducive to exposing problems in systems, which are the real loci of medical errors.³⁹⁷

393. Recently, scientists have shown that avoiding aversive stimuli activates the same neural substrate—the brain’s medial orbital frontal cortex—as is activated when rewards are received. See Hackjin Kim et al., *Is Avoiding an Aversive Outcome Rewarding? Neural Substrates of Avoidance Learning in the Human Brain*, 4 PLOS BIOLOGY 1453 (2006).

394. On the relationships among punishment, negative reinforcement, escape, and avoidance, see BENJAMIN J. SADOCK ET AL., KAPLAN & SADOCK’S SYNOPSIS OF PSYCHIATRY 145-46 (2007). Evasion often seems preferable to law-abiding behavior. As the popularity and sales of radar detectors attest, many fast drivers choose to retain the rewards of traveling quickly without getting a speeding ticket.

395. Richard A. Nagareda, *In the Aftermath of the Mass Tort Class Action*, 85 GEO. L.J. 295, 313, 314 (1996) (noting that the tort system “transfers money in the form of damages for past injuries” but is not a system that “regulates behavior by imposing limitations upon future conduct”).

396. See David A. Hyman & Charles Silver, *The Poor State of Health Care Quality in the U.S.: Is Malpractice Liability Part of the Problem or Part of the Solution?*, 90 CORNELL L. REV. 893, 916 (2005) (reporting “an *inverse* relationship between the magnitude of the malpractice risk and the rate of negligent injuries” leading to a reduction in patient injuries, but arguing that injury prevention should be a key factor in debates about malpractice litigation).

397. David M. Studdert et al., *Medical Malpractice*, 350 NEW ENG. J. MED. 283, 287 (2004).

Drawing lessons from the rofecoxib litigation, Jennifer Wolsing suggests that the threat of tort action actually discourages drug manufacturers from undertaking actions that might promote public welfare, such as conducting and publishing additional studies beyond the bare minimum required for FDA approval. Instead, the potential for tort litigation and other legal sanctions encourages companies to publish only the minimum necessary results, “to provide conspicuous warnings detailing every possibility of harm” and to actually “keep drugs on the market, . . . rather than to withdraw them abruptly, to avoid the ‘red flag’ effect of alerting plaintiffs and trial lawyers that a drug may be dangerous.”³⁹⁸ How manufacturers will actually respond to the recent spate of litigation is an empirical matter. But the potential profits from off-label uses of pharmaceutical remain powerful incentives for the actions that have led to lawsuits, and those profits have not been countered by incentives for other behavior that might better promote patients’ welfare.

A second problem with the bad-behavior-deserves-punishment response is that it implies that the only reason drug manufacturers will behave responsibly and sell good products is to avoid punishment. We suspect, however, that pharmaceutical companies recognize that their long-term self-interest is in producing and selling good, effective products, and that their product promotions usually reflect sincere-if-humanly-imperfect beliefs that they are making money by doing something good—helping patients with illnesses. Viewed in this light, drug industry practices that have recently been characterized in medical journals and lay media as nefarious and corrupting—the recruitment of academic physicians as influential “thought leaders,” sponsoring continuing medical education events, even selective publishing of study results—are logical responses to beliefs about the value of products and the escalating need to respond to what competitor companies do to promote their products.

Finally, criticism and punishment of drug companies does not get at what we believe is the real problem behind over-enthusiastic adoption of SGAs: inadequate information about the value and real effectiveness of the new drugs. As Part II explains, until 2005, the best scientific data suggested that newly available antipsychotic treatments had clear advantages over the drugs psychiatrists previously used. Psychiatrists should now understand that those advantages emerged in the artificial, carefully controlled, placebo-comparison studies that drug companies were (and remain) required to conduct to win marketing approval for their products. But when SGA-over-FGA advantages that emerged from drug-approval studies did not translate into real-world benefits, it surprised the very investigators who designed the real-world studies.³⁹⁹ Moreover, the adverse effects particularly associated with SGAs—hyperlipidemia, diabetes and increased weight gain—are not uncommon in populations with serious mental illnesses and are not unique to per-

398. Jennifer Wolsing, *The Vioxx Litigation: Disincentivizing Patient Safety Through Misdirected Tort Rules*, 75 DEF. COUNS. J. 209, 212-13 (2008).

399. See *supra* note 166 and accompanying text.

sons taking SGAs; they are, however, much less obvious than the neuromotor problems caused by high-potency FGAs that psychiatrists wanted to avoid. The SGA side effects display a feature common to other subjects of mass tort litigation, in which problems and injuries “emerge progressively as the relevant latency periods run their course.”⁴⁰⁰ Mere reliance on the tort-based sanctions or punishments for violating advertising regulations may not be the best means to address what is really behind these latent harms: gaps in scientific information.

How, then, could regulatory and other reforms provide incentives to create and quickly promulgate information about drugs? We offer three proposals.

B. Promoting Information

1. *Comparative Effectiveness Studies*

As earlier portions of this Article have explained, psychiatrists developed more accurate views about the value of SGAs only after release of results from CATIE, CUtLASS, and other studies sponsored by agencies independent of drug companies. These research efforts are examples of so-called “comparative effectiveness” studies, which have been championed lately as ways giving doctors and patients unbiased data that can help them “[k]now more about the effect of different health interventions[,] ... improve the treatment of diseases, help Americans better manage and prevent illness, and ... lower health care costs for everyone.”⁴⁰¹ Although definitions of what constitutes a “comparative effectiveness” study vary, the core notion is that more studies comparing outcomes of different treatments or services, relative

400. Nagareda, *supra* note 395, at 314. As Professor Nagareda further explains, “[A]ny solution [regarding mass tort litigation]—at least one other than protracted litigation of thousands of claims over the span of many years—must entail not only the disposition of present-day lawsuits but also an attempt to determine the status of future claimants.” *Id.* The problem, he suggests, is that compensating future victims is accomplished through the tort system rather than through institutions better suited to the task:

[T]he job of addressing, on a prospective basis, entire categories of persons at risk of disease in the future is a familiar feature of administrative decisionmaking. Risk assessment and the selection of an appropriate policy response are tasks within the ordinary business of many regulatory agencies, such as the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the Occupational Safety and Health Administration (OSHA) Under current law, [however,] the major obstacle to the use of administrative bodies lies in their traditional inability to facilitate transfers of money between private parties, whether in the form of damages or by way of compensation prescribed in a settlement agreement.

Id. at 315.

401. Mike Mitka, *Comparative Effectiveness*, 300 JAMA 1290 (2008) (quoting statement by Senator Max Baucus, co-sponsor of the Comparative Effectiveness Research Act of 2008 (S. 3408)).

effectiveness of treatments, and the different options available for treating particular medical condition in particular patients would lead to more effective, less costly medical care.⁴⁰²

Currently, medical professionals have no overarching source for obtaining or accessing data on comparative effectiveness of treatments. As one commentator has noted,

The rapid growth of medical knowledge and technology means it is much harder for doctors and other health care providers to keep up to date. Indeed, the problem of information and practice transference is rendered almost impossible by the fact that health care is now a highly statist and corporatist venture. Today, there is no such thing as a free market in health care⁴⁰³

Lack of comparative effectiveness data keeps patients from availing themselves of the best treatments and from exercising “the personal freedom . . . to choose the health care that, in the professional judgment of their doctors, best serves their personal needs.”⁴⁰⁴

Amplifying the funding for and potential sources of comparative effectiveness data would help to offset the huge resources that pharmaceutical companies have available to openly promote approved uses and covertly promote unapproved uses of their products. Currently, pharmaceutical companies have shied away from conducting the time-consuming and costly studies needed to have their products approved for multiple, on-label uses. The knowledge that their products might be faced with increased independent scrutiny through comparative effectiveness studies might spur pharmaceutical companies to explore getting their products approved for additional indications. Pharmaceutical manufacturers also might experience less need to promote their drugs for off-label uses if they knew that doctors would learn (legally!) about their products’ value for off-label uses through comparative effectiveness studies.⁴⁰⁵

402. See Michael M. Gaba & Renee R. Wentzel, *The Role and Scope of Comparative Effectiveness in Our Evolving Health Care System: Balancing Treatment Choices with Budget Reality*, HEALTH LAW & LIFE SCIENCES NEWSLETTER, Feb. 12, 2009, available at <http://www.hklaw.com/id24660/PublicationId2563/ReturnId31/contentid53900/#1>.

403. Helen Evans, *Comparative Effectiveness in Health Care Reform: Lessons from Abroad*, THE HERITAGE FOUNDATION, Feb. 4, 2009, available at <http://www.heritage.org/Research/HealthCare/bg2239.cfm>.

404. *Id.*

405. Dr. Richard A. Friedman, professor of psychiatry at Weill Cornell Medical College, has commented on the prescribing of newer drugs for psychiatric patients versus older ones with time-tested comparative effectiveness research, and on the ultimate “need [for] head-to-head trials comparing new and standard treatments.” Richard A. Friedman, M.D., *New Drugs Have Allure, Not Track Record*, N.Y. TIMES, May 18, 2009, at D6, available at <http://www.nytimes.com/2009/05/19/health/19mind.html>. As Friedman also explains, “[P]hysicians continue to believe that they are immune to the influence of drug companies, despite strong evidence to the contrary.” *Id.*

The February 2009 \$787 billion stimulus package contains a provision to create a Federal Coordinating Counsel for Comparative Effectiveness Research and provides the Agency for Health Research and Quality with \$700 million to conduct the relevant research.⁴⁰⁶ Although some argue that federal oversight is not the best way to address all questions arising in the comparative effectiveness debate,⁴⁰⁷ the stimulus package represents a real first step towards providing new, independent sources of information about drugs.⁴⁰⁸ Furthermore, Margaret Hamburg, the newly-confirmed FDA Commissioner,⁴⁰⁹ has expressed a desire to have the FDA involved in the health care reform process—including comparative effectiveness research.⁴¹⁰

2. Information in Exchange for Litigation Protection

Even with the renewed emphasis on comparative effectiveness studies reflected in February 2009 legislation, relying on government funds alone is a woefully inadequate strategy to improve the quality of medical information. Even with recent increases in funding, moneys available for government-sponsored independent research are dwarfed by the funds drug companies spend on advertising and promotion. Approaches that recognize this and that incentivize companies to do more beneficial research thus stand a better chance of protecting patients than relying only on independent sources of research.

Wolsing has offered an “evidentiary reform proposal” that does just this. Under her proposal, if manufacturers conducted post-marketing studies and fully disclosed the results, the disclosure would create a rebuttable presumption that the manufacturer did not know about the adverse drug effects discovered in the study.⁴¹¹ Wolsing notes that the most common products liability claim is negligent failure-to-warn regarding which a defendant’s prior

406. Katherine Skiba, *As Obama Signs \$787 Billion Stimulus, The Question Is, Will It Work?*, U.S. NEWS & WORLD REPORT, Feb. 17, 2009, available at <http://www.usnews.com/articles/news/stimulus/2009/02/17/as-obama-signs-787-billion-stimulus-the-question-is-will-it-work.html>.

407. See Evans, *supra* note 403.

408. To appreciate the significance, it helps to compare the recently allocated resources to those proposed just a few months ago. Had it been passed, S. 3408 would have provided total funding for fiscal year 2009 of just \$5 million, with funding increases to \$300 million a year by 2013. See *Baucus-Conrad Proposal Can Improve Quality, Lower Costs Throughout American Health Care System*, Aug. 1, 2008, available at https://www.ecri.org/Documents/CERC/Comparative_Effectiveness_Baucus_Conrad_August_News_Release.pdf.

409. See Jacob Goldstein, *It’s Official: Peggy Hamburg Will Lead FDA*, WALL ST. J. HEALTH BLOG, May 19, 2009, <http://blogs.wsj.com/health/2009/05/19/its-official-peggy-hamburg-will-lead-fda>.

410. *Hamburg Welcomes FDA Role in Health Care Reform Debate*, 15 FDA WK. 18, May 8, 2009, available at 2009 WLNR 8793152.

411. See Wolsing, *supra* note 398, at 224.

knowledge of danger is a key element.⁴¹² Wolsing's proposal offers the particular advantage of motivating manufacturers—through litigation protection—to engage in vigorous monitoring after drugs receive FDA approval. This is the point in a product's history at which the general public is exposed to undetected adverse effects, yet it *follows* the period during which the FDA has the most power to influence drug manufacturers. Currently, manufacturers have reasons not to initiate post-release studies of their products⁴¹³ and to withhold data about post-approval outcomes. Wolsing's proposal counters these motives by giving drug makers "the prospect of a favorable tort position in the event of litigation."⁴¹⁴

3. Patent Protection and FDA Exclusivity

Through the Drug Price Competition and Patent Term Restoration Act of 1984 (hereinafter "Act"; also known as the Hatch-Waxman Amendments), an amendment to the federal FDCA, the government created a non-patent⁴¹⁵ system for protecting both the interests of pioneering drug manufacturers and generic drug manufacturers.⁴¹⁶ Congress's intent under the Act was to "strengthen incentives for continued innovation for research-based firms while simultaneously expediting and encouraging earlier market entry of generic drugs."⁴¹⁷ Although new drugs are expected to enjoy a longer period of market exclusivity versus their generic counterparts under the Act,⁴¹⁸ the Act also encourages and enables generic manufacturers to challenge the still-valid patents of pioneering drug companies.⁴¹⁹ Generic manufacturers can do this by either showing that their product does not infringe on pioneering company's patent or by showing that the pioneering company's patent is invalid.⁴²⁰

412. *Id.* at 225, n.104, citing Michael Rustad, *In Defense of Punitive Damages in Products Liability: Testing Anecdotes with Empirical Data*, 78 IOWA L. REV. 1, 65-66 (1992) and Kellen Cloney, Note, *AIDS Vaccine Manufacturers v. Tort Regime: The Need for Alternatives*, 49 WASH. & LEE L. REV. 559, 571 (1992).

413. Manufacturers would fear that any such study might generate findings that would discourage doctors from prescribing their drugs. Wolsing, *supra* note 398, at 225.

414. *Id.*

415. For purposes of space, this Article does not discuss patent protection for pharmaceutical companies in depth. We note, however, that such "protection allows a researched-based pharmaceutical firm to recover the tremendous investment necessary to discover and develop new drugs; [and] . . . also ensures the company's ability to further profit from its innovations before generic drug manufacturers can copy and market the drug at a greatly reduced cost." Ashlee B. Mehl, Note & Comment, *The Hatch-Waxman Act and Market Exclusivity for Generic Drug Manufacturers: An Entitlement or An Incentive?*, 81 CHI.-KENT L. REV. 649 (2006).

416. *Abbott Laboratories v. Young*, 920 F.2d 984, 985 (D.C. App. 1990).

417. *See* Mehl, *supra* note 415, at 650.

418. *See infra* note 408.

419. Mehl, *supra* note 415, at 650. The term "pioneer drug companies" refers to the "research-based drug company," *id.* at 653, that originally develops a particular drug.

420. *Id.* at 653.

Invalidity, for instance, can be argued based on theories of anticipation, obviousness,⁴²¹ or fraud during the patent application process.⁴²²

Despite Congress's intent under the Act, in addition to the importance behind the availability of generic drugs,⁴²³ the ability of generic manufacturers to undermine previously valid patents limits the financial rewards of pioneering companies that initially procured them. While market exclusivity periods exist for the pioneering manufacturers,⁴²⁴ the Act does not do much more to recognize and reward their ingenuity. If increased protection for pioneering manufacturer's products—either in the form of strengthened patent coverage or lengthened exclusivity periods—were coupled to requirements to conduct and disclose results of post-marketing studies on side effects and real-world effectiveness, however, pharmaceutical companies might find it more attractive to develop and publish bodies of data that would strengthen knowledge about existing products.

VI. CONCLUSION

The lessons of SGA drug litigation are many. Pharmaceutical companies sometimes respond to short-term market incentives that serve neither their own long-term interests nor the interests of patients who use their products. Prescription drug makers skillfully exercise their largely unopposed control over the production, promulgation, and interpretation of information about their products. Individual physicians who make decisions about prescription drug selection respond to incentives (such as ill-placed fears of litigation, ease of prescribing, or immediate convenience) that do not necessarily coincide with their patients' long-term health interests. Individual physicians and even larger organized groups of physicians have at-best-very-limited ability to discern general trends of and outcomes from prescription choices. Most patients

421. See *Abbott Laboratories v. Sandoz, Inc.*, 544 F.3d 1341, 1344 (Fed. App. 2008) (drug manufacturer sued a generic manufacturer for patent infringement, and the federal appellate court granted a preliminary injunction against the generic manufacturer). As the *Abbott* court explained, "Anticipation' in patent usage means that the claimed invention was previously known and described in a printed publication, explicitly or inherently." *Id.* at 1345. Invoking the argument requires one to provide "documentary evidence, [that shows] every claim element and limitation ... set forth in a single prior art reference, in the same form an order as in the claim." *Id.* A prima facie case for obviousness, on the other hand, is present "when the ranges of a claimed composition overlap the ranges disclosed in the prior art." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. App. 2003).

422. 60 AM. JUR. 2D. § 919 *Patents* (2008).

423. See Mehl, *supra* note 415, at 649, n.5.

424. As Mehl explains, "the Act provides an increased term of market exclusivity on the back end of the patent term to offset the patent term lost on the front end while the pioneer awaits FDA approval." *Id.* at 653-54. Ultimately, this can result in a "total extension" time of "up to five years." *Id.* at 654. See also 25 AM. JUR. 2D. § 123 *Drugs and Controlled Substances* (2008) (noting that the length of an exclusivity period is tied to the "pharmaceutical novelty" of a particular drug.)

and doctors have no immediate, personal incentive to make economical drug selections. Those entities and agencies that pay medication bills are reluctant to restrict prescription choices to control costs.

The most important lesson from SGA litigation is that viewing pharmaceutical companies as villains and doctors as unwitting, corruptible dupes ignores the circumstances of and reasons for their judgment errors. Fear of public exposure and condemnation will motivate doctors to avoid sources of these negative reinforcements but may not get them to make smarter prescription decisions. Fear of litigation may motivate drug makers to produce better products, but drug makers may conclude they can more easily avoid lawsuits by doing things that do not improve their products or make publicly available information about them.

However, getting better information to physicians might help them to make better decisions about drugs and to avoid the types of mistakes that psychiatrists' improvident adoption of SGAs exemplifies. Given incentives to produce information about their products' problems and knowing that their products will undergo extensive independent scrutiny, pharmaceutical manufacturers will have clear reasons to create and promote products that further the public good. Lawsuits, fines, and public opprobrium are all appropriate responses to past misbehavior. But the best way to get drug companies and doctors to improve their future behavior is to give them unambiguous reasons to do so.