United States Court of Appeals
For the Eighth Circuit

No. 13-1350

Timothy Boehm

Plaintiff - Appellant

v.

Eli Lilly & Company

Defendant - Appellee

Appeal from United States District Court
for the Eastern District of Arkansas - Little Rock

Submitted: September 26, 2013
Filed: March 10, 2014

Before LOKEN, COLLOTON, and BENTON, Circuit Judges.

LOKEN, Circuit Judge.

Zyprexa (active ingredient olanzapine) is an "atypical" or "second generation" antipsychotic drug manufactured and sold by Eli Lilly & Company ("Lilly"). Timothy Boehm's doctors prescribed Zyprexa to treat his bipolar disorder from January 2003 until March 2007, when he developed symptoms later diagnosed as tardive dyskinesia ("TD") -- an involuntary movement disorder long recognized as

a side effect of antipsychotic drugs. Boehm brought this action, later removed by Lilly, asserting personal injury and product liability claims. The district court[1] granted summary judgment dismissing the failure-to-warn claim, applying the Arkansas learned intermediary doctrine[2] and concluding that Lilly adequately warned Boehm's treating and prescribing physicians of the risk of developing movement disorders like TD. After Boehm dismissed his remaining claims,[3] the district court entered final judgment dismissing the complaint. Boehm appeals the summary judgment order, including the district court's decision to exclude expert testimony that fifteen percent of Zyprexa users will develop TD after three years of use. Reviewing the exclusion of expert evidence for abuse of discretion and the grant of summary judgment *de novo*, we affirm.

I.

The testimony and medical records of two physicians who prescribed Zyprexa to treat Boehm's bipolar disorder are relevant to the summary judgment issues on appeal. Dr. Forrest Miller, a general practitioner, first prescribed Zyprexa in January 2003, when Boehm complained of sleep problems, overwhelming anxiety, a racing mind, and depression. Dr. Miller's notes record that Boehm had been taking lithium, but it was not effectively controlling these symptoms and was relatively unsafe for

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[1]The Honorable D.P. Marshall, Jr., United States District Judge for the Eastern District of Arkansas.

[2]"This doctrine provides that a drug manufacturer may rely on the prescribing physician to warn the ultimate consumer of the risks of a prescription drug. The physician acts as the 'learned intermediary' between the manufacturer and the ultimate consumer." West v. Searle & Co., 806 S.W.2d 608, 613 (Ark. 1991).

[3]The district court dismissed two claims without prejudice. At oral argument, Boehm agreed to accept dismissal of those claims with prejudice to ensure that we have a final order to review.

a patient like Boehm who was not monitored regularly. Dr. Miller prescribed Zyprexa and an antidepressant. In the following months, Dr. Miller noted that Boehm gained weight (a common Zyprexa side effect). But Boehm liked Zyprexa much better than lithium, and his bipolar disorder was doing "extremely well." Dr. Miller testified that he planned to continue prescribing Zyprexa to Boehm "until it quits working." Though Boehm saw Dr. Miller only sporadically, pharmacy and clinic records show that Dr. Miller refilled Zyprexa prescriptions and provided Boehm Zyprexa samples through June 30, 2006.

In August 2006, Dr. Gregory Kaczenski, a psychiatrist, began treating Boehm when he was hospitalized for increased depression and irritability. After Boehm's discharge, Dr. Kaczenski continued prescribing Zyprexa until late August, when he prescribed a different second-generation antipsychotic, Geodon, because Boehm wasn't sleeping well and his appetite had increased. Dr. Kaczenski again prescribed Zyprexa in October when Boehm reported that he preferred Zyprexa to Geodon. In March 2007, Dr. Kaczenski noted that Boehm had "some difficulty with articulation" and "a repetitive movement of his neck, pulling his head towards the left shoulder." Suspecting either dystonia or TD, Dr. Kaczenski stopped prescribing Zyprexa because it was the most likely cause of these involuntary movements. Another physician subsequently diagnosed Boehm as suffering from TD caused by antipsychotic drug use. Boehm also claims to have torticollis, a type of dystonia.[4]

Dr. Miller and Dr. Kaczenski testified that they were well aware of the risks and benefits of antipsychotics. Dr. Miller became familiar with the side effects of older, "first-generation" antipsychotics, including movement disorders, when he attended medical school across the street from a state hospital and observed patients

[4]TD involves repetitive involuntary muscle movements. Dystonia involves involuntary sustained muscle contractions. Torticollis is a type of dystonia that involves twisting of the neck muscles. Boehm alleges that painful involuntary neck-twisting motions make him unable to work and cause mental anguish.

who suffered from these side effects. Dr. Kaczenski's experience with the side effects of first-generation antipsychotics began with his residency at a state hospital, where it was "very, very common" to see patients suffering from movement disorders. Because of these side effects, Dr. Miller does not prescribe first-generation antipsychotics, and Dr. Kaczenski avoids prescribing them. Both doctors instead prescribe atypical second generation antipsychotics like Zyprexa. In their experience, these newer drugs are effective in treating serious psychiatric diseases, such as schizophrenia and bipolar disorder; while they can cause the same movement disorders as the first generation drugs, they do so much less frequently. Both doctors continue to prescribe Zyprexa.

Since Zyprexa first came on the market, Lilly's FDA-approved package insert has expressly warned about the risk of developing TD:

> *Tardive Dyskinesia* -- A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. . . . Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.
>
> The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. . . .
>
> There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. . . .
>
> Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. . . . In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

> If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

(Emphasis added.) The package insert also notes: "There is no body of evidence available from controlled trials to guide" maintenance treatment of bipolar disorder with Zyprexa, meaning treatment for longer than a month.[5]

Dr. Miller testified that his practice is to read a drug's package insert before ever prescribing it, and to re-read the insert occasionally to refresh his memory. Dr. Kaczenski consults the Physicians' Desk Reference, which contains package insert information, and re-reads package inserts when they are updated. Dr. Kaczenski testified that Lilly's package insert was adequate to warn him of the risk of TD with Zyprexa use. Independent of the package insert, Dr. Miller and Dr. Kaczenski learned about Zyprexa's side effects from their own clinical experience and from speaking with their colleagues. Both doctors testified that an alternative warning about the risk of movement disorders would not have changed their decisions to prescribe Zyprexa to treat Boehm's bipolar disorder.

Based on the express TD warning it gave all physicians, and the testimony of Boehm's prescribing physicians that they read the warning and considered it adequate in deciding to prescribe Zyprexa, Lilly moved for partial summary judgment on the failure-to-warn claim, relying on the learned intermediary doctrine.

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[5]The package insert also reported that the incidence of dystonia (including torticollis) in a Zyprexa clinical trial was not significantly higher than with a placebo. On appeal, Boehm asserts that this was far short of an adequate warning. We agree with the district court that "Boehm has not produced any reliable evidence to show an increased risk of torticollis and dystonia associated with Zyprexa [and therefore] has not demonstrated the need for a warning."

II.

In opposing summary judgment, Boehm argued that Lilly failed to adequately warn physicians of the risk of developing TD after long-term use of Zyprexa. Boehm focused on additional deposition testimony by Dr. Miller and Dr. Kaczenski. After Dr. Kaczenski described weight gain and movement disorders as two side effects that can occur with long-term Zyprexa use, he was asked:

> [Boehm's counsel]: I'm going to ask you about something that -- a figure that I have seen here, that 15 percent -- and I will ask you if you are aware of this. But 15 percent of those who have taken neuroleptics, such as Zyprexa, for three years, develop tardive dyskinesia?
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> [Dr. Kaczenski]: Yes, that's a number I have known for a long time.

Counsel used that answer in cross-examining Dr. Miller at his subsequent deposition:

> [Boehm's Counsel]: Did you receive any information that once a patient is prescribed Zyprexa for three years, one in six patients will develop tardive dyskinesia? Were you told that?
>
> * * * * *
>
> [Dr. Miller]: No.
>
> Q: All right. If you had known that, and that is an established fact in this case pursuant to Doctor Kaczenski's deposition testimony * * * -- that the inciden[ce] of tardive dyskinesia increases to one in six patients after three years of use, would you still have prescribed that to Tim Boehm?
>
> * * * * *
>
> A: Not for that long.

Q: All right. That's just too long, isn't it?

A: That's too long.

To satisfy its duty to warn, the manufacturer of an "unavoidably unsafe" but beneficial prescription drug must make "an adequate warning" to prescribing physicians of the risks of adverse side effects. West, 806 S.W.2d at 613, applying comment k to § 402A of the Restatement (Second) of Torts and the learned intermediary doctrine. After initial briefing, the district court concluded "that this testimony [by Dr. Miller], if supported, could create a triable issue" as to the adequacy of Lilly's TD warning. But the court noted that "Dr. Kaczenski did not offer the 15% risk figure on his own; the percentage was part of a leading question." Accordingly, the court "requested briefing on whether . . . the alleged 15% risk was supported by [scientific] evidence that would be admissible under Daubert [v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993)]."

In response, Boehm relied on the opinion of his expert, psychiatrist Dr. Stefan Kruszewski. Based on "clinical experience and review of relevant literature," Dr. Kruszewski opined that "Zyprexa is capable of a high rate of incident tardive dyskinesia/dystonia after three years of use, affecting between 15-20% of those prescribed the drug." When Lilly challenged that opinion as lacking scientific support, Dr. Kruszewski submitted two supplements to his report. The first supplement cited two additional sources. First was an article by Dr. Patricia Deegan published on the National Empowerment Center website claiming: "Different studies quote different rates of tardive dyskinesia ranging from 15%-20% for people using [antipsychotics] for more than three years." The article stated that Zyprexa "has been found to cause TD" but listed no sources for its information. The second new source was a webpage where Dr. Peter Breggin advertises his work as an expert witness in TD-related cases. Without citing a source, the webpage claims: "The rates for TD are astronomical. In otherwise physically healthy adults, 5%-8% per year will

develop the disorder, with cumulative rates in the range of at least 15%-20% for the first three years." Dr. Breggin claims it is "simply untrue" that "the newer or atypical antipsychotic drugs cause TD at a very low rate." Again, the only Zyprexa-specific claim was that it can cause TD.[6]

Dr. Kruszewski again supplemented his report with a 2010 peer-reviewed study comparing TD incidence rates for users of first-generation and second-generation antipsychotic drugs.[7] The study concluded: "[T]he incidence rate of TD with atypical antipsychotics, while modestly reduced, remains substantial . . . . Despite the feeling among some clinicians that TD is much less of a problem now in the atypical era, such a conclusion may unfortunately be premature." As Lilly pointed out, two implications of the study data suggest that bipolar patients taking Zyprexa can expect better results than other patients. First, the Woods study notes: "Little TD advantage for atypicals was apparent in schizophrenia subjects, while a relatively strong advantage was estimated in affective disorder subjects." Second, based on available data differentiating specific drugs, the study reported that "olanzapine [Zyprexa] showed the lowest relative TD rate" in the second-generation group.

The district court concluded that Dr. Kruszewski's first supplement -- a blog post and website advertising -- "are a deficient foundation" to support Dr.

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[6]The cite for Dr. Deegan's article is Tardive Dyskinesia and Tardive Dystonia: where you can turn for help, National Empowerment Center, http://www.power2u.org/articles/selfhelp/tardive.html (last visited Dec. 10, 2013). Dr. Breggin's cite is Selected Tardive Dyskinesia (TD) cases, Psychiatric Drug Facts with Dr. Peter Breggin, http://breggin.com/index.php?option=com_content&task=view&id=184 (last visited Dec. 10, 2013). Copies of these internet materials are on file in the Clerk's Office.

[7]Woods, S.W., et. al., Incidence of Tardive Dyskinesia with Atypical Versus Conventional Antipsychotic Medications: A Prospective Cohort Study, J. Clin. Psychiatry 71(4): 463-474 (2010) (the "Woods study").

Kruszewski's 15% risk figure. Though the second supplement was a peer-reviewed study in a well respected journal, the court reasoned, the Woods study "was not designed to establish the risk of a particular drug, only the risk of a class of drugs to which Zyprexa belongs." The Woods study "does not even attempt to establish that Zyprexa is a twin to conventional antipsychotics," and it "indicates that Zyprexa carries a lower risk of [TD] than other atypical antipsychotics." Concluding there "is too great an analytical gap to extract from the Woods study the 15% incidence rate Dr. Miller said would have changed his prescribing decisions," the court excluded all evidence of that risk percentage under Daubert. The court then granted summary judgment dismissing Boehm's failure-to-warn claims because there was no genuine issue of material fact as to the adequacy of Lilly's TD warnings.

III.

On appeal, Boehm argues the district court erred in excluding Dr. Kruszewski's expert opinion that 15% of Zyprexa users will develop TD after three years of use. Because the grant of summary judgment turned on this ruling, we will review it first. Junk v. Terminix Int'l Co., 628 F.3d 439, 447 (8th Cir. 2010), cert. denied, 132 S. Ct. 94 and 95 (2011). "We reverse a trial court's decision on the admissibility of expert evidence only on the basis of a clear and prejudicial abuse of discretion." Id.

In determining whether to admit a qualified expert's opinion testimony under Rule 702 of the Federal Rule of Evidence, the district court acts as a gatekeeper to "ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." Daubert, 509 U.S. at 589. If "opinion evidence . . . is connected to existing data only by the *ipse dixit* of the expert," a district court "may conclude that there is simply too great an analytical gap between the data and the opinion proffered." Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997).

Here, after giving Boehm ample opportunity to supplement Dr. Kruszewski's initial, inadequately supported opinion, the district court reasonably concluded that Boehm had not provided sufficient scientific support for that opinion. The internet materials in the first supplement provided no supporting data or sources for their general assertions relating to Zyprexa; the Woods study, while peer-reviewed, was not designed to establish a TD incidence rate for Zyprexa and in fact contained findings that undermined Dr. Kruszewski's opinion that Zyprexa causes TD in bipolar patients at the same 15-20% rate as first-generation antipsychotics. On this record, we conclude that it was well within the district court's substantial discretion to exclude Dr. Kruszewski's 15% risk opinion.

IV.

Boehm further argues the district court erred in granting summary judgment dismissing the failure-to-warn claim, even without Dr. Kruszewski's 15% risk opinion. The learned intermediary doctrine does not apply, Boehm argues, because he presented substantial evidence that Lilly's warning to physicians as to the risk of developing TD after long-term use of Zyprexa was inadequate. The district court carefully summarized "the essential and undisputed material facts" that warranted the grant of summary judgment absent reliable scientific evidence of a known 15% risk factor for long-term use of Zyprexa:

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

> in their opinion the drug helped him. These two main prescribers thought Lilly's warning adequate. Both are still prescribing Zyprexa to other patients.

After careful consideration of the extensive summary judgment record, we agree. On appeal, Boehm places great emphasis on the testimony in which Dr. Miller agreed that prescribing Zyprexa for three years was "too long" given the 15% risk of developing TD. But that testimony was based on Boehm's counsel instructing Dr. Miller that a 15% risk factor for Zyprexa users had been established by Dr. Kaczenski's testimony, which was untrue. On this record, the district court properly applied the learned intermediary doctrine in dismissing the failure-to-warn claim.

V.

Boehm further argues the district court erred in rejecting his contention that Lilly's overpromotion of Zyprexa negated an otherwise adequate warning of the risk that users will develop movement disorders including TD. A few courts have recognized an overpromotion "exception" to the learned intermediary doctrine. The Supreme Court of Arkansas has not addressed the issue. The exception applies in "unusual cases" where a plaintiff can "establish with *individualized* proof" that a drug manufacturer's excessive promotion of its product "caused the [plaintiff's] physician to initiate or maintain the prescription at issue." In re Zyprexa Prods. Liab. Litig., 649 F. Supp. 2d 18, 33 (E.D.N.Y. 2009) (emphasis in original).

Here, the district court expressed doubt that the Supreme Court of Arkansas would recognize an overpromotion exception to the learned intermediary doctrine. But in any event, the court concluded, the exception would not apply in this case because Boehm presented "no evidence that any representation by a salesperson affected a prescribing doctor's decision to continue Boehm on Zyprexa," and because

"[t]here is no reliable evidence that Zyprexa had significantly more risk of movement disorders than the drug reps allegedly said it had." We agree.

The summary judgment record includes substantial evidence that Lilly aggressively marketed Zyprexa to doctors, including Dr. Miller and Dr. Kaczenski, instructing its marketing representatives to make personal calls to promote Zyprexa by discussing bipolar symptoms and stressing Zyprexa's "safety," "efficacy," and "ease of use" for treating bipolar patients. But there is no evidence that any representative made statements to Dr. Miller or to Dr. Kaczenski that negated the package insert warning, and there is no evidence their prescribing decisions were affected by the Lilly representatives' statements regarding the risk of TD. Therefore, even if Arkansas would recognize this exception, Boehm failed to prove that Lilly overpromoted Zyprexa, that its promotional efforts negated the written warnings, or that these promotional efforts had any effect on the decisions by Dr. Miller and Dr. Kaczenski to prescribe Zyprexa for the continued treatment of Boehm's bipolar disorder. Accord Dean v. Eli Lilly & Co., 387 Fed. App'x 28, 30 (2d Cir. 2010) (unpublished); Patteson v. AstraZeneca, L.P., 876 F. Supp. 2d 27, 34-37 (D.D.C. 2012); In re Zyprexa Litigation, 649 F. Supp. 2d at 33.

The judgment of the district court is affirmed.
