FACT SHEET

TORT LITIGATION AGAINST PHARMACEUTICAL COMPANIES INVOLVING PSYCHIATRIC DRUGS:

LESSONS FOR ATTORNEYS AND ADVOCATES

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Hundreds of cases have been brought in the last several years against pharmaceutical companies arising from deaths and injuries attributed to drugs used to treat psychiatric disorders. These cases have revealed much that is not commonly known about these drugs, and have resulted in a number of cases which develop the law regarding the application of *Daubert v. Merrell-Dow*, 509 U.S. 579 (1993) to the testimony of psychiatric experts. Because so many of our clients take psychiatric drugs, this Fact Sheet reviews what is currently known about some of the most commonly used medications, including the recent publication of expert consensus recommendations which contain warnings and cautions about the medical hazards associated with use of these drugs. The Fact Sheet also summarizes the status of pending litigation involving psychiatric drugs, and discusses how the law in these cases may be applicable to the work of P&A attorneys and advocates.

The Food and Drug Administration (FDA) requires that pharmaceutical companies provide labelling for drugs including 1) contraindications (e.g. people taking Mellaril should not be prescribed Haldol, or people with a history of diabetes should not be prescribed Zyprexa); 2) warnings (e.g. Clozaril is associated with aplastic anemia, which can be fatal); 3) precautions (e.g. people who are suicidal and who are prescribed SSRIs should be closely monitored for the first month); and 4) adverse reactions, which are divided into several categories, including common, infrequent and rare (e.g. stroke in elderly patients withdementia who are taking Risperdal). The most urgent warnings are those known as “black box” warnings, in which drug companies are required to (or voluntarily) post warnings in bold black print in a bold black box. These warnings appear in the Physician’s Desk Reference and in the package inserts for the drugs, which doctors are presumed to read (see below).

One aspect of drug regulation that many people do not know is that

psychotropic drugs have different names and different warning labels in different countries. Thus, pharmaceutical companies can and do publish more stringent warnings in Europe or Canada than in the United States, and it is not uncommon for the companies to pull a drug off the market earlier in Europe or Canada than in the United States. In many cases challenging the failure to warn, plaintiffs' lawyers have introduced evidence of more strongly worded warnings on labels in other countries, to mixed effect (see below).

The psychiatric drugs in question

Clozaril (clozapine) Developed by Sandoz (which became Novartis) and approved by the FDA in 1989. A new formulation of Clozaril was approved in 1997. From the beginning, Clozaril was known to be associated with fatal cases of aplastic anemia, and anyone on Clozaril must have his or her blood drawn every week for the first six months to check white blood cell counts. In 2001, an article by an FDA researcher in *The American Journal of Medicine* warned of a causal relationship between clozapine and hyperglycemia and diabetes. A majority (62%) of adverse events relating to hyperglycemia and diabetes occur within the first month of taking the drug, and doctors are warned that unexplained fever, fatigue and malaise in patients taking Clozaril should be investigated.

More recently, Clozaril has been strongly associated with possibly fatal heart problems from myocarditis (inflammation of the heart lining). In 2002, Novartis added warnings about myocarditis to the black box warnings after receiving 82 reports, some of which included fatalities. A consensus conference of psychiatric and medical experts convened to develop recommendations for the physical health monitoring of patients with schizophrenia treated in outpatient settings made explicit recommendations that patients taking Clozaril be specifically monitored for myocarditis. [1] I could not find any litigation against Clozaril based on myocarditis or cardiomyopathy. One case was found based on failure to warn against abrupt discontinuation, *Presto v. Sandoz*, 226 Ga. App. 547 (1997). The verdict was for the defendant on the basis of learned intermediary doctrine, see below.

Desyrel (trazodone): Manufactured by Bristol Myers Squibb, and introduced in 1982. Desyrel can cause priapism, an extremely painful, involuntary, and long lasting erection that can result in permanent medical damage. Juries tend to be very sympathetic to painful medical side effects[2] of psychiatric drugs, see *Hooper v. Capobianco and Thrifty Payless d/b/a Rite-Aid*,

No. 99 AS 01792 (Superior Court, Sacramento County September 10, 2001) (available on LEXIS under Verdicts Directory)(jury verdict of $3,424,017 for plaintiff, with two million dollars for pain and suffering reduced by court to total damages of $1,674,017) and *McDonald v. Thrift Drug*, Case No. 1907 (Superior Court, Pennsylvania, Sept. 21, 2000))(available on LEXIS under Verdicts Directory)(damages of $10,500,000 awarded by jury in priapism case involving Trazodone lowered to $1,500,000 based on pre-trial agreement). The drug Serzone is "the chemical and pharmacologic analog of trazodone," and was recently withdrawn from the market by Bristol-Myers Squibb after reports of liver failure (see below).

Effexor (venlafaxine) Made by Wyeth Labs. On October 15, 2004, the FDA ordered Wyeth and other manufacturers of SSRI antidepressants to add a black box warning to Effexor's labels warning physicians about prescribing this drug for children or adolescents. The proposed warning included notification that the average risk of suicidal thinking or behavior associated with taking Effexor was twice the risk associated with taking a placebo. The FDA order included proposed language and invited pharmaceutical companies to comment on the proposed language. Apparently some (but not all) pharmaceutical companies have responded with comments, but as of Jan. 1, 2005, no drug company has complied with the FDA's order. Effexor is banned in the United Kingdom for use with children because of concerns about increased suicidality. In addition, Effexor cannot be prescribed to anyone in the UK except by specialists because of concerns about association with irregular heartbeat and fatalities from arrhythmia. Its discontinuation effects or withdrawal difficulties are reputed to be even harsher than those of Paxil. No published class litigation is currently pending involving Effexor.

Geodon (Ziprasidone) First introduced in 2001 by Pfizer. Associated with sudden death from QT (heartbeat) prolongation. Pfizer has warned that this drug should not be taken by people with histories of cardiac arrhythmia, or who are taking quinidine or droperidol. A consensus conference of psychiatric and other medical experts convened to develop recommendations for the physical health monitoring of patients with schizophrenia treated in outpatient settings made explicit recommendations for cardiac monitoring of persons taking Geodon. [3] Despite the seriousness of this side effect, no published cases were found on LEXIS concerning this drug.

Mellaril (thioridazine) Manufactured by Sandoz (now Novartis) and approved by the FDA in 1959. In 2000, the FDA required Novartis to add a black box warning that it is associated with the risk of sudden death, due in part to its association with QT prolongation (irregular heartbeat).

The only use for which it is approved by the FDA is “the management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs.”Any other prescription of Mellaril is an off-label use. The FDA has also warned that the following drugs should never be used in association with Mellaril: Prozac, Luvox, Paxil, Inderal, Haldol and Chlor-Trimeton. This is because these drugs inhibit one of a group of liver enzymes that metabolize thioridazine, and thus lead to build-up of the drug associated with a greater risk of heart disturbance. A consensus conference of psychiatric and other medical experts convened to develop recommendations for the physical health monitoring of patients with schizophrenia treated in outpatient settings made specific recommendations for cardiac monitoring of persons taking Mellaril. [4]Despite the seriousness of this side effect, no published cases were found on LEXIS concerning this drug. Public Citizen has warned people not to take this drug because of its risk of sudden death, see www. Citizen.org./eletter/articles/mellaril.htm.

The drug Serentil (mesoridazine) is chemically very similar to Mellaril and carries many of the same risks (see below).

Neurontin (gabapentin) Manufactured by Parke-Davis, a subsidiary of Warner-Lambert (bought by Pfizer in 2000). Although it is only approved by the FDA as a supplementary treatment for partial seizure after maximum tolerated doses of older drugs are used, Parke-Davis promoted its off-label use for many other conditions, including bipolar disorder, for years. Neurontin garnered $2.9 billion dollars in sales in 2003. Pfizer recently pled guilty to medical fraud involving this off-label use (among others), since Neurontin actually works less well than a placebo in treating bipolar disorder. The fraud was disclosed by a whistle-blower, David Franklin, who will receive over 26 million dollars under the False Claims Act. There are many pending cases against Pfizer over Neurontin, but they all involve fraud in marketing, rather than alleging that the drug actually caused any harm. The case law of interest arising out of the Neurontin litigation is about the right of public access to discovery documents from cases against pharmaceutical companies. A recent case permitted public access to all non-confidential discovery documents in the case, holding that “parties operating under a blanket protective order cannot rely on an unreasonable expectation that such an order will never be altered,” *United States ex rel David Franklin v. Parke-Davis*, 210 F.R.D. 257, 261 (D.Mass. 2002).

Paxil: (paroxetine)(known as Seroxat in the United Kingdom) Paxil is manufactured by GlaxoSmithKline. It was originally approved for depression in 1992, and shortly thereafter for panic disorder and obsessive-compulsive disorder. In 1999, Paxil was approved for the treatment of "social anxiety disorder." In 2001, the FDA approved Paxil for "generalized anxiety disorder"and post-traumatic stress disorder. The same year, a jury found that Paxil had caused a man to go on a murderous rampage, killing his wife, daughter, and granddaughter before taking his own life, and awarded over six million dollars in damages, *Tobin v. SmithKlineBeecham*, 164 F.Supp.2d 1278 (D.Wyo. 2001), In 2003, it was approved by the FDA for the treatment of premenstrual dysphoric disorder. Annually, GlaxoSmithKline nets 2.1 billion dollars from Paxil. On October 15, 2004, the FDA required Pfizer to add a black box warning to Paxil indicating that it might cause some minors to become suicidal, and that studies had shown that this suicidality occurred for people taking Paxil at a rate twice as high as for people taking a placebo. Pfizer has not added this warning as of January 1, 2005.

Paxil, as well as Prozac, is more often linked in litigation to injurious and even homicidal behavior against others than other SSRIs such as Zoloft, which are more frequently linked to suicidal behavior. The charge that Paxil causes violent behavior is also being litigated in the murder case of juvenile Christopher Pittman, who was prescribed first Paxil and then Zoloft before he killed his grandparents at the age of twelve. It is important to remember that SSRIs do not have identical properties or effects on all patients; for example, Paxil's half life is much shorter than many other SSRIs, which causes far more difficulties for people attempting to wean themselves off Paxil (see below).

In other litigation, New York City has sued GlaxoSmithKline, alleging that it was forced to pay unlawfully high Medicaid prices for Paxil. Medicaid spent more than 23.1 million dollars on Paxil for New York City residents in 2002.

As noted above, a significant problem with Paxil is that it may be addictive in the sense that people suffer extremely adverse effects, such as panic attacks, racing hearts, nausea, stomach pains, insomnia, and other withdrawal symptoms if they try to cease taking it. Drug companies dispute that this makes a drug addictive. They argue that the properties of addictiveness require that a person must take more and more of the same substance to achieve the same effect. Drug companies prefer the term "withdrawal symptoms" or "discontinuation effects" to "addiction." Whatever the name, this is a problem particularly associated with Paxil. One of the differences between Paxil and other SSRIs is its half-life. While Prozac wears off in two to four days, Paxil leaves the system in twenty hours.

Short half-lives are associated with addiction—Paxil causes withdrawal symptoms three times as often as Zoloft and four times as often as Prozac. Warnings about withdrawal are placed on Paxil's label in a number of European countries. A presentation at the American Psychiatric Association in 1993 found that up to 42% of individuals suffered withdrawal symptoms when they ceased taking Paxil. In 2001, the FDA ordered GlaxoSmithKline to begin warning consumers that they might suffer withdrawal when tapering off Paxil. GlaxoSmithKline complied by warning about "discontinuation effects" rather than "withdrawal." A number of lawsuits have been filed around the country charging that GlaxoSmithKline did not effectively warn about Paxil's addictiveness. These lawsuits are consolidated in the Southern District of California, and emphasize the difference in the warning labels in warning labels in other countries, such as France and Ireland, where users are warned of "dizziness, sensory disorders and sleep disturbances" if they abruptly to use Paxil.

Prozac (fluoxetine)(known as Sarafem when prescribed for premenstrual dysphoric disorder): Eli Lilly first began marketing Prozac in the United States in 1988. By 1990, an article in *The American Journal of Psychiatry* noted that six depressed but previously non-suicidal patients had experienced intense, violent, suicidal thoughts shortly after beginning Prozac, which abated when they ceased taking the drug.[5] Beginning in 1990, concerns began to be raised about a possible connection between Prozac and increased suicidality. In October 1990, the Church of Scientology filed a petition with the FDA claiming that Prozac caused suicide and asking that it be withdrawn from the market. In May 1991 the Public Citizen Health Research Group petitioned the FDA to require a black box warning that Prozac might be associated with suicide in a small number of patients. Both petitions were rejected. By 1992, the Federal Judicial MultiDistrict Litigation Panel had consolidated over 75 lawsuits against Lilly in the Southern District of Indiana, which involved both suicidal and homicidal behavior attributed to the drug. Prozac is the only antidepressant which has been conclusively linked to increases in suicidality, in a large study by Jick, Kaye and Jick., showing that individuals who take Prozac are more than twice as likely to attempt suicide as those taking other anti-depressants[6]. In 1997, the FDA rejected yet another petition to expand the suicidality warning on the Prozac label. The following year, a court refused to dismiss punitive damage claims against Lilly, citing evidence that it suppressed adverse studies, *Forsyth v. Eli Lilly*, 1998 U.S.Dist.LEXIS 541 (D. Hawaii 1998). For a substantial summary of studies linking Prozac to suicide, see *Cloud v. Pfizer*, 198 F.Supp.2d 118, 1122-1126 (D.Ariz. 2001)(litigation involving Zoloft but summarizing SSRI literature).

In 2003, the FDA approved Prozac to treat depression and obsessive

compulsive disorder in children and adolescents aged 7 to 17 years. Prozac is actually the only one of these drugs which has been shown in any study to be effective as a treatment for depression in adolescents. Like Paxil, however, Prozac has also been linked to behavior injurious to others. On October 15, 2004, the FDA required Eli Lilly to add a black box warning to Prozac indicating that it might cause some minors to become suicidal, and that studies had shown that this suicidality occurred for people taking Prozac at a rate twice as high as for people taking a placebo. Eli Lilly has not complied with this order as of January 1, 2005. Concerns have also been raised about the effects on babies if the mothers take Prozac while pregnant, www.cerhr.niehs.nih.gov/news/fluoxetine_final.pdf.

Eli Lilly's most recent difficulties have emerged with the publication in the January 2005 issue of the *British Medical Journal* of "missing" documents indicating that the company was aware of a link between Prozac and increased suicidality as early as 1988, and suppressed theinformation.[7]

Risperdal (Risperidone): Risperdone was developed by Janssen Pharmaceutica (which has since been taken over by Johnson& Johnson). It has been prescribed for schizophrenia since 1993. In December 2003 the FDA approved its use for short-term treatment of mania in bipolar disorder. In early 2003, Janssen warned doctors that the use of risperidone in elderly patients with dementia might increase the risk of cerebrovascular accidents (e.g."strokes."), see www.janssen.com/ourcompany/news_detail.jsp?id=041603. That year, Risperdal's worldwide sales were 2.5 billion dollars. In 2004, the FDA forced Jannsen to issue a letter to doctors acknowledging that it was linked to excess blood sugar and diabetes, and to recommend regular testing of individuals taking Risperdal for diabetes. There have been no reported cases involving Risperidone, however.

Serentil (mesoridazine): Manufactured by Boehringer Ingelheim, it is chemically very similar to Mellaril (see above). It is associated with many of the dangers of Mellaril, including potentially fatal heart arrhythmias. A consensus conference of psychiatric and other medical experts convened to develop recommendations for the physical health monitoring of patients with schizophrenia treated in outpatient settings made specific recommendations for cardiac monitoring of persons taking Mellaril. [8] In an unusually candid admission about Serentil's characteristics, the National Institute of Health's website on drug information answers the question"Why is this Medication Prescribed?" with "…It can also reduce hyperactivity and uncooperativeness."[9] This web site also notes that if the liquid concentrate of Serentil comes into accidental contact with skin, it should be washed immediately because it is a powerful skin irritant.

Serzone: (nefazodone) Bristol-Myers Squibb began selling Serzone in 1994 as an antidepressant. In 2002, the FDA added the strongest type warning (black box) about liver failure, after reports of at least 94 adverse liver reactions, including 55 liver failures and twenty fatalities. There is a class action suit pending regarding liver damage related to the drug. Serzone was also alleged to cause priapism, a persistent and painful erection which can cause permanent injury. *Thom v. Bristol-Myers Squibb*, 353 F.3d 848 (10th Cir. 2003)(charging makers of Serzone with insufficent information about the risks of priapism).

Bristol-Myers Squibb voluntarily pulled Serzone from the U.S. market in June 2004 (it had been taken off the market previously in Europe, Canada, Australia and New Zealand, but the company continued to sell the drug in the United States).

Zoloft: (sertraline) (known in the United Kingdom as Lustral). Zoloft was developed by Pfizer and first approved by the FDA for the treatment of depression in 1991. Over the next few years, the FDA approved Zoloft for the treatment of adult obsessive-compulsive disorder (1996), panic disorder (1997), pediatric obsessive-compulsive disorder (1997), and post-traumatic stress disorder (1999). The FDA never approved Zoloft as a treatment for pediatric depression. There have been hundreds of cases alleging a connection between Zoloft and the suicide of a previously non-suicidal individual, including, in one of the most famous cases, a thirteen year old boy, *Miller v. Pfizer,* 356 F.3d 1326 (10th Cir.), *cert. denied* 2004 U.S.LEXIS 6230 (Oct. 4, 2004).

Zoloft was among the drugs covered by the FDA order of October 15, 2004, requiring drug manufacturers to warn about dangers of suicidality when the drug is prescribed to children and adolescents. Testimony about Zoloft before the public hearing of the FDA's Psychopharmacologic Drugs and Pediatric Advisory Committees on September 13 and 14 also concentrated on Zoloft's lack of proven efficacy in treating depression. In a 1991 internal FDA memorandum, Dr. Paul Leber, who was principally involved in the investigation, analysis and approval of the SSRI class of drugs, noted that numerous countries around Europe had already rejected or were about to reject approval of Zoloft because Pfizer could not prove efficacy. Dr. Leber wrote, "In recommending [the approval of Zoloft for adults], I have considered the fact that the evidence marshaled to support [Zoloft's] efficacy as an antidepressant is not as consistent or robust as one might prefer it to be." In September 2004, Dr. Leber was quoted in the Denver Post as saying "Second generation antidepressants were

approved by a regulatory process that requires only a limited proof of efficacy and safety." [10]

Zyprexa (olanzapine): Zyprexa is manufactured by Eli Lilly, and was introduced on the market in 1996. Zyprexa is Eli Lilly's top selling drug, garnering 3.7 billion dollars in sales per year. Zyprexa was originally approved for schizophrenia and then for the short-term treatment of acute manic episodes associated with Bipolar I disorder. However, it is prescribed for other "off-label" uses, and at least one case has charged that it contributed to a child's death when it was prescribed for attention deficit/hyperactivity disorder, *Tardy v. Eli Lilly*, 2004 Me.Super.LEXIS 168 (August 4, 2004)(autopsy reports "acute hyperglycemia due to acute olanzapine toxicity).

Zyprexa has been linked in multiple studies with diabetes and severe hyperglycemia. Patients taking Zyprexa are ten times more likely to develop diabetes than the general population. Whether the link with diabetes is direct or secondary to acute weight gain associated with Zyprexa (itself a health hazard of considerable dimension) is a matter of controversy. Although many psychiatric drugs include weight gain as a side effect, it is particularly noticeable as a side effect of Zyprexa. A number of cases have just been consolidated in the Eastern District of New York. Most, but not all, of the cases center around the connection between Zyprexa and diabetes, *In re Zyprexa Products Liability Litigation*, 314 F.Supp.2d 1380 (Multidistrict Litigation Panel 2004).

II. Law that has Emerged from these Cases

Cases against pharmaceutical companies are based on a variety of legal claims,including strict liability, failure to warn, negligence, breach of warranty, and fraudulent misrepresentation.

A. Background: The Centrality of Warnings about Drug Side Effects to Drug Litigation

1. The "Unavoidably Unsafe" Exception to Strict Liability

The doctrine of strict liability—that a manufacturer of a defective and unreasonably dangerous product is strictly liable for damages to a consumer harmed by that product-- has been held not to apply to products that are beneficial but "unavoidably unsafe" when used for their intended purpose. No litigation has addressed the question of whether off-label use is use outside the intended purpose of the drug. "Unavoidably unsafe" products are those which "in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs…Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous." Restatement (Second) of Torts, 402A, comment k.

The question of whether psychiatric drugs are unavoidably unsafe has been a subject of some litigation, since a finding that they are not would leave pharmaceutical companies vulnerable to strict liability claims. However, in most cases, plaintiffs appear to concede that psychiatric drugs fall into this category, and focus on whether the drug company properly warned of the dangers accompanying ingestion of the drug.

2. The Learned Intermediary Doctrine

The "learned intermediary" doctrine shields pharmaceutical companies from liability for failure to directly warn consumers of the dangers of psychiatric drugs if the companies provide adequate warnings to prescribing physicians, who are presumed to act as "learned intermediaries" between the manufacturer of the drug and the patients who use it. Therefore, the law does not require the pharmaceutical company to warn the consumer of known dangers associated with the use of their drugs. Rather, it requires the pharmaceutical company to warn doctors, *Thom v. Bristol-Myers Squibb*, 353 F.3d 848 (10th Cir. 2003) (charging makers of Serzone with providing insufficent warnings about the risks of priapism).[11] Thus, the pharmaceutical company's duty ends if it can be shown that it appropriately warned physicians about the side effects of the drugs it manufactures. If the pharmaceutical company can show that the doctor did not read the warnings accompanying the drug before he or she prescribed the drug, the plaintiff loses a failure to warn case against the pharmaceutical company, since the content of the warnings is irrelevant if it does not influence the prescribing physician's decisionmaking, *Motus v. Pfizer,* 358 F.3d 659 (9th Cir. 2003). The learned intermediary doctrine also generally protects pharmacies and pharmacists from charges that they should have warned the consumer of dangers of the drug, *Tardy v. Eli Lilly* 2004 Me.Super.LEXIS 168 at *8-9 (August 4, 2004).

In order for the learned intermediary doctrine to apply, "the physician `must be an intervening and independent party between the patient and manufacturer,'" *Talley v. Danek Medical, Inc.*, 179 F.3d 154 at 164 (4th Cir. 1999). A rather surprising number of prescribing doctors in these lawsuits have financial ties to the pharmaceutical companies which manufacture the drugs they prescribe, but courts have repeatedly rejected arguments that the learned intermediary doctrine should not apply when doubts have been cast on the doctor's impartiality in recommending the drug, *Miller v. Pfizer*, 195 F.Supp.2d 1095, 1129 (D.Kan. 2002)(court finds that no reasonable jury would discredit prescribing doctor's testimony based solely on the fact that he was a paid consultant to Pfizer and made speeches around the country praising Zoloft at the time he prescribed the drug to plaintiffs' son); *Talley v. Danek Medical Inc.*, 179 F.3d at 157 and 164 (4th Cir. 1999)(rejecting claim that learned intermediary doctrine should not apply where prescribing physician was consultant receiving $250,000 a year from defendant as well as 25,000 shares of stock , a travel budget, and research funds, when there was "no evidence that the consulting relationship…interfered with Dr. Matthre's independent medical judgment").

No court has yet considered whether the learned intermediary doctrine will be or should be affected by the burgeoning direct marketing by pharmaceutical companies to individuals, including TV and print ads, and by the increasing availability of pharmaceuticals through the internet. However, some courts have held that even if a drug company voluntarily provides sheets of information or pamphlets about their drugs for patients, it does not void the learned intermediary doctrine because the patient is still expected to rely primarily on his or her doctor for judgment about the appropriateness of the drug and instructions on how to use it.

The learned intermediary doctrine does not, however, protect the drug company if it does not give adequate warnings to the physicians. Therefore, the adequacy of the warning becomes a crucial concern in litigation against pharmaceutical companies. Ironically, the FDA's recent action in finally requiring black box warnings about the possibility of SSRIs increasing suicidality may spell the death knell for any subsequent litigation against those drug companies for suicides caused by use of the drugs, with the liability falling entirely on the prescribing doctor. On the other hand, pharmaceutical company liability for any suicide or suicide attempt that is demonstrably linked to the use of SSRIs may be stronger during the current period between the FDA's October 15, 2004 order to add the warning as a black box warning—a time when the pharmaceutical companies knew of an extremely serious danger and physicians theoretically did not-- and the time that the pharmaceutical companies actually comply with the

order. Pharmaceutical companies may argue that physicians would have to be aware of the FDA order because of the media publicity which has attended the issue, but the learned intermediary doctrine requires that the pharmaceutical companies—not the media—warn the physicians of any significant dangers associated with their products.

3. Inadequate Warnings and Causation

In order to prove damages in a tort case involving psychiatric drugs, the plaintiff must show that the drug actually caused the harm alleged. This is not a difficult proposition if the harm is medical, such as seizures or priapism, but it is exceedingly difficult when the harm resembles a symptom of the underlying condition the drug is intended to treat, such as increased suicidality for people suffering from depression.

One benefit of proving that a pharmaceutical company's warning is inadequate is that it creates a rebuttable presumption of causation, i.e., a finding of inadequate warnings creates a presumption that if the warning had been adequate, the doctor would have not prescribed the drug or would have alerted the patient, and the patient would not have taken the drug. Restatement (Second) of Torts, 402A, comment j.

The presumption is rebuttable, however, and pharmaceutical companies have won cases when they show that either the physician did not read the warning, so that it did not matter whether it was adequate or not, or when the physician testifies that he or she would have recommended the drug anyway, even if the warning had been written as the plaintiff alleges it should have been, *Miller v. Pfizer*, 196 F.Supp.2d 1095, 1101 (D.Kan.2002); *Woulfe v. Eli Lilly*, 965 F.Supp. 1478 at 1481 (D.Okla. 1997)(dismissing case under learned intermediary doctrine when psychiatrist would have prescribed Prozac to suicidal patient even if he had been aware of the contents of the warning label used for Prozac in Germany).

B. Expert Witness Testimony, *Daubert*, and Developments in Psychiatric Drug Litigation

Although researchers had been debating whether SSRIs contributed to suicidality since the early 1990s, and watchdog organizations had challenged the FDA to investigate this issue, litigation challenging the sufficiency of warnings on the newer SSRIs introduced after Prozac did not take off until the victory in *Estate of Tobin v. SmithKlineBeecham*, 164 F.Supp.2d 1278 (D.Wyo. 2001). *Tobin*, in which the jury awarded over six million dollars in damages, received a great deal of attention nationally, and plaintiffs' attorneys began to bring a large volume of litigation, frequently using the same experts used in *Tobin*.

The pharmaceutical companies, and Pfizer (manufacturer of Zoloft) in particular, fought these cases vigorously. They concentrated their attacks primarily on discrediting and precluding plaintiffs' expert testimony. In the process, they caused judges to focus far more attention on the application of *Daubert* to testimony in cases involving psychiatric experts. It should be noted that the target of the pharmaceutical companies was the testimony of plaintiffs' experts regarding causation: the link between the psychiatric drugs and the suicides or homicides they were alleged to have caused, rather than testimony involving diagnosis, dangerousness, competence, systems reform, or any of the other subjects for which we generally hire expert witnesses. However, as noted below, the judicial scrutiny can spill over into areas of greater interest to mental health lawyers.

1. Post-*Daubert* and pre-*Tobin*

When the Supreme Court decided *Daubert v. Merrell-Dow*, 509 U.S. 579 (1993), many commentators believed its insistence on what appeared to be a relatively rigorous scientific basis for expert testimony would disqualify a substantial amount of expert psychiatric and psychological testimony, since much of the testimony has no substantial basis in scientific research or methodology. Rather, most testimony by mental health professionals is based on clinical experience. However, courts were too accustomed to relying on psychiatric testimony in cases ranging from criminal to civil commitment to tort law. Many courts simply found that expert testimony based on psychiatric or psychological observation and analysis did not readily lend itself to analysis under the factors laid out by the Supreme Court in *Daubert*, and continued to admit the testimony despite *Daubert* challenges.[12] At first, courts simply limited *Daubert*'s scope to "novel" scientific methodology or testimony, *Jugle v. Volkswagen of America, Inc.*, 975 F.Supp. 576, 580 (D.Vt. 1997). [13]Then the Supreme Court decided *Kumho Tire Co. v. Carmicheal*, 526 U.S. 137 (1999), holding that *Daubert* applied, albeit flexibly, to all forms of expert testimony, including social science testimony.

The pre-*Kumho* approach frequently taken by courts to *Daubert* challenges of psychiatric testimony, even in early cases against pharmaceutical companies over the effects of their drugs, was to cite to the expert's credentials and experience, thus conflating the question of whether the expert was qualified to testify on the subject with the *Daubert* issue, which properly challenges not the expert's credentials or experience but the scientific methodology underlying his or her conclusions—the scientific basis for the expert's conclusions. In these cases, the expert's methodology was often simply clinical judgment, making the distinction between methodology and credentials even more murky. This kind of practice makes it difficult for attorneys to challenge any testimony by a reasonably well-credentialed mental health expert, no matter how clear it is that little or no scientific basis exists for the testimony. The prime example in this area is testimony predicting dangerousness, which is given every day in courts deciding on sentencing (including death sentences) and civil commitment. As noted above, there is very little traditional scientific basis for the conclusions of many expert mental health witnesses, so that courts which, as a practical matter, needed the testimony, have generally equated credentials with admissibility under *Daubert*.

A prime example of this can be seen in the pre-*Tobin* case of *Forsyth v. Eli Lilly*, 1998 U.S.Dist.LEXIS 541 (D.Hawaii Jan. 5, 1998), which featured Dr. David Healy, among others, as an expert. The court's *Daubert* analysis, at *33-39, is typical. After citing the requirements of *Daubert v. Merrell-Dow*, including the four factors courts may use to judge whether a theory or technique constitutes "scientific knowledge", the court applies them. Its entire *Daubert* analysis follows:

Dr. Healy is an experienced and well-qualified psychopharmacologist who has reviewed medical records, depositions in this case, published studies and other relevant material. Dr. Healy intends to testify that "Prozac was a substantial cause of William Forsyth's murder of his wife and his subsequent suicide." Dr. Healy has authored medical articles on Prozac and suicidality and published a review of the literature on this topic. His published articles were subject to peer review and appear to have a particular degree of acceptance within the scientific community. Dr. Healy relies on the Jick study to testify to evidence that Prozac causes suicide, homicide, or suicide-homicide. The Court finds that Dr. Healy's opinion is supported by scientific methodology and procedures.

Forsyth v. Eli Lilly at *33 (D. Hawaii Jan. 5, 1998).

In 2000, after *Kumho*, Rule 702 of the Federal Rules of Evidence was rewritten to conform to *Daubert*. It now provides that " witness qualified as an expert…may testify…in the form of an opinion…if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case."

Neither *Kumho* nor the alteration in the Federal Rules of Evidence appeared to affect the admissibility of expert witness testimony by mental health professionals. Courts continued to liberally admit such testimony, as reflected in the *Tobin* case itself.

2. The *Tobin* case

In the *Tobin* case, Dr. David Healy, an internationally known neuropsychopharmacologist whose testimony was accepted in the *Forsyth* case, and Dr. John Maltsberger, a psychiatrist and suicidologist, testified that taking Paxil had caused Donald Schell to go on a violent rampage, killing his wife, daughter, and granddaughter, and then himself.

Dr. Healy's and Dr. Maltsberger's theory of the relationship between SSRIs and suicide, adopted from the research literature in the area, is that SSRIs cause akathisia (known by the World Health Organization as 'hyperkinesia'), a motor restlessness and extreme internal agitation that increases suicidality because it is "often accompanied by unendurable emotional pain, and patients destroy themselves in order to escape it." *Smith v. Pfizer*, 2001 U.S.Dist.LEXIS 12983 at *19 (D.Kan. Aug. 14, 2001).

The trial took on political overtones when Dr. Healy rejected reliance on the methodology of epidemiological studies and randomized controlled trials [RCTs]

that purported to show no connection between Paxil and suicidality. In his opinion, most epidemiological studies of psychiatric drugs are so expensive that generally the chief funders of the studies are the very pharmaceutical companies whose products are being tested. In his opinion, "the portrayal of [randomized controlled trials and epidemiological studies] as gold standards owes everything to a strategy which involves occupying the playing field rather than one which in actual fact delivers what is claimed for it," *Miller v. Pfizer*, 196 F.Supp. 1062, 1066 (D.Kan. 2002). In the place of randomized control trials, Dr. Healy and Dr. Maltsberger substituted Koch's Postulates, a series of factors designed to assist in determining general causation and whether a drug may cause a certain reaction, Reference Manual on Scientific Evidence (1st Ed. 1994). Applying Koch's Postulates, they argued, the causal connection between Paxil, akathisia, and uncontrollable violence of Mr. Schell was clearly demonstrated. The jury accepted their testimony, and returned a verdict of over $6 million against the pharmaceutical company.

Defendant SmithKlineBeecham appealed the verdict in *Tobin*, but the judge upheld it, with a finding that was typical of much post-*Daubert* judicial practice involving testimony in the psychiatric arena: "This Court finds that its initial ruling on the defendant's *Daubert* motion that: `Dr. Healy's education, experience, training and extensive research regarding SSRIs, serotonin, and depression, qualify him to offer expert testimony with regard to general causation in this litigation," *Estate of Tobin v. SmithKlineBeecham*, 164 F.Supp.2d 1278, 1283 (2001). The judge in *Tobin*, like most post-*Daubert* judges (erroneously) equated a *Daubert* challenge with a voir dire on whether the expert was qualified to testify. Dr. Healy's credentials were impeccable, and therefore he was permitted to testify.

Another factor in the judge's refusal to overturn the jury verdict, however, was the traditional deference to jury verdicts. The evidence at trial must be considered in the light most favorable to the plaintiff and only if a reasonable jury could not have found for the plaintiff can the judge overturn the verdict. The pharmaceutical companies' subsequent strategy was to prevent cases from ever reaching a jury by disqualifying the expert testimony on which plaintiff relied. This strategy has been successful in the majority of federal cases, although many state courts have resisted taking decisions from the jury.

3. The Swing of the *Daubert* Pendulum: Cases since *Tobin*

In some cases against pharmaceutical companies since *Tobin*, defendants have not only insisted on the application of *Daubert* to the admissibility of expert psychiatric testimony, but they have also filed challenges under *Daubert* to each step of the methodology utilized by the expert, and to every article or study forming the basis for the expert's opinion, see *Miller v. Pfizer*, 196 F.Supp.2d 1062, 1065 (D.Kan. 2002). This elevates *Daubert* analysis to a level of punctiliousness far beyond that which the Supreme Court intended in *Daubert* and in its later decision in *Kumho Tire Co. v. Carmicheal*, 526 U.S. 137 (1999), and generally beyond what most courts require in other cases. For example, in one case a judge appointed two experts to advise her whether the plaintiff's expert's "methodology and his application of it in this case, constitute valid, scientifically reliable reasoning in support of his opinions [on general and specific causation]." *Miller v. Pfizer*, 356 F.3d 1326, 1329 (10th Cir. 2004). The Supreme Court in *Daubert* assumed that judges were generally capable of making a judgment regarding the reliability of expert testimony. The judge's function as "gatekeeper" did not have to involve such a detailed and intensive inquiry that judges would not feel competent to undertake it.

In contrast to the perfunctory approach taken by district courts prior to *Tobin*, the district court in *Miller* excluded Dr. Healy's testimony based in part on the conclusion that *Daubert*'s peer review requirement had not been met. The court found that although Dr. Healy had published peer-reviewed articles on the theory that Zoloft caused suicide, his specific calculations of the risk of suicide had not been subject to peer review. The district court was lauded by the Court of Appeals for the Tenth Circuit as "thorough" in its *Daubert* analysis. *Id.* at 1330 and 1335. Even more surprisingly, the Tenth Circuit affirmed the district court, holding that the judge "did not exceed the scope of *Daubert* inquiry by, for example, considering Dr. Healy's credibility or weighing the evidence." *Id.* (Compare with the judge's correct holding in *Tobin* that "whether Dr. Healy has become more of an advocate than a scientist [is] an issue of credibility for the jury to determine," *Estate of Tobin v. SmithKlineBeecham*, at 1285.)

Another district court disqualified an expert from testifying regarding causation, quoting with scorn the expert's statement that he was "relying upon textbooks, treatises and other papers to reach an opinion," *Smith v. Pfizer*, 2001 U.S.Dist.LEXIS 12983 at *26 (D.Kan. 2001). This was clearly insufficient in the court's view, and the judge made clear that only the testimony of epidemiologists or psychopharmacologists would be allowed to show general causation. This runs counter to the holdings of courts in other cases, which do not require either epidemiologists or epidemiological studies for testimony to be admissible under *Daubert.*

Courts in cases involving psychiatric drugs have also consistently rejected case studies under *Daubert*, although courts applying *Daubert* in other contexts accept case studies, ruling that problems with the size of the sample or the lack of a control group are matters to be weighed by the jury, *Pick v. American Medical Systems*, 958 F.Supp. 1151 (E.D.La. 1997).

For example, in *Blanchard v. Eli Lilly,* 207 F.Supp.2d 308 (D.Vt. 2002), the court found that plaintiff's expert witness (Dr. Maltsberger of *Tobin*) was eminently qualified in suicidology, and that a psychological autopsy is a generally accepted methodology for trying to determine what led to a suicide. Under a correct reading of *Daubert*, the finding that the expert's methodology is appropriate should be the end of the inquiry; it is not the function of the court to decide whether the expert's conclusion is accurate. As long as there is "fit" between the method (psychological autopsy) and the question on which the expert is testifying (what caused plaintiff's decedent to commit suicide), the testimony should be admissible. However, the court ruled that Dr. Maltsberger's opinion as to the cause of the plaintiff's suicide was not admissible. While a large and controversial body of research exists linking Prozac to suicide, the mechanism posited by the researchers largely involves akathisia (uncontrollable and very unpleasant agitation or restlessness), mania or disinhibition. In the plaintiff decedent's case, there was evidence that the murder-suicides were very carefully planned. The psychiatrist's opinion was that the disinhibition caused by Prozac led to behavior that caused her great shame and shattered her self-esteem, and that this was a contributing cause of her suicide.

The court, while acknowledging that the psychiatrist's opinion might well be correct[14], ruled it inadmissible. Essentially, the court required the expert to show either a number of very specifically similar cases in his clinical experience (that patients of his experienced suicidal thoughts or violent behavior without contemporaneously experiencing akathisia, mania, hypomania, or disinhibition) or research supporting his hypothesis, id at 320.

4. Comparison with Other Litigation

It seems fairly clear that cases involving challenges to the adequacy of warnings on psychiatric drugs have been subject to more rigorous standards and analysis than other cases involving expert psychiatric witnesses or other mass tort cases against drug manufacturers. The drug company litigation is *sui generis* in a number of ways, described briefly below.

a. General Causation

The question of what evidence plaintiffs must proffer to meet the first causation requirement: to show that defendant's product can, in general, cause the result that plaintiff claims it caused, varies widely from court to court. For example, in the mass tort litigation involving Meridia, a diet drug alleged to cause heart attacks, in which defendants alleged that the very condition which caused the patients to take the drug—obesity—caused the cardiac problem, the court concluded that plaintiffs do not need expert epidemiological testimony to prove general causation.*In re Meridia Products Litigation* 328 F.Supp.2d 791 (N.D. Ohio 2004). All courts in cases challenging the adequacy of warnings relating to psychiatric drugs have held that epidemiological expert testimony is required to prove general causation, *Smith v. Pfizer*, at *22. A district court in the Ninth Circuit held an expert's evidence on general causation inadmissible in part because "Dr. Johnstone also has not provided sufficient epidemiological evidence of causation," *Cloud v. Pfizer*, 198 F.Supp.2d 1118 at 1134 (D.Ariz. 2001), even as it acknowledged that the Ninth Circuit did not require epidemiological evidence to prove general causation, *id*. On the other hand, a court excluded testimony by experts regarding whether Propulsid caused QT elongation, citing the absence of peer review studies, and rejecting the plaintiffs' common-sense explanation that since Propulsid had been withdrawn from the market because of health concerns, it would be both difficult and unethical to conduct such research, *In re Propulsid Product Liability Litigation* 261 F.Supp.2d 603 (E.D.La. 2003).

In addition, to show general causation, the 9th Circuit has specifically held that experts can rely on the published research of others to support their findings, *Metabolife International v. Wornick*, 264 F.3d 842, 845 (9th Cir. 2001), while the court in *Smith v. Pfizer* disqualified an expert for relying solely on scientific materials. "In effect, plaintiff argues that the jury may rely on a witness who has `relied upon' textbooks, scientific articles and `other papers' to reach his opinion, but who has no expertise to explain the basis for his opinion. Such a holding would defeat much of the purpose of Fed.R.Evid. 702 and the rule of *Daubert* and its progeny." *Smith v. Pfizer*, 2001 U.S.Dist.LEXIS 12983 at *26(D.Kan. Aug. 14, 2001).

The court held that as a matter of law psychiatrists are not qualified to testify as experts to establish causal associations between drugs and side effects or symptoms. The court held that a psychiatrist is not qualified to testify as an

expert regarding the ability of clinical trials, scientific studies, or case histories to establish an association or causal relationship between Zoloft and akathisia, emergency suicidality, or violent behaviors. The court held that only epidemiologists can testify about whether the evidence establishes an association and the strength of the association, and only pharmacologists can testify about the mechanism whereby the drug affects the person. Smith at *24.

The procedural barriers erected by courts in the cases against pharmaceutical companies involving psychiatric drugs have also been substantial. Dr. David Healy delivered his expert report in *Miller v. Pfizer*, and after court-appointed experts submitted their own report questioning Dr. Healy's methodology, the court permitted him to answer their questions only by reference to material in his previously submitted expert report, limiting him from introducing anything not already in the record to answer questions he had not known would be asked when he created his expert report.

b. Specific Causation

This addresses plaintiffs' requirements in proving that defendant's drug specifically caused the injury claimed by the plaintiff, and corresponds more closely to the ordinary role of psychiatric experts in cases involving people diagnosed with psychiatric disabilities. In other cases, courts have permitted doctors to rely on records and established treatises, and have even allowed experts to deviate somewhat from established treatises, *S.M. v. J.K.*, 262 F.3d 914 (9th Cir. 2001)(rejecting defendant's *Daubert* challenge to plaintiff's psychiatric expert as unreliable because he had deviated from DSM III-R in his diagnosis of PTSD). However, in at least one case involving psychiatric drugs, the court required the specific causation expert to show that the methods he used to reach his conclusions had been peer-reviewed, *Cloud v. Pfizer,* 198 F.Supp.2d 1118, 1136-37 (D.Ariz.2001)(also noting that Dr. Johnstone had not considered alternative causes for plaintiff's decedent's behavior, and that he had reached his opinion before reviewing all the records).

c. Minimum requirements for psychiatrist to testify about source of behavior

Of interest in general, courts in these cases have prescribed the minimum requirements for a mental health professional to testify as to whether a drug

caused certain behavior or to testify about causation of an illness. Courts require the expert to have "consider[ed] the possible causes of the behavior at issue, [the individual's] medical history and treatment, the circumstances existing when the behavior occurred, the effect of the drugs based on doctor's clinical experience, [individual's] history of alcoholic abuse and medical and research literature." *Smith* at *27, see also *Cloud v. Pfizer* 198 F.Supp.2d 1118, 1135-37 (D.Ariz. 2001).

C. Preemption: Doctrine and Politics

The FDA, the agency charged with protecting the safety of consumers, has appeared in court to take the side of the pharmaceutical companies which manufacture psychiatric drug. Perhaps unusually for an administration which decries federal centrality and supports state's rights, the FDA under George W. Bush's leadership has filed amicus briefs with courts considering litigation against pharmaceutical companies asserting that the FDA's regulatory decisions regarding the adequacy of warnings preempts tort claims that the warnings are inadequate, *Motus v. Pfizer,* 127 F.Supp.2d 1085 (C.D.Ca. 2000).

Not only has the federal government argued that it has an interest in ensuring "that state tort law does not undermine the agency's authority to protect the public health" but it has asserted that to add warnings about increased suicidality would be "to require a statement that would be false or misleading, and thus contrary to federal law." *Needleman v Pfizer,* 2004 U.S.Dist.LEXIS 15495 at *6-7 (N.D.Tx. Aug. 6, 2004)(*quoting* the federal government's brief in *Motus*).[15] Several courts accepted this argument and dismissed cases against pharmaceutical companies. In the case of *Needleman,* the court dismissed the case less than three months prior to the FDA ruling that pharmaceutical companies must add a black box warning that SSRIs did indeed increase the risk of suicidality.

Under the logic of the government's arguments, the black box warnings should now be considered heavily in determinations of general causation, and indeed in other cases, FDA action has weighed heavily in proof of general causation, *In re Meridia Products Litigation* 328 F.Supp.2d 791 (N.D.Ohio 2004).

Conclusion

Because so many of our clients take these drugs, we should keep abreast of developments involving both the safety of the drugs and legal developments. Regrettably, experience suggests that some prescribing physicians either do not keep up with these developments, or do not inform their patients, or both. Recent news has highlighted the inability or unwillingness of the FDA to credit the reports of its own experts regarding dangers of the drugs it regulates. It will assist us as counsellors and negotiators on behalf of our clients to be aware of these dangers and of the independent research regarding them. In addition, we should be aware of the legal developments relating to these drugs, and their implications for our clients, both directly and as they affect the development of the law regarding negligence and admissibility of expert testimony.

[1] Stephen R. Marder, Susan M. Essock, Alexander L. Miller, Robert W. Buchanan, Casey E. Daniel, John M. Davis, et al, "Physical Health Monitoring of Patients with Schizophrenia," 161 *American Journal of Psychiatry* 1334 (2004).

[2] It is more difficult to prove that psychiatric drugs cause effects such as suicidality or agitation when those may also be symptoms of the condition for which the patient is taking the drug.

[3] Stephen R. Marder, Susan M. Essock, Alexander L. Miller, Robert W. Buchanan, *et al*. at n. 1.

[4] *Id.*

[5] Martin Teicher and Jonathan Cole, "Emergence of Intense Suicidal Preoccupation During Fluoxetine Treatment," 147 *Am.J. of Psychiatry* 207 (1990). See also Anthony J. Rothschild and Carol A. Locke, "Reexposure to Fluoxetine After Serious Suicide Attempts by Three Patients: The Role of Akathisia," 52 *J.Clinical Psychiatry* 491 (1991), in which severe suicidality developed in three patients upon taking Prozac, subsided when they discontinued the drug, and reappeared when they (with informed consent) resumed taking the drug.

[6] Jick, Kaye and Jick, "Antidepressants and the Risk of Suicidal Behaviors, " *Journal of the American Medical Association*, July 21, 1995. The authors of the article downplay the finding, pointing out that because it is almost impossible to die from an overdose of SSRIs, it is possible that physicians prescribe them for their most suicidal patients. There is no research supporting this hypothesis.

[7] Jeanne Lenzer, "FDA to Review "Missing" Drug Company Documents," www.bmj.bmjjournals.com/cgi/content/full/330/7481/7.

[8] *Id.*

[9] www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682306.html. Whether being uncooperative is a condition for which people generally seek treatment is not addressed.

[10] Testimony of Karen Barth Menzies before the FDA Psychopharmacologic Drugs and Pediatric Advisory Committees, Sept. 13-14, 2004.

[11] Although tort law is individually developed in each state, at least forty-six states have adopted the learned intermediary doctrine, and the Wyoming federal court predicts that Wyoming will adopt it, see *Thom* at 852.

[12] See also Michael H. Gottesman, "Admissibility of Expert Testimony After *Daubert*," 43 Emory Law Journal 867, 875 (1994); C. Robert Showalter, "Distinguishing Science from Pseudo-Science in Psychiatry: Expert Testimony in the Post-*Daubert* Era," 2 Va.J.Soc.Pol'y &L. 211 (1995), Christopher Slobogin, "Doubts about *Daubert*: Anecdata as a Case Study," 57 *Washington and Lee Law Review* 919 (2000).

[13] But see *Gier v. Educational Service Unit No. 16*, 66 F.3d 940 (8th Cir. 1995) and *Nichols v. American National Insurance Co.*, 154 F.3d 875 (8th Cir. 1998) for exclusions of psychiatric expert testimony post-*Daubert* and pre-*Kumho*.

[14] "Given Dr. Maltsberger's credentials and experience, his belief is not to be lightly dismissed, but it remains just that, a belief, `an insightful, even an inspired hunch…that….lacks scientific rigor." *Id* at 320 [citation omitted].

[15] However, not all courts have accepted the government's preemption arguments, *Cloud v. Pfizer,* 198 F.Supp.2d 1118, 1121 (D.Ariz. 2001).