SSRIs, Suicide, and Liability for Failure to Warn of Medication Risks

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When can pharmaceutical companies be held liable for failure to disclose medication risks—such as the link between selective serotonin reuptake inhibitors and suicidality of young people? The companies have claimed that Food and Drug Administration approval of labeling information, required by federal law, should preempt liability in state courts. Thus injured patients would either be left without recourse or be compelled to sue the clinicians who prescribed the medication. A recent U.S. Supreme Court decision, however, rejected the preemption defense and opened the door to patients' suits that seek compensation. This column explores the application of this new approach and its implications for the mental health professions. (*Psychiatric Services* 62:347–349, 2011)

Two days after starting Paxil (paroxetine), a selective serotonin reuptake inhibitor (SSRI)–type antidepressant prescribed by her nurse practitioner, 23-year-old Tricia Mason committed suicide. In retrospect, Tricia's decision to end her life was not a complete surprise. She had a family history of depression and had confided suicidal thoughts to her friends over the previous several months. Indeed, she had told one male friend that she had "mixed some chemicals together and was keeping them so that she could drink them and commit suicide," although she later promised to dispose of the toxic mixture. When questioned by her nurse practitioner, however, Tricia denied being suicidal and offered no indication that she would ingest cyanide a mere 48 hours later (1).

In the wake of their daughter's death, Tricia's parents filed suit against the company that manufactured and marketed Paxil in the United States, SmithKline Beecham, a multinational pharmaceutical company that does business under the name GlaxoSmithKline (GSK). Tricia's parents alleged that the Paxil had caused Tricia's suicide and that the company had "failed to adequately warn prescribing physicians and patients of the risk that Paxil can increase the chances of suicidal behavior in patients suffering from depression and other psychiatric disorders." With that allegation, the Masons stepped into a complex and evolving area of law and into one of the most contentious issues in psychiatric practice.

Drug warnings and learned intermediaries

As in many states, in Illinois, where the Masons filed suit, pharmaceutical manufacturers are commonly insulated from liability for failing to warn patients of the serious risks of their medications by the "learned intermediary rule." Although manufacturers have a responsibility to notify physicians (and presumably other prescribers) of the inherent risks of their products, the clinicians bear the obligation of communicating that information to their patients. The rationale for this rule is that physicians are better situated than manufacturers to discuss these issues with patients and can more accurately weigh the risks and benefits for a particular patient (2). Generally, pharmaceutical manufacturers discharge their duty by issuing prescribing information in package inserts, in publications such as the *Physicians' Desk Reference,* and online. At that point, liability for failure to disclose a significant risk shifts to physicians' shoulders.

When Paxil was prescribed for Tricia Mason, however, the manufacturer's prescribing information did not include a warning that the medication might heighten the risk of suicide. The only reference to suicide was a general note about its association with depression and a suggestion that prescribers be sensitive to the possibility of overdose in deciding the quantity of medication to be prescribed (1). Indeed, GSK claimed that in 2003, when Paxil was prescribed for Tricia Mason, it had no knowledge that the medication was linked to an increased risk of suicide. It was not until three years later that GSK changed the warning accompanying its medication to include the information that "Young adults, especially those with MDD [major depressive disorder], may be at increased risk for suicidal behavior during treatment with paroxetine." The data cited by the company indicated an increased incidence of suicidal ideation in the 18- to 24-year-old age cohort, although it also noted that the difference between treated and placebo groups did not quite reach statistical significance.

Whether GSK knew before Tricia Mason's death of the trend toward an increased risk of suicide among younger patients treated with Paxil is a contentious issue that, as far as the Masons' case is concerned, may someday be settled by a jury. GSK,

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however, had another line of defense that it hoped would keep the Masons' case from ever going to trial. The company claimed that even if it had evidence of an increased risk of suicide, any obligation it might have had under state law to issue a warning to prescribers was preempted by federal law, specifically by the authority of the Food and Drug Administration (FDA).

Federal preemption of the duty to warn

The basis for federal law to overrule or preempt state law rests in the Supremacy Clause of the U.S. Constitution, which establishes that federal law shall be "the supreme law of the land." Preemption operates in one of two ways. Congress can explicitly indicate its intention for a federal statute to trump state legislation and court decisions, as it did with the provisions of ERISA, the Employee Retirement Income Security Act, which regulates workplace benefits such as pensions and health insurance (3). Because of ERISA's express preemption clause, for example, health insurers and managed care companies cannot be sued under state law for damages related to denial of benefits (4). Preemption can also occur when Congress' intent is implied by the very nature of a law it passes, either because the law is meant to set national policy in an entire field of activity (for example, laws related to foreign affairs) (5) or because it would be impossible to obey both state and federal law. This latter type of implied preemption, deemed "conflict preemption," is what GSK claimed in *Mason.*

GSK's preemption argument centered on the role of the FDA in overseeing the introduction of new drugs to the market. Before a new medication can be marketed in the United States, the manufacturer must submit documentation of the medication's safety and efficacy to the FDA. Along with evidence concerning the drug itself, a company will submit proposed labeling, including text of package inserts. The final form that the labeling takes, which must be approved by the FDA, is typically the subject of negotiation between the company and the agency (6). For the past decade, the FDA has argued in a series of court briefs that its regulatory process necessarily preempts state law in the area, including state common law requirements for disclosure of hazardous side effects. The agency essentially maintains that it is the sole authority empowered by the federal Food, Drug and Cosmetics Act (FDCA) to determine whether warnings provided to prescribers are adequate and that requiring companies to conform to state disclosure requirements could create a conflict with its judgments.

If the FDA's position were accepted by the courts, claims such as the Masons' against GSK, grounded as they are in state law, would be preempted and summarily dismissed, and there would be no obvious recourse under federal law. Indeed, for much of the past decade, that is exactly what happened to most claims concerning inadequate labeling of medications (1). But the playing field shifted dramatically in 2009 with the U.S. Supreme Court's decision in the highly publicized case of *Wyeth v. Levine* (7). Diana Levine had gone to a local clinic in Vermont for relief of a migraine headache. The clinic injected Phenergan, an antinausea drug, into Ms. Levine's arm using an intravenous "push," instead of via the safer intravenous drip or intramuscular methods. When the injection went awry, the drug ended up in an artery of her arm rather than in a vein and produced gangrene in the arm, which then required amputation.

Levine's claim that the prescribing information should have included an explicit warning about the potentially calamitous consequences of an incorrectly administered intravenous push was upheld on state law grounds by the Vermont Supreme Court. Wyeth, the manufacturer, with its state appeals exhausted, applied for review by the U.S. Supreme Court on preemption grounds. In a 5-to-4 opinion, the justices held that Congress had not intended the FDCA to completely preempt state regulation (7). Moreover, it rejected Wyeth's contention that it would have faced an impossible conflict in meeting both state and federal requirements. The Court noted that although the FDA had approved the initial product labeling, cases of intra-arterial injection leading to gangrene and amputation had been accumulating since the 1960s and Wyeth could have acted at any point to call physicians' attention to the danger. FDA regulations permit a manufacturer to issue stronger warnings without agency review, although the FDA would ultimately have to approve them. In this case, the justices found that Wyeth had not presented clear evidence that the FDA would have rejected such a step.

In addition, the Court offered strong policy reasons for allowing states to hold drug manufacturers liable for inadequate prescribing information. "The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge. State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times" (7).

Mason and the future of claims regarding failure to warn

When the Masons' claim against GSK was initially filed in federal district court in Illinois, which occurred before the decision in *Wyeth,* the court dismissed the case on the grounds that any state law obligations that GSK may have had were preempted by federal law. The Masons then appealed to the Federal 7th Circuit Court of Appeals, and in the meantime, the U.S. Supreme Court's decision in *Wyeth* appeared. Deciding the *Mason* case in light of *Wyeth,* the circuit court found that GSK could have acted on its own before 2003 to change Paxil's labeling so as to include information about the risk of suicide—as it did in 2006—and that clear reasons did not exist to believe that the FDA would have rejected

such a move (8). Thus it reversed the dismissal by the district court and remanded *Mason* for further proceedings. GSK's renewed efforts to have the case summarily dismissed before trial on the grounds that the plaintiffs had not provided sufficient evidence to support their claims were rejected by the trial court (1).

Unless GSK settles the claims against it, the case appears to be headed for trial. At that point, a jury will get to hear and weigh evidence on whether Paxil and other SSRIs truly increase the risk of suicide among younger patients (the subject of no small degree of contention in the psychiatric literature [9]), whether GSK was aware of the risk, whether a firmer warning would have dissuaded the nurse practitioner from prescribing Paxil, and whether Tricia Mason's suicide was caused by her two days of treatment with the medication. Similar questions litigated in other cases have led to varying outcomes (10).

Beyond the outcome of this particular case, though, the U.S. Supreme Court's decision in *Wyeth* and its application to SSRIs by the 7th Circuit have important implications for prescribers of psychotropic medication. If manufacturers cannot be held liable when they have failed to warn of risks that they knew or should have known existed, aggrieved patients and family members will be left with only one recourse to obtain compensation for their injuries: suits against clinicians and the facilities in which they work. Although statutes of limitation in most cases will preclude additional suits such as *Mason* based on pre-2006 labeling of Paxil (the FDA ordered a "black box warning" about suicidality of young people for all antidepressants in 2007), similar issues are likely to arise in the future—perhaps with regard to SSRIs and suicidality of adults. Post-*Wyeth,* claims in such cases will focus on manufacturers' responsibility, granting clinicians a rare break from litigation that is likely to be much appreciated.

There are other reasons why a policy of asking manufacturers to bear the costs of failures to disclose substantial risks makes sense. In the absence of clinician negligence, injured patients and their families will still have recourse to compensation for the harms they experienced. Moreover, as the Supreme Court noted in *Wyeth,* pharmaceutical companies often have superior information about adverse consequences and are in the best position to issue a warning to the medical profession. Finally, because pharmaceutical companies are the primary entities that reap the financial benefits from sales of their medications, there is a sound economic basis to require these companies to internalize the costs of preventable unfortunate outcomes.

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