A matter of trust: clinical trial evidence vs. physicians' judgment in the courtroom. (Risperdal on trial in Texas cont'd.)

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(A disclaimer: The views expressed here are my own, and I do not speak for my department or university.)

In my first post on the Risperdal suit that commenced in Austin this week, I said that the outcome of the case potentially concerns much more than the $579 million plus penalties that Johnson & Johnson might have to return to Texas Medicaid. I spoke of "the system of influence that has molded a reliable pipeline for creating blockbuster markets as readily out of unworthy as worthy drugs." A key source of influence wielded by pharmaceutical companies lies in the design, reporting, publication, and dissemination of clinical trial data.

What is clinical trial data? In the past 20-25 years, large-scale randomized controlled trials (RCTs) have become the gold standard for evaluating the efficacy and safety of newly devised medicines, and for researching new indications of existing ones. The theory behind RCTs is that use of statistical evidence flattens clinical variance in treatment outcomes and is therefore a more reliable way to demonstrate true drug effects.

The movement supporting the reliance on RCTs is called evidence based medicine, or EBM. Belief in the scientific merits of EBM has downgraded the value of case studies, which now rarely appear in the medical literature where once they were prominent. Clinical experience, the traditional foundation of expert medical knowledge, has been supplanted by EBM.

Much of the Risperdal case will turn on the presentation and interpretation of clinical trial data associated with the drug. The plaintiff has already made several references to CATIE and CUtLASS, two antipsychotics effectiveness trials. Many regard these trials as trustworthy because they were conducted not by drug companies, as most trials are these days, but by independent researchers. CATIE was carried out in the US, CUtLASS in the UK.

Results from CATIE and CUtLASS were published in the mid 2000s

nearing the time Risperdal was headed off patent. Both found that Risperdal and other second generation antipsychotics (SGAs) did not outperform the older drugs (FGAs) on measures of efficacy or tolerability. Additional studies pointed out that SGAs carried a whole panel of side effects different from and in addition to those associated with the FGAs. For most, this was an unexpected finding because prior studies of SGAs, such as the ones that supported the recommendations of TMAP (Texas Medications Algorithm Project), had ostensibly shown the reverse. If the scientific evidence supporting claims to SGA superiority were dubious, not to say rigged, then TMAP looks even more like a scam.

Perhaps in anticipation of this, but also just maintaining the long-held company line, already in the opening statement the defendant proclaimed as to the scientific failings of CATIE, contrasting it to the many studies published showing the reverse. The defense put a map up on the screen showing the many places in the world where studies of Risperdal had been completed, calling it “one of the most studied drugs in history.

While RCT evidence will form an important part of the case, it cannot by itself, however, be expected to prove or disprove the defense’s claim for the superiority of Risperdal as an antipsychotic agent. It cannot for several reasons.

First, there is too much evidence supporting diametrically opposite claims. The accuracy of studies can never be fully substantiated. No clinical study is perfect. Flaws can always be identified that will encourage skeptics to deem a given conclusion invalid. A limited community of clinical researchers (virtually known to each other by name) is qualified to interpret the highly specialized studies associated with antipsychotics, and these people are entrenched in disagreement with each other—disagreement sometimes made rancorous by accusations of researcher bias.

Apart from the illimitable controversy over the interpretation of trial results, use of this kind of evidence is moreover problematic in a courtroom because the type of verification deemed sufficient for a clinic, and that required of a court, are quite different. Courts require absolutes (guilty/innocent) while medical practitioners commonly make do with probabilities since this is the best they have.

Besides all that, no one can expect jurors to be able to make sense of RCT results anyway, no matter how patiently they are explained. In the end, most jurors will have to proceed on the basis of how well they trust the expert chosen to present scientific testimony. Re-enter clinical experience.

The first MD expert the plaintiff called to the stand on the afternoon of

January 11th, Dr. Jim Van Norman, was a good choice in this regard. He is a psychiatrist who completed all his training and licensing in Texas. He has been practicing in Travis County, where the court is located, for 23 years. He is married to a psychiatrist and has two kids. He is the director of a community mental health center—exactly the sort of clinic that treats uninsured and Medicaid patients the budget of which was allegedly targeted by Janssen through the TMAP initiative.

Van Norman supervises the equivalent of fifteen full-time "prescribers" (I wonder if anyone besides me noted the unconcerned substitution of prescriber for psychiatrist) who treat about 6000 adults and 1100 children per year—twice what they are budgeted to do. (This stated shortage of budgetary resources foreshadowed, like in a good drama, the feeling of outrage over the alleged crime of promoting a drug that cost 45 times as much as pills that work just as well.) In reply to the State's attorney, Van Norman estimated that he has treated some 10,000 patients over the course of his career.

The State's attorney Tommy Jacks asked: When Risperdal was first introduced to you by sales reps in the 1990s, what did they claim were the virtues of the drug?

Risperdal was supposed to treat negative symptoms of schizophrenia, he said. It was represented as safer on EPS [extra pyramidal symptoms]… and cheaper in the long run because they'd keep people from going into the hospital. Their pitch was "efficacy, safety, and cost-effectiveness."

Jacks: Do you have budget responsibility for your clinic?

Yes.

What's the difference in cost between [branded] Risperdal and FGAs?

Risperdal costs 40-50 times as much.

Jacks then asked Van Norman about TMAP and TIMA (Texas Implementation of Medication Algorithms, which is what TMAP evolved into). Did it affect procedures? Yes. How?

This line of questioning is important because it has been one of the defendant's recurrent claims that TMAP in no way constrained doctors to a particular medication choice: "It was just a guideline," they say. If TMAP was not enforced in any way, its origin is essentially irrelevant to the alleged $579 million overage being claimed by the plaintiff.

Van Norman explained that each clinic is separately contracted annually

with the State. With respect to TMAP, the contract contained provisions specifying that if a physician chose to deviate from the algorithm (e.g., choosing not to prescribe an SGA as a first-line treatment), s/he had to document why s/he chose to do this. Failure to do so could lead to sanctions and financial penalties.

Van Norman explained that beyond the paperwork there was considerable pressure for clinicians not to stray from the guidelines. Physicians were required to attend training programs and quarterly meetings. The message from upstairs, meaning from Steve Shon's office since he was the medical director for Mental Health and Mental Retardation (MHMR) for the state, was: It's time for you guys in CMH [Community Mental Health] to enter modernity, the 21st century… There was a constant drumbeat that using FGAs was not giving patients good care. No one wanted to look like they were practicing 2nd-rate medicine.

Van Norman, who didn't conceal his skepticism on the matter of how TMAP was being implemented, recounted how on one occasion he asked Shon's assistant what was happening with all the drug money coming into the state. He was asked to apologize.

Jacks asked Van Norman about his current use of SGAs and FGAs. Van Norman does sometimes prescribe SGAs, but he was greatly influenced by the CATIE and CUtLASS studies, which he described as unbiased by drug company funding, and now he more frequently uses the FGAs, especially haloperidol and perphenazine. Jacks asked him if he prescribes these medications in the same manner he did in the early 1990s, before the introduction of Risperdal. This was a question calculated to bring out an important point for the plaintiff's argument. Namely, the standard SGA manufacturer's line, and the one also held by the defendant, is that FGAs cause EPS, Tardive Dyskinesia (TD) and other motor problems that SGAs do not. In keeping with more recent views on antipsychotic dosing (see, e.g., Healy 2008), lower dosages of both FGAs and SGAs typically do not affect the benefit profile of the drugs by much but greatly reduce the patient's risk profile for side effects. Based on his experience, Van Norman confirmed just this point. He added that the FGAs had the benefits of not exposing the patient to the high risk for diabetes associated with SGAs and there was considerable cost savings not just because of the lower price of the drugs but because the patients taking FGAs had less need of monitoring for lipids, glucose tolerance, and weight gain.

He expatiated a bit more on the side effects of the SGAs in comparison with the FGAs. He and his colleagues, he said, were frequently astonished by the speed and severity of weight gain some patients experienced on SGAs—20-30 lbs. in three months. On even the tiniest doses of Risperdal (1 mg), some women developed hyperprolactinemia, causing them to

lactate—a distressing symptom for someone who is not nursing.

Jacks: And TD? Have you seen that in [use with] the older drugs?

Van Norman: Not under my care.

TMAP was apparently abandoned a year and a half ago and the new PORT (Patient Outcomes Research Team) recommendations do not distinguish between FGAs and SGAs.

It may only have been my perception, but I thought that the cross-examining defense attorney, John McDonald, seemed stunned by some of Van Norman's testimony. What Van Norman was saying was almost certainly a radical departure from the brief J&J/Janssen would have given him.

McDonald stuck to his team's conventional strategy:

- Try to discredit the witness by showing that he was speaking outside his area of expertise (in this case, that Van Norman is not a clinical researcher and so cannot evaluate the veracity of CATIE or similar studies).
- Reiterate the point that TMAP never dictated what a physician could or could not do ("Dr Van Norman, you're not suggesting to this jury that you'd ever not treat a patient well because of some extra paperwork!")
- Extract from the witness that he currently uses Risperdal in his practice, on one occasion even prescribed it to an 8- or 9-year-old child (potentially significant because the plaintiff accuses the defendant of promoting off-label prescription of the drug to children).

After these points the defense attorney used the questioning time to try to discredit the CATIE and CUtLASS studies. CATIE used an uncommon FGA, perphenazine, for its comparison, he averred. This is true, Van Norman said.

McDonald: And CUtLASS [also] uses only one [FGA comparator] drug.

VN: No, two.

McDonald: Neither of these are available in the US—

VN: Haldol was in the study and it is available in the US.

McDonald: You believe that multiple drugs should be available. (Appeal to

the sanctity of consumer choice.)

VN: Yes, one size doesn't fit all.

McDonald: When you prescribe Haldol, do you monitor for TD?

VN: Yes.

McDonald: Please describe to the jury what that looks like.

VN: (Describes it.)

McDonald: *Scary* effects!

VN: Can be.

Defense: The patient who gets these symptoms might stop taking their medicines.

VN: Yes.

The attorney for the plaintiff came in one more time to confirm that Dr. Van Norman saw no difference between SGAs and FGAs with respect to most measures, except that the SGAs were worse on weight gain and diabetes.

If the reader is already informed about these drugs and the scientific controversy surrounding them, s/he will not be surprised by Van Norman's testimony. Alternatively, if the reader has not heard much about the SGAs before, there will seem nothing shocking about Van Norman's testimony. Everyone in between—including *most* psychiatrists and even some medical anthropologists who have ventured speculation and recommendations based on available hearsay about the scientific standing of SGAs as against other options—may soon be obliged to reconsider their long-held beliefs.

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