I'm not a researcher. Although I went to Caltech and learned how to do research, the rules of scientific research have always kept me away. I suppose famed Caltech physicist Richard Feynman would accuse me, like he did all "social scientists" of not being willing to work hard enough to know anything for sure. I'd prefer to say that I'm not willing to be reductionistic and objectively detached enough to break down what I'm interested in learning about into questions that can be researched scientifically. Fortunately for psychiatric researchers the dominant medical model in psychiatry is reductionistic and objectively detached enough to be interested in questions that can be researched scientifically. As a result, these researchers dominate almost all of our professional publications. However, I tend to throw their work away because I'm still not interested in these questions.

The CATIE study was an exception. I was in Tokyo presenting my "Thoughtful Psychopharmocology" paper when I found out that Dr. Liberman was there presenting the CATIE study so they gave me a reprint. Now CATIE wasn't just any study. It was the most expensive government funded study of psychiatric medications ever performed partly because it was an attempt to do a "real world" study with "real world" patients at 57 "real world" treatment sites without pharmaceutical company money and influence. I was so shocked at their outcomes that I wrote this on the plane on my way home from Japan and e-mailed it to a bunch of colleagues.

Should the CATIE Study Be a Wake-Up Call?

(2005)

Like many other people I was surprised by the media reports that the CATIE study found no substantial difference between the atypical antipsychotics and Trilafon. When I got a copy of the article in the New England Journal of Medicine, I was amazed to read how poorly all of their patients had fared.

The numbers are truly stunning: Overall, 64 - 82 % of patients dropped out of treatment in an average of 3.5 – 9.2 months. While in treatment, they only benefited symptomatically for an average of 1 - 3 months. The yearly hospitalization risk rate was 29 - 66 % although only 28% reported an exacerbation in the 3 months prior to the study. 64 - 70 % had substantial side effects, though only 30 - 36 % told their doctor about them without additional "systematic questioning."

How could this array of wonderful medications, that I personally have used over long periods to help hundreds of people improve their lives and even recover have done so poorly? I wonder if a placebo would've done worse. No wonder there wasn't any difference between the medications; everyone did very poorly.

If my own practice did this poorly, I'd …well, I'd decide that my treatment system was in shambles and in need of total transformation. I'd begin by investigating to see what I'd done wrong. Here's what I'd look at:

1) *How's the relationship between the doctor and the patient?* People tend to stay in treatment and do better with doctors they feel listen to them, care about them, and respect them,

because they in turn respect, trust, and work with their doctor. Unfortunately, the authors didn't report any survey results of how the patients felt about their doctors.

2) *How much does the patient understand and believe in the medications?* I'm not asking if they signed a consent form. I'm asking if they internalized an explanation of how the medications would specifically help them improve their lives. People may comply with medications for awhile out of obedience alone, but long term treatment depends on really believing that they help. Unfortunately, the authors didn't report on the patients' satisfaction with their doctors' explanations or their level of understanding of their medications.

3) *Are the medications improving people's lives?* Our overall purpose is not just symptom relief, but helping people have better lives. These patients were described as generally unemployed, unmarried, and often substance abusing. Did the patients get jobs, girlfriends, or sobriety (or money, housing, education and legal assistance)? Unfortunately, the authors report symptom outcome measurements, but not quality of life outcome measurements.

4) *Were the medications integrated into other services and supports?* Medications alone are rarely an effective treatment. Integrating them into a case management team and including rehabilitation, psychoeducation, and substance abuse treatment as well as quality of life services and supports like supportive housing, employment, and education usually works better. Unfortunately, the authors don't report what other services and supports the patients received, if any.

5) *Were the medications part of the patients' recoveries?* Recovery based services are more effective than custodial based services. Recovery solidifies improvements and increases self-responsibility for treatment. Unfortunately, the authors don't report on either internal , subjective measures of the recovery process (e.g. hope, empowerment, self-responsibility, or attaining meaningful roles) or external indicators of recovery (e.g. engagement, risk reduction, increased skills and community supports).

Unfortunately, I don't have any answers to my questions. Although this study purports to be "real world," they didn't include any of the things I most value in my daily practice. Why not? There are scales for answering all of these questions. The authors are clearly very sophisticated, competent, well funded, and striving for relevancy, but, in my opinion, they don't succeed.

They conclude that "antipsychotic drugs, though effective, have substantial limitations in their effectiveness in patients with chronic schizophrenia." I would instead conclude that antipsychotic drugs, though effective, cannot benefit patients unless attention is paid to the doctor – patient relationship, the patients' understanding of and belief in the medication, integrating other services and supports, and being imbedded in a recovery program. I believe that these medications work for me much better than they did in the 57 sites used because our overall treatment program is better. More than anything else, this study proves that even the best and most expensive medications have little effect as used within our present system. In short, they don't work by themselves.

What I most need from our researchers is to test my clinical conclusions. What needs to be added to medications for them to work effectively?

I hear a great deal of talk about "evidence based practice" and "research informed clinical treatment." There is an increasingly frustrated group of effective clinicians urging "practice based evidence" and "clinically informed research." I don't think the CATIE study should be a wake-up call to "clinicians, patients, families, and policymakers." I think it should be a wake-up call to researchers. If we are to achieve the President's Commission's vision of a transformed mental health system, mental health research must be transformed too.

When I got home, I was amazed at the furor CATIE had caused. Everyone was scrambling around madly trying to explain why we should still be allowed to prescribe enormous amounts of very expensive medications when it appeared that an old, cheap pill did just as well. Had the pharmaceutical companies hoodwinked us?

Many mental health advocates would probably agree to dramatically cut down these expensive drugs if we thought the money would go to other mental health services, but we know full well it won't. What would happen is we'd lose the anti-stigma and lobbying support we've been getting from the pharmaceutical companies (like Eli Lily's Reintegration Awards, AstraZeneca's Recovery Celebrations, or Jansen's Japanese consumer exchanges) and our budgets would go down. As a result every major mental health advocacy organization tried to explain why CATIE didn't mean we should use cheaper pills.

Apparently, my e-mail met their needs, since soon it was posted on a variety of web sites and a reduced version was even published as a "Taking Issue" letter in the Psychiatric Services Journal, the first time they've published anything I've written. Dr. Liberman responded that I didn't really understand the study and that much more useful information was to follow in more articles and lectures. He didn't respond to my urgings for person centered, recovery oriented research. I don't think he understood the paradigm shift I was suggesting.

I wrote this e-mail after the next CATIE installment was published, but by then the fear of cut backs had passed, business stayed as usual, and my 15 minutes of fame was over.

Still Not Happy with CATIE

(2006)

Since my reaction to the first CATIE article attracted so much interest and response and even ended up published, I felt obligated to carefully read the two new articles in the American journal this month and share my thoughts.

I have to say I'm still disappointed by CATIE. I had such high hopes that this "real world" study would focus on people instead of illnesses. I have to remind myself that even the most ethical, well intended study is intended to collect data, not to treat people and that research, even when done by clinicians, creates a different human interaction than treatment. I just didn't realize how much of the positive effects of medications would be lost when the human healing factors were changed.

It seems that almost the only people who did well in CATIE were in the Clozaril group. This group was really very different than the other groups and not just because they received Clozaril; the human factors were also different. As I understand it they didn't respond to, but tolerated, their first medication and then chose to be randomized into a Clozaril group. Since most of the poor responders chose not to have even a chance of getting Clozaril, I assume these people actually wanted Clozaril. They, and their doctors, knew they were getting Clozaril, reputed to be the most powerful, but most difficult to tolerate, even potentially lethal, medication we have. And they were seen far more often than the other patients because of the blood draws. As the authors note, any or all of those factors could've had a dramatic biasing effect causing them to stay in the study longer and benefit more, so it's hard to know how good Clozaril really is. (I'm a big believer in the powers of positive expectations, hope, mutual perseverance, and human contact. That may well have been enough to explain their success. Too bad everyone didn't get them. I wonder how well Seroquel would've worked if everyone would've thought it was Clozaril.)

Beyond the Clozaril group, the outcomes were variations of dismal. Again, few people stayed on their medications or showed substantial improvement and many of them were hospitalized. The worst news is buried in the "Other adverse reactions" section of the second article where they mentioned in passing that two of the Geodon patients and one of the Risperidone patients committed suicide. I was surprised they didn't comment on that tragedy. I seem to remember that even though we now have a black box warning about suicidality and antidepressants in adolescents that none of the thousands of study patients actually killed themselves. I began to wonder if anyone who didn't get placebo or taken off medications had ever committed suicide while enrolled in a careful medication study before. I assume that if I had three suicides in my program in a relatively short period I'd have investigators breathing down my neck, but it's never happened to me.

One of the innovations in this study was to organize the data around treatment discontinuation instead of treatment response. The authors were right in their response to my first letter that I 'm confused about what they mean by "discontinued treatment." They seem to have elevated this concept far above what I'm accustomed to, using it as their primary outcome measure, dividing it into different subtypes, and even using it to triage people into further phases of the study. I would call learning how medications affect people both positively and negatively and both the patient and I making changes based on what we've learned "treatment," not a series of "discontinued treatments." Blinding, while useful to avoid biases in head to head trials, cripples our ability to learn from medication responses and

may at least partially explain why so few people were treated effectively in this study. One message of CATIE may well be that to get good results for more than a few weeks doctors and patients have to experiment and learn together what medications help people the most with the least side effects. That collaborative process may be at the core of successful psychiatric practice. If so, it's of great concern that collaborative learning has also been eliminated from clinics all over the country that provide only once every two month doctor visits.

An accompanying editorial noted that it's comforting that this study, financed by the government and conducted by highly experienced, well regarded researchers, more or less confirms the findings of more suspect pharmaceutical company sponsored studies. That may be true qualitatively – yes, Zyprexa does make more people gain weight than anything else does and Risperidone raises prolactin levels - but it's far from true quantitatively. What happened to the nice 70% response rates and low 10% drop out rates I'm used to with the pretty graphs of how people get better? Why am I looking at graphs of people discontinuing treatment and tables of figures showing them not getting any better? If I didn't know from my own experience that these medications work well for me I'd be far from comforted.

If we assume that these medications do work well – and I do, though I realize not everyone does – what's going on here? We have to remember that the CATIE study was a highly unusual, even courageous study. It was a serious attempt to study real world patients in real world conditions. To be fair, it was probably even more difficult in some ways than the real world because of the elaborate sometimes blinded study protocol and the need for so many measurements and complicated consents. The two possibilities I'm left with for what's going on are: 1) People in the real world do much worse than I thought and we really do need to overhaul our system, or 2) This study removed a great deal of the positive healing effects of real world treatment without realizing it. Either way, the message is clear to me: We need to get more serious about studying and using the human healing that often accompanies medications. If CATIE is to be believed the medications just don't work very well alone.

The crucial question remains unanswered, "Can the reductionistic and objectively detached methodology of scientific research be adapted to study recovery and provide an evidence base for our recovery based practice?"