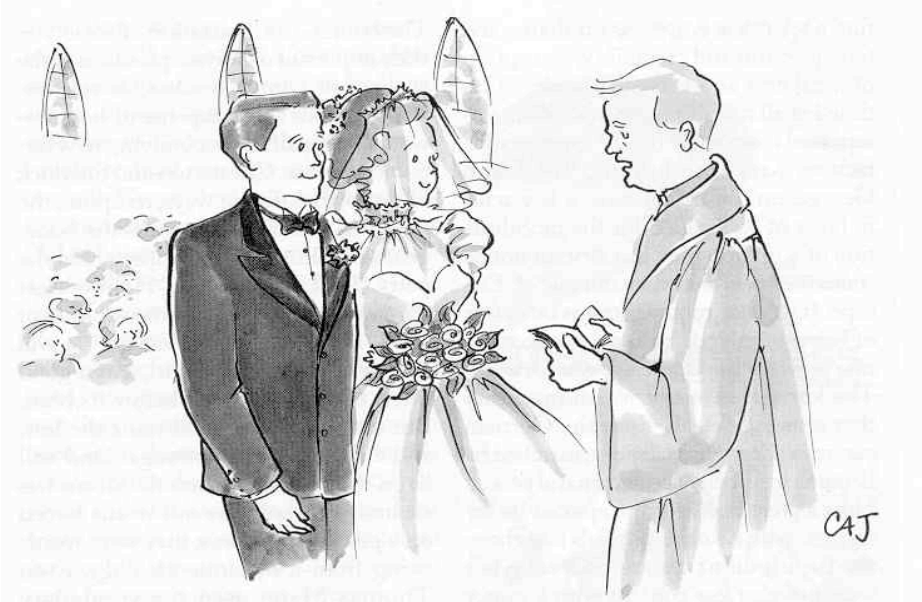
Is Evidence-Based Medication Treatment the Answer?

Kevin Turnquist M.D.

Even the staunchest defenders of current psychiatric practice would have to admit that there are some significant problems with the way we treat our patients these days. Perhaps no other issue separates psychiatry from the other medical disciplines as much as our reliance on experimental treatments for the major mental disorders.



"You may now begin your insane experiment."

Many psychiatrists may object to the view that the way they provide treatment to their patients is experimental. But one can easily review a dozen consecutive medication regimens of as many patients and be forced to conclude that each and every patient is receiving treatment that is to some degree "experimental". The psychiatrist may claim that since no research objectives are involved there is no experimentation either. After all, they're just doing their best to relieve the pain and suffering that their patients experience. What's experimental about that?

The major issue here is whether there is adequate research evidence to prove that the treatment being provided is safe and effective for the disorder that is being treated. By that simple standard one would have to reluctantly conclude that many, if not most, of our medication treatments in modern psychiatry are still experimental. And even when there is good research evidence to guide our prescribing practices there is no guarantee at all that we psychiatrists will know about it or base our decisions on it.

The majority of patients with major mental disorders now receive a complex cocktail of psychotropic medications to treat their conditions. It's common to see patients on five or more psychiatric medications. Anyone who reviews a lot of cases has seen records of patients taking double-digit psychotropics. In none of these instances could the psychiatrist point to any good research - or any research at all for that matter - that has addressed the responses of patients taking the five or ten different psychiatric medicines.

We have nothing to suggest that these combinations are effective or safe. If the patient improves we can't really say whether it was one of the medicines that did the trick, the whole lot of them, or one of a host of other factors that weren't being examined. We have almost no research about whether these medications are safe and effective for years on end when given individually, much less when we give them in bunches.

Voodoo Psychiatry?

Perhaps it's time for our profession to swallow hard and admit that we're still in an experimental phase. When we prescribe medications in combinations that have not been adequately researched that's experimental treatment. When we use medications that have been approved for one disorder in the treatment of a different disorder that they haven't been tested in that's experimental treatment too (although we psychiatrists much prefer the term "off label" to "experimental"). Even using medication dosages that haven't been studied and approved should really qualify as experimental.

Using medications for conditions that they weren't designed to treat happens all of the time in psychiatry. As soon as a new anticonvulsant is released we psychiatrists immediately start giving it to our patients with Bipolar Disorder. This took place with Neurontin (gabapentin) for several years. It had achieved a regular and respected place in the treatment of Bipolar Disorder before some good research finally became available. That research showed that Neurontin was no better that placebo for reducing or preventing manic symptoms. There is a long list of other drugs to prevent seizures that our profession has taken from the neurologists and given to our patients before there was any evidence to support the practice.

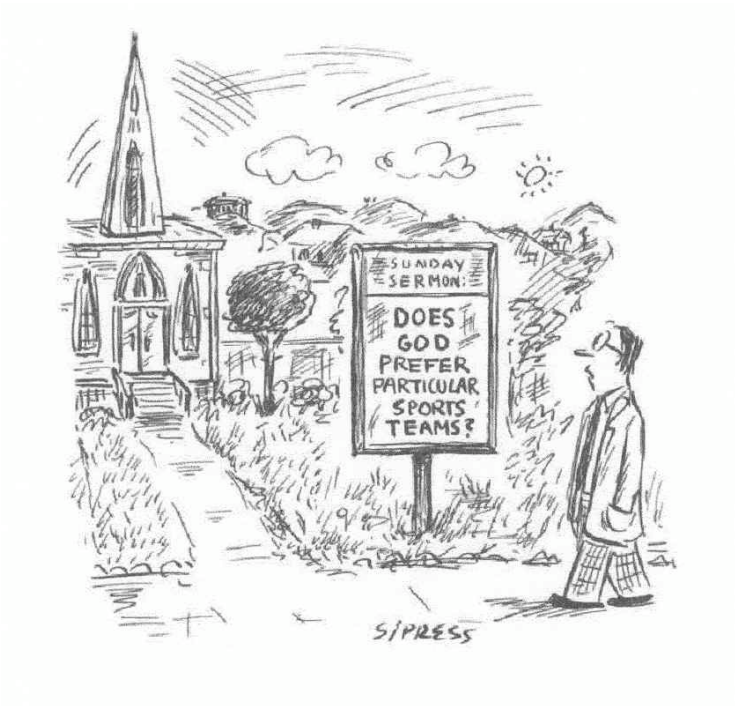
The psychiatric profession is filled with examples of using unproven treatments for our patients. Children are routinely given antidepressants, antipsychotics, and mood stabilizers in the absence of any long term studies to address their safety and efficacy. One study that came out recently found 69% of depressed children responded to an antidepressant drug - compared with 59% that responded favorably to placebos. That 10% improvement over sugar pills was heralded as the long awaited proof that antidepressants are useful in the treatment of childhood depression.

Kids as young as three years old have received ECT (shock treatment) for depression. Patients with Anorexia Nervosa are given essentially any and every class of psychiatric medication, despite the fact that no medicine has ever been proven helpful in that

disorder. We know of one unfortunate woman with anorexia who died after being given three different antipsychotic medicines, against her will, via a nasogastric tube. The facts that she had never been psychotic in her life and that antipsychotic medications haven't received any research support in her disorder did not protect her

The ways that we psychiatrists dose these medications can get pretty idiosyncratic too. When good data is available about the dosage ranges that are effective for any particular medication that information may not correlate at all with the amounts of these drugs that we prescribe for our patients. We're often more likely to use drugs or dosages that have worked for us in the past than to adjust our prescribing practices based on new research findings.

Psychiatrists are often too busy to keep up with the flood of data about medications that comes out each month. When we do look at it the research may be confusing or seem biased. If we're forced to choose between written information and the things that our clinical experiences tell us are true we'll usually go with our own observations.



Valid assumptions about cause and effect are always hard to come by in any area of life. The responses of our individual patients may readily lead us to make conclusions about various treatments but those assumptions may not be at all consistent with the findings of large-scale research studies using controlled conditions. Like other humans, we're prone to believing conclusions that are in agreement with the way that we already see things and disregarding the rest.

Of course, making valid comparisons about treatment responses to any medication depends on using those drugs on people that have very similar sets of problems and testing them in environments that are as similar as possible too. As was reviewed in prior chapters, we tend to have problems in those areas. Our diagnostic practices are often shabby and we typically send our patients home to live in places that are quite detrimental to their functioning.

The diagnosis that a person is given is no longer a predictor of the medication that they will receive anyway. It's now so common to see medication regimens consisting of an antidepressant, a mood stabilizer, an antipsychotic, and a minor tranquilizer - often with stimulants or side effect medications thrown in for good measure - that these combinations offer no hint at what disorder the psychiatrist believes that he or she is treating.

Psychiatry is still at a stage in its development where we aren't that different from witch doctors. Despite all of our fancy words and medications with catchy names, a great deal of the improvements experienced by our patients come about as a result of our inducing hope and the expectation of change. While it's natural that there would be a push for more science and less art in our field that will only come about when the science gets a whole lot better - and more honest - than it is today.

Evidence Based Treatment to the rescue

There are a number of treatments for mental illness that now have achieved the status of "Evidence Based". "Assertive Community Treatment" teams that deliver care to individuals right in their homes and help with day to day problems now have that degree of research support. So does the idea of providing "Integrated Treatment" for people that have both mental illnesses and chemical dependency. Teaching people how to manage their own illnesses to the extent possible, providing education to family members about mental illness, and developing supportive employment programs for mentally ill people are other areas where it's been decided that there is now enough research data available to warrant inclusion as Evidence Based Treatment or "Best Practices".

Some states try to incorporate all of these treatment approaches into their public mental health systems. Others aren't getting on board with any of this yet. The expense of these approaches will limit their use until someone can show that it's actually cheaper to provide these sorts of care to severely mentally ill people than it is to withhold them. But the final area of the Evidence Based Treatments is enough to excite any administrator or policy maker. Using "medication algorithms" to determine what psychiatric treatment will look like within their agencies has tremendous appeal.

With psychiatrists prescribing confusing, idiosyncratic, and tremendously expensive combinations of medications to our severely ill patients it's no wonder that a backlash would develop. That backlash has taken the form of an emphasis on using decision trees and research based formulas to make choices about what medication will be given to whom. But, as is always the case when dealing with the care of the mentally ill, things are

much more complicated than they may initially seem.

On the surface, it is very hard to argue with the tenets of Evidence Based Treatment. EBT holds that treatment should always be directed by the best available clinical evidence about which treatments are safest and most effective for any particular disorder. Isn't this what anyone should expect when they see a physician? Who would knowingly place themselves under the care of a Doctor who hasn't bothered to learn the basic facts about the treatments that he's using?

There are now a wide variety of sources that summarize the clinical evidence about the medication treatment of the major psychiatric disorders. Some provide explicit guidelines about how treatment should optimally proceed. The American Psychiatric Association publishes treatment guidelines for most of the common disorders. The Cochrane Group reviews available data for most medications and some non-medication treatments. The Texas Medication Algorithm Project distills the clinical evidence into specific, step- by-step treatment guidelines for each of the Major Mental Disorders. A variety of other efforts to translate the clinical evidence about psychiatric treatments into specific guidelines are available too.

A fair summary of these efforts to look at psychiatric treatment would be that there is rarely any good evidence to support one particular medication over another in its class for the treatment of any psychiatric disorder. A few exceptions exist but for the most part we're in the position of choosing our medications based on the side effect profiles that will be easiest for our patients to tolerate rather than picking on the basis of improved chance of response. In most cases the newer and more expensive drugs offer better side effect profiles but don't actually work any better for relieving symptoms than the medications that we've had around for decades.

Another recurring theme in the EBT literature is that most patients who are going to respond to medications will respond to modest doses of a single medication. There is some research support for adding second medications in a few conditions but recommendations are that if a two-drug regimen is used that should probably occur after several trials of single medications used alone. There is essentially no research support for the multiple medication regimens that we frequently utilize in American psychiatry today. In fact a recent review looking at patients treated with multiple antipsychotic drugs (an increasingly common practice) found that those patients had poorer outcomes than those who were treated with single agents.

In the face of these impressive compilations of years of research data about what current psychiatric treatment should really look like we're left with several important questions. Why is there such a disparity between the way psychiatrists treat people and the research evidence about best practices? Why are psychiatrists reluctant to embrace the research-based treatment guidelines? Is Evidence Based Treatment really the way out of the messy situation that the psychiatric profession is currently enmeshed in?

Garbage in- Garbage out

Curiously enough, the limitations of the EBT approach come down to the fact that there is such a scant amount of good evidence in the research literature to guide our selection of treatments. This fact is puzzling indeed. Every month we have a flood of research articles coming out in peer-reviewed journals. These vast majority of the reports in the psychiatric literature these days address the responses of patients with various mental disorders to the drugs that the psychiatrists are providing for their treatment. The studies are usually pretty well controlled and active medications are usually compared with placebos to see how much real benefit they provide for the specific disorders.

It would seem that having adequate research data should be the least of our problems as psychiatrists. Yet the conclusion of almost every objective review that is done on the data supporting *any* treatment, of any disorder, with psychiatric medications is that more and better studies are necessary before we can draw firm conclusions. How can we understand this?

The most obvious problem with the available "Evidence" for our psychiatric treatments is that nearly all of the studies about medications are funded by the corporations that manufacture them. Like it or not (and many of us don't), health care in America is a for-profit enterprise. The companies that make these drugs and study their effects are doing it to make money. Lots of money. A top selling psychiatric medication can provide literally billions of dollars in revenues for the company's shareholders. When that kind of money is involved the results are predictable.

Companies utilize all sorts of tricks to make the data supporting their drugs look better and to discredit their competitors' products. Rating scales and statistical analyses can be rigged to maximize apparent benefits. Sometimes patients that are given the active medication are compared to patients who were abruptly taken off their medication and switched to placebo. The people whose drugs were suddenly stopped might get worse because of that fact alone, thus inflating the difference between active drug and placebo.

Sometimes drug companies compare their products to competing drugs by using doses of the competitor that they know will be unlikely to be effective or will cause uncomfortable side effects. Another trick comes in the ways that are used to define "response" to a medication. Typically this involves using standardized rating scales. If a particular symptom decreases by a certain number of percentage points on serial ratings that is defined as response and pretty soon the pharmaceutical salesman are out knocking on physicians doors trumpeting their success. Whether this "response" actually translates into a better life for the patients that take the drug isn't always considered. Nor is the fact that many patients don't see enough benefit from taking the drug to continue it unless they’re forced or coerced into doing so.

The fact that all of the available drugs in a given class are about equally effective leaves the drug companies in a precarious position. Bringing new drugs to market is very expensive and the patents on them are time-limited. So they try to make as much money

as they can as fast as they can. They do whatever is necessary to get a leg up on the competition.

Most psychiatrists are aware of a recent phenomenon - the publication of official looking "journals" that are delivered right to our homes. We don't even have to order them or pay for them. But when we look closely we see that these publications are funded directly by the pharmaceutical companies. And the "research" reported in them always makes their companies products look wonderful - everyone gets better and no one has bad side effects. Of course these 'throwaway" journals are also used as vehicles to attack the opposition.

As psychiatrists we're exposed to so much research, of such wildly varying quality, that it's hard for an individual to know what to make of it all.

One area that we don't see much research about is the practice of combining medications. The reasons for this may be intuitively obvious. It's hard enough to truly assess the effects of one medication for even an eight week trial. Introducing a second medication introduces a lot more variables and potential for confusion. And remember who is funding most of these drug studies. There is nothing in it for drug companies to assess the way their products work in combination with drugs from another company. They don't even like to fund studies combining their products with lithium, as lithium is an element that is hard to make money off of. So when we do see studies on combination therapy it's frequently a pair of drugs produced by the same company. The recent release of Symbyax - a combination of Prozac and Zyprexa (both produced by Eli Lilly) is a good example.

Another weakness in the available data around medications is that developing "evidence" depends on the drug company's willingness to fund the research. Companies often become motivated to invest money in new research as they are faced with losing the patents on their medications. They desperately need to find a new market niche to keep the profits from the drug flowing.

For example, all of the SSRI antidepressants are likely to be about equally effective for the treatment of anxiety disorders but the "evidence" will be limited to the companies that were motivated to fund the studies on the use of their products in these disorders. Individual medications end up being advertised as "the only SSRI approved for Generalized Anxiety Disorder" or "the first FDA approved treatment for Social Phobia" but the actual differences between members of the SSRI class in treating these disorders are usually negligible.

Then there is that other small problem about the available data regarding psychiatric medications. When there are studies that show that a drug is *not* helpful in a given condition we're unlikely to ever hear about them. The drug companies actively limit access to information that casts their products in a negative light. They do that, of course, because tailoring the public's perception of their products is essential to maximizing profits. Until there is a mechanism to ensure that *all* available research data on a medication is made available, that it's analyzed objectively by knowledgeable people

who don't have a stake in the outcomes, and is disseminated to Doctors in ways that they can access and understand, the use of Evidence Based Treatment to guide medication decisions will always be a flawed process.

That nasty law of thirds

Drug comparison studies also add to our confusion. Suppose a company want to make its drug look better than a competitor. They find a cohort of people who don't respond to the competing drug - let's call it drug "X". Then they switch the people to their own drug "A". Lo and behold, about 30% of patients who didn't respond to drug "X "got better on the new wonder drug "A". Obviously "A" must be a much better product, right?

There's only one catch. If you run the experiment in reverse you get the opposite results. "X" will treat about a third of the people who don't get better with "A". A common finding in large scale meta-analyses is that when you treat non-responders to one drug in a class a fair percentage will get better when you switch them to any other drug in the class. This 30% or so is awfully similar to what has been termed "the law of thirds" in the placebo response. And the placebo response is one that psychiatrists don't particularly like to talk about.

The law of thirds works like this: Give a population of people suffering from just about any disorder an inert placebo and a curious thing happens. About a third get a lot better, a third get a little bit better, and a third don't respond at all. That makes it awfully hard to evaluate the effects of active medications. They have to be proven to be better than placebo and placebos work pretty darn well. Antidepressant medications, for example, are only about 20 % or so better overall compared with inert placebos.

An awful lot of new medications that drug companies invest money in developing fall by the wayside because they can't beat placebos. The amazing power of beliefs and expectations in humans is hard to overestimate. In fact there were essentially no active treatments for specific diseases until the twentieth century yet there have been physicians or healers throughout human history. And many of their patients got better long before the advent of "scientific" medicine.

When evaluating the issue of placebo response Doctors have occasionally asked some questions that the drug companies just don't want to address. The "double blind" drug studies are the gold standard of the industry. In these studies the patients are randomized to receive either active drug or placebo. Neither the Doctor nor the patient is supposed to know who is getting active drug and who's getting sugar pill. But are these studies really "blind".

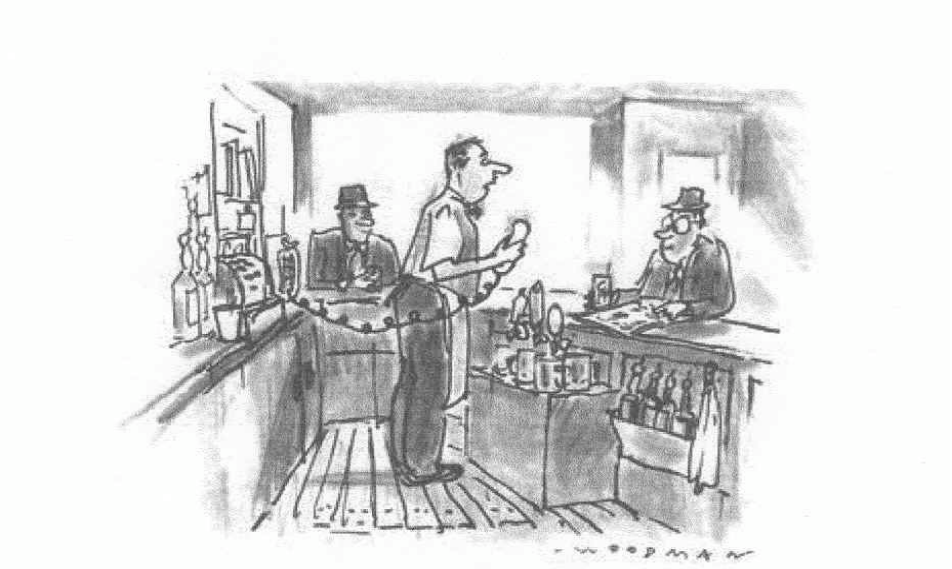
As you might imagine, it turns out that in many cases either the Doctor, the patient, or both can quickly figure out who's getting the active treatment. The presence or absence of various side effects may tip them off. Sometimes it's a rapid calming or some other ancillary benefit of the active medication. Research that has looked at this has found that

the typical drug studies are nowhere near as "blind" as we'd like to believe. And this makes the studies much more subjective than they're supposed to be.

If the patient is convinced that he's getting the active drug he's more likely to respond. The Doctors ratings may be biased in favor of the active drug as well. Of course researchers must produce research in order to maintain a flow of grant money to do more research. So this is a subject that many psychiatric researchers have dismissed with a nod and a wink for decades.

But the placebo issue goes much deeper than this. An obvious question is "what if we leveled the playing field by using placebos with similar side effects to the active drug". When the Cochrane Group looked at the available literature comparing antidepressant medications to placebos that had similar side effects (we call these "active placebos") much of the difference between antidepressants and placebos evaporated. In only two of nine large scale analyses did the antidepressants maintain statistical superiority to placebo.

"Placebos" come in many forms besides sugar pills. Anything that allows a person a greater degree of hope and an expectation of improvement is likely to make at least some people feel lot better. One of the confounding factors in early attempts to assess the results of psychotherapy was that they used people who were put on a waiting list for therapy as the comparison group for the people that got the actual treatment. As you might guess by now, a fair number of people on the waiting lists got better too. Just getting on the list meant that they had recognized that they had a problem, had taken steps to deal with it, and had at least some expectation that they would improve. Those are all extremely powerful medicines for humans.



"It's the loony bin. They want to know if you're coming back."

Look at all of the other factors that are involved in doing drug studies. Most of them take place in hospitals. The average length of stay in an inpatient psychiatric ward in America these days is somewhere in the neighborhood of five days, regardless of the disorder that you go in with. Most people leave the hospital feeling better than they did when they went in. And the main form of treatment that the Doctors deliver almost always involves prescribing a new medicine or making adjustments in existing medication regimens.

There's only one problem. Just about any medicine that we psychiatrists prescribe takes a lot longer than five days to even *start* to work. So our patients are improving enough to leave the hospital before the medication changes begin to take effect. Some caring attention, having their problems taken seriously, a safe place to sleep, decent meals. and a strong expectation that things will change as a result of being in the hospital are just a few of the possible contributors to their improvement. And all of those factors are typically present when we do our large scale studies to assess the effects of new medications.

So IS evidence-based treatment the answer?

The real answer to this question depends on another question: "The answer for who?"

Unfortunately, EBT has not yet reached a stage where it's the answer for psychiatrists. There just isn't enough decent evidence out there yet, or any good systematic way to use what is available, to truly base our treatment decisions exclusively on an EBT approach.

EBT is about the last thing that pharmaceutical companies will see as an answer to our current problems with psychiatric treatment. A move towards simple medication regimens and using generic drugs whenever there is no clear advantage for the more expensive versions is not something that they'll ever embrace.

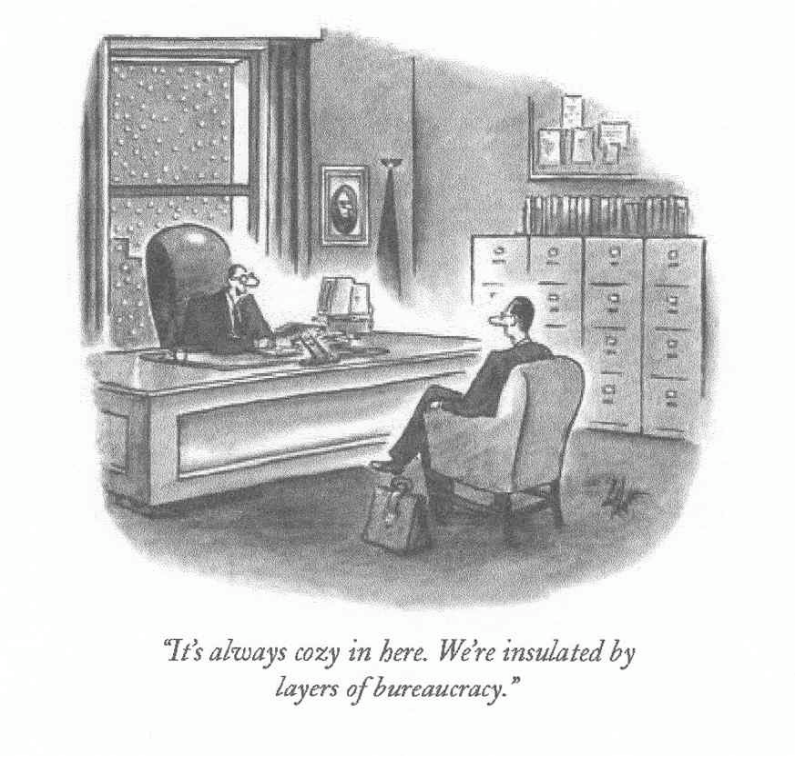
And in reality, the connections between the American Psychiatry industry and the pharmaceutical companies are still so strong that it's almost silly to talk about them as though they were discrete entities.

While it may be in the best interests of our patients for them to advocate for Evidence Based Treatment we shouldn't expect much impetus from that direction. Mentally ill people are notoriously difficult to organize in any meaningful way. In fact some of us psychiatrists are on record saying that when our patients start forming gangs we're going to find a new profession. The sadder truth is that most patients don't know anything about EBT and many have already come to expect that they'll be treated rather shabbily anyway.

Strangely enough, the main push to get evidence--based medicating into operation will actually come from administrators.

While the common stereotype of the private practitioner working alone in his office still exists, these days most psychiatrists are no longer their own bosses. Many of us, especially those of us who treat severely ill or indigent patients, work for large organizations. State or county governments, the Veterans Administration, and Health Maintenance Organizations are the big employers. Each one of these organizations has its dense bureaucracies. In most cases the bureaucrats that work for these organizations either have no experience treating the severely mentally ill or they used to treat them but no longer have any actual contact with them.

It would be fair to say that most people who move up in these bureaucracies don't choose that path because of a deep love of - or talent for - clinical work. But they still must find a way to somehow "direct" the clinical care that is delivered in their organizations. And EBT has given them their first real shot at accomplishing that.



"It's always cozy in here. We're insulated by layers of bureaucracy."

People who have observed large mental health systems for a long enough time are aware of a curious phenomenon. About every five years or so some new issue surfaces that excites the administrative structure. "Continuous Quality Improvement", "Mission and Value Statements","Diversity Awareness", and “Person-Centered Planning” are a few of the recent ones.

When each of these new approaches takes hold the organizations respond in a certain way. Many meetings are held with other bureaucrats, sometimes for months on end, until finally some pronouncements are issued to the clinicians. The clinicians are then expected to change the way that they do business with their patients in response to the new way that The Administration sees things.

Seasoned clinicians usually don't even take the time to read the high sounding decrees about how the business of caring for the mentally ill has now changed. They are aware that the administrators live in a very different world, one that is far removed from the realities of day to day clinical practice. Some even believe that the administrators inhabit a strange "virtual world". So one can anticipate that whenever administrators try to impact the actual clinical practice of psychiatry we shrinks won't be responding with overwhelming enthusiasm or gratitude. And we're likely to dismiss EBT as yet another in a long line of administrative initiatives that will count for nothing in the long run.

So there are credibility problems. Even if there *was* a clear and proven way to treat each and every mental disorder, psychiatrists would be wary - and resentful - of having the bureaucrats telling them how to practice. Many would reject a move to institute EBT even if it didn't have all of those problems around the actual "evidence" that is supposed to guide treatment.

"Let the healing begin!"

When it comes down to the most basic level, psychiatric treatment is still about the clinical judgment of an individual Doctor as he interacts with an individual patient. If there are bad outcomes that Doctor will be held responsible for the choices that he made. And when people do get better we're not inclined to attribute the improvement to the wisdom of administrators who decided from afar what sort of treatment the patient was going to receive.

If Evidence-Based Treatment isn't the answer then what is?

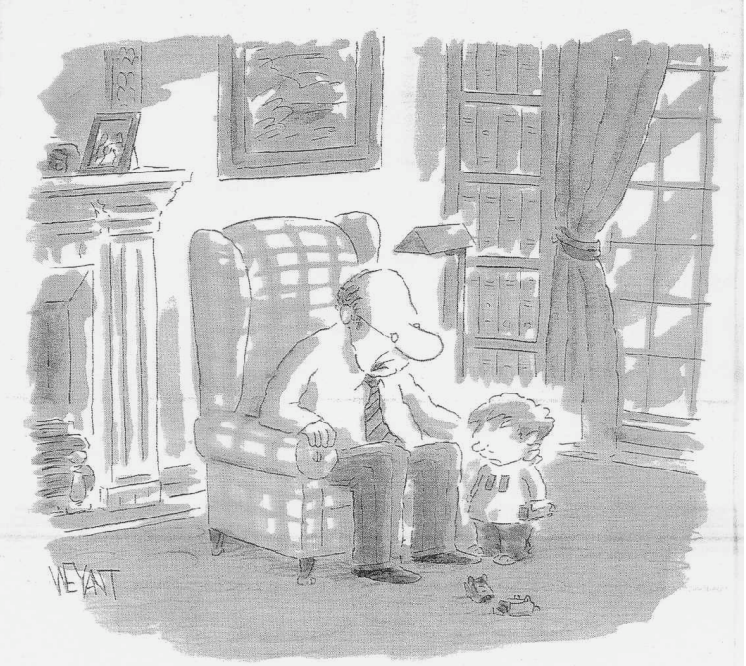
Many of the clinician's attitudes about administrators and the bureaucracies that they live in are rooted in human factors. Nobody likes to be told what to do. Everybody is inclined to see their bosses as people who don't know as much as the people doing the actual work. And anyone who has spent much time with psychiatrists knows that when it comes to having human foibles we're in a class by ourselves.

Many of us who work with the severely mentally ill are convinced that our mental health system has enough resources to provide a decent quality of life for each of the people we serve, if only there were better decisions made about how to prioritize those resources. We have an extremely expensive mental health system but many of our clients live in hopeless poverty and can't access adequate treatment for their conditions. That's another factor that fuels our ambivalence about the bureaucrats and makes objectivity about their initiatives difficult to come by.

A more unbiased look at EBT would suggest that it will be an increasingly important part of any solution that we come up with for our broken mental health system. As we accumulate more and better evidence about various treatments the EBT approach will become more valuable. There are already a few large-scale drug comparison studies taking place out there that aren't funded by the drug companies and we can't wait to see the results.

Exposure to EBT will become an important part of the education of young psychiatrists and will gradually be incorporated into board examinations. Future generations of shrinks will almost certainly pay more attention to the information that is generated by better studies of our treatments. Hopefully, in a couple of decades our current treatment approaches will look like something out of the Flintstones.

While EBT hasn't evolved sufficiently to guide us in the nuances of current treatments, having a basic knowledge of the research literature is certainly not too much to expect of our psychiatrists. It would be fair to ask that each of us be able to demonstrate an adequate understanding of what EBT has discovered so far. When we depart significantly from the prescribing and diagnosing patterns that have the best research support it should be incumbent upon us to be able to show that we knew what the literature said about the best treatments available, and that we had a good reason for trying something that didn't have that level of research support.



"Remember, son, when life gives you a lemon, call the attorneys."

Of course the real impetus for change in this area will probably come from the attorneys. Nothing changes the behavior of physicians quicker than the threat of a lawsuit. Once the lawyers grab onto information about Evidence-Based prescribing practices and start questioning Doctors during malpractice cases about why they departed from the clinical evidence you'll be amazed at how fast we can learn this stuff.

More and better good drug studies that the drug companies aren't involved in. A complete registry of *all* medication trials, regardless of the results. A systematic method to evaluate and synthesize all of the data that are generated. Reliable ways to get the best information into the hands of the psychiatrists, again without using drug companies as intermediaries. These are some of the steps that will make EBT a reality, one that will truly improve the psychiatric treatment that our patients count on us for.

And eventually we may become sophisticated enough to study those special clinicians who already know how to provide the best treatment available. Everybody in the field knows a few of them. Their patients always seem to have good outcomes. The Doctors remember whose life it is that their dealing with and the clients feel valued and respected as equal human beings. Their treatment relationships include laughter, understanding, and honesty. Medications are viewed as a helpful adjunct to treatment, rather than treatment itself. When Evidence-Based Treatment can start to teach us about how those guys actually operate we won't be able to sign up for the trainings fast enough.