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Before Prozac

HISTORY OF FORGOTTEN PSYCHIATRIC MEDS

If you are an older physician, you remember the days when we prescribed barbiturates and tricyclic antidepressants regularly. If you've trained in the last decade, these meds are thought of as pharmacological footnotes in history. Might we have dismissed the most effective therapeutics in Psychiatry. Welcome to the Clinician's Roundtable. I am Dr. Leslie Lundt and with me today is Dr. Edward Shorter. Dr. Shorter is the Hannah Chair in the History of Medicine and Professor of Psychiatry at the University of Toronto. His main research focus-wise in the rich field of psychiatric history where he has published several authoritative texts including his most recent book – Before Prozac: The Troubled History of Mood Disorders in Psychiatry.

DR. LESLIE LUNDT:

Welcome to ReachMD, Dr. Shorter.

DR. EDWARD SHORTER:

Hi, Leslie, thank you.

DR. LESLIE LUNDT:

Now, in your book, you've criticized psychiatrist as having a heard mentality. Explain that first?

DR. EDWARD SHORTER:

Well, one of the problems in Psychiatry is that the brain is still kind of a black box. Nobody really knows what causes anything and as a result, Psychiatry finds it very difficult to disprove bad ideas. This is a basic problem. Somebody proposes a moon beam theory of psychosis and it's impossible to disprove, a moon being theory of psychosis and so clinicians started to get behind it and there is a slow ball movement and before you know it, everybody is in the psychoanalysis, everybody is into cognitive behavioral therapy, everybody is following whatever the latest fad of the moment is, whether it's SSRIs now or whether it's amphetamines in the late 1930s. This does not happen in Nephrology or Cardiology where you can prove that ideas wrong with data. The appropriate data don't really exist in Psychiatry.

DR. LESLIE LUNDT:

Now, you make a compelling case in your book that we may have unnecessarily thrown out highly effective medications. One of the examples you used is Miltown and as I was reading out, I thought Miltown, what? Tell us about that.

DR. EDWARD SHORTER:

This is a drug that was introduced in 1955 by the Carter Company, which soon was to become Carter-Wallace and Miltown was marketed as Equanil via us and via detailed forces much stronger than Wallace's and so actually many more tablets of Equanil than Miltown were sold. It was really the first block-bluster drug in Psychiatry. How it works is today just this unclear as it was then, but it was clear from an overwhelming number of open studies, anecdotes that it was highly effective against mixed anxiety depression and anxiety and it was discarded only when the FDA really got up a false alarm about it being addictive. It is not any more addictive than any other drug, it's effective against mixed anxiety depression and so it vanished from the radar with the loss of what was probably really quite an effective agent, certainly more effective than the SSRIs, but we will never know that because nobody will ever do an RCT, a randomly controlled trial, putting Miltown against Prozac or whatever the current agent is, simply because Miltown would probably win and this would be a disaster for the company that funded the trial. So, one of the problems is that we no longer have independent government agencies funding drug trials. The only drug trials are funded by the drug companies and they would never ever put their precious agent of the moment up against any off-pattern compound that might well beat it.

DR. LESLIE LUNDT:

And the FDA doesn’t require them to, all right?

DR. EDWARD SHORTER:

No, it doesn’t. The FDA insists only that drugs be tested against placebo and not against the most effective agent that's already on the market, so this is really a recipe for what the FDA refers to as diluting the formulary, filling up the shelves of the drug stores with agents that may be less effective than their previous competitors, but this doesn’t seem to bother them because they go right on it and continue to do it.

DR. LESLIE LUNDT:

You have also suggested that we prematurely abandoned the original antidepressants like the MAO inhibitors and tricyclics. Why is that?

DR. EDWARD SHORTER:

Well, there have been several generations of antidepressant agents that have now been forgotten. The first generation of effective antidepressants, effective for non-melancholic depression were the amphetamines, which came out in the late 1930s and the most effective antidepressant among the amphetamines is, guess what, methamphetamine, which today is responsible for so much damage on the streets, but clinically it was quite effective as an antidepressant and the other amphetamine is still on the market. Methamphetamine, of course has gone, but they aren’t indicated for depression any more. In your depressed elderly patients for

example, amphetamine might well be the agent of choice. It's just that the Drug Enforcement Administration fines terribly upon physicians who prescribe amphetamine for any other than very narrow indications and so that's one generation of antidepressants that we have lost sight of. In the early 1950s, a couple of generations of new antidepressant drugs came along. The MAOIs, the monoamine oxidase inhibitors, appeared on the market in the early 1950s and they had considerable success as antidepressants for more serious melancholic depression. They have been lost sight of entirely now for that indication. In 1957, the first of the tricyclics, imipramine hit the market, licensed in the US in 1959. The tricyclics remain probably the most single effective psychopharmaceutical agent for melancholic depression and yet they are rarely prescribed except by older and experienced psychiatrists. Many younger clinicians today simply wouldn't prescribe TCAs because they are under the erroneous belief that they carry an overwhelming burden of unacceptable side effects and that the SSRIs are really much more tolerable. The problem with this analysis is that there are a load of side effects from the SSRIs, but also the SSRIs are considerably less effective and so if you are trying to balance the side effects against the expected therapeutic benefits with the TCAs, sure there are anticholinergic effects, but the expected benefits are very considerable. With the SSRIs, there are actually a fair number of side effects and the expected benefits just aren't that great.

DR. LESLIE LUNDT:

If you are just joining us, you are listening to the Clinician's Roundtable on ReachMD, the Channel for Medical Professionals. I am Dr. Leslie Lundt, your host and with me today is Dr. Edward Shorter of the University of Toronto. We are discussing the history of forgotten psychiatric meds.

Now, Dr. Shorter, have we just been brainwashed that the SSRIs are just as good as these older medicines?

DR. EDWARD SHORTER:

The drug companies have certainly brainwashed the profession today in favor of the SSRIs. Billions of dollars are at stake in persuading clinicians to prescribe these agents, but guess what most of the SSRIs are now off patent and so the volume of advertising on behalf of the SSRIs has just dropped off dramatically. In fact, there are very few patent-protected antidepressants that are still on the market. This is one of the problems. The pipeline in mood psychopharmacology is so empty; however, you can get the SSRIs now generically and the trade name such as Prozac are still trademark protected and so there is still enormous impetus on the part of physicians to prescribe the SSRIs and awareness that there are alternative agents that might well be more effective is really lacking. Indeed, the drug companies have done a good job of persuading the disciplines that the burden of side effects from the TCAs and the older antidepressant classes is unacceptable that's completely wrong, the data says something very different.

DR. LESLIE LUNDT:

No, not just drug companies have been to blame for this, but also institution like Psychiatry, how do you think the DSM has affected our prescribing habit.

DR. EDWARD SHORTER:

Well, it's effective in great length by imparting this bogus diagnosis called major depression and this is a therapeutic disaster, a classification disaster. It began in 1980 with the launching of the third edition of DSM III. The problem for the drafters of DSM III was getting the psychoanalysts on side. Previously, Psychiatry had distinguished clearly between 2 different kinds of depression, melancholic depression and non-melancholic depression. The psychoanalysts had favored kind of depression that was really a kind of psychoanalytic invention called neurotic depression and DSM III abolished neurotic depression because Robert Spitzer, the architecture of DSM III, was really implacably opposed to psychoanalysis and yet the psychoanalyst picked up a big fuss about the abolition of

neurotic depression and they threatened to torpedo the draft of DSM III out of APA National Meeting before it was even accepted and so Spitzer felt he had to do something and so he created this big diagnosis of major depression that would make everybody happy because there was something in there for all of the squabbling factions and so that was a shrewd political move on his part, but it wasn't a scientific move. The creation of major depression had nothing to do with science. It became the only diagnosis that you would use for an acutely depressed patient of whatever severity. Now, the problem here is that previously Psychiatry had sorted out different depressions, not necessarily on the basis of severity, but on the basis of there being at least 2 very different kinds of illnesses. There was melancholia, which was a well-defined illness with slowed movement and mentation, despairing about the future in an unremitting way, striking neurovegetative symptoms and the distinctive biological profile, high cortisol, positive dexamethasone test, and some of our older listeners will remember the DST that was incorrectly thrown out of Psychiatry. Okay, so that was melancholia and that has always been acknowledged in Psychiatry as a separate disorder going way back in time over previous centuries and then there had always been some kind of diagnoses that indicate non-melancholic illness and by non-melancholic illness, we are talking here about constitutional depression something you are born with, reactive depression, mixed depressive anxiety pictures, all of those fit into the kind of non-melancholics too. Okay, now, there is a lot of differential responsiveness here. This is the important point. With melancholia, the agents of choice are convulsive therapy and the tricyclics and may be even the MAOIs and they are distinctively effective in melancholia. You wouldn't necessarily use them for non-melancholia. For non-melancholia by contrast, you use agents that you wouldn't use for melancholia. For non-melancholic illness, the SSRIs. Hey why not, but the benzodiazepines were even better, meprobamate is probably even better still. So, all 3 of these drug classes are inappropriate for melancholic illness. They hit the nail right on the head for non-melancholia and major depression washed all that together into the same pot, okay that was 1980. So, when the SSRIs came along 7 years later, in 1987, Prozac is the first of the SSRIs to hit the market. Guess what we have got a perfect drug here for major depression, this mixture of melancholia and non-melancholia and people have now forgotten that there are 2 distinctive disorders that are mixed into the pot. They see major depression as a distinctive illness and guess what we have got a perfect drug for it. So, it's really a perfect glove that fits the perfect hand and that's where we are today, seeing the basically 1 drug class that is suitable for the relief of major depression and that drug class is called the SSRIs. The diagnosis itself is low risk; the SSRIs tend to be ineffective in depressive illness of any kind, although actually fairly effective for anxiety and obsessive-compulsive disorder.

DR. LESLIE LUNDT:

Well, as usual, Dr. Shorter you have taught us a lot that history can inform us from our treatment decisions of today.

DR. EDWARD SHORTER:

Well, nice of you to say that, Leslie.

DR. LESLIE LUNDT:

Thank you for being on our show.

DR. EDWARD SHORTER:

Pleasure talking with you.

DR. LESLIE LUNDT:

We have been speaking with Dr. Edward Shorter, the author of – Before Prozac: The Troubled History of Mood Disorders In Psychiatry,

about the changing landscape of psychiatric medications over the last 50 years.

I am Dr. Leslie Lundt, you are listening to ReachMD.com on XM160, the Channel for Medical Professionals. Please visit our web site at www.reachmd.com, which features our entire library through on-demand pod casts or you can give us a ring toll-free with your comments and suggestions at (888-639-6157). Thank you for listening.