

Manufacturing Depression by Gary Greenberg

A new drug trial promised to be the magic bullet that would rid Gary Greenberg of his depression. But, as this exclusive extract from his acclaimed new book, *Manufacturing Depression*, reveals, he couldn't hide his suspicions at the motives of the pharmaceutical giants who peddle the pills

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- Gary Greenberg
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Toward the end of my second visit to Massachusetts General Hospital, just before I got my pills, the psychiatrist leading the trial for a new antidepressant treatment, George Papakostas, asked me how long it had been since I had felt good for any appreciable time.

"Good?" I asked him.

"Symptom free," he said.

"For how long?" I asked.

"Thirty days," he said. "Or more."

I wanted to remind him that I was a writer, that I counted myself lucky to feel good from the beginning of a sentence to the full stop.

I wanted to ask him if he had ever heard of betrayal, of disappointment, of mortality.

But after having spent nearly two hours co-operating with him, helping him to transmute my messy words into precise data – the formulaic questions of the Hamilton Depression Rating scale that had determined that my complaints added up to "major depression" – I somehow didn't feel free to remind him that we hadn't really agreed that I had symptoms. I'd submitted to his alchemy. I couldn't just turn myself back into lead.

"I'm sorry," I said. "But I have no idea what a month of feeling good would feel like."

I'm sure this only confirmed his diagnosis.

But "30 days" was ringing in my ears as I left his office with my brown bag full of pills. And much as I wanted to dismiss the very possibility of that symptom-free month, chalk up the idea to a laughably circumscribed view of humankind, much as I

wanted to point to Aristotle and Abraham Lincoln and other important sad sacks as evidence against the neurochemical reductionism that lay behind this whole antidepressant enterprise, I had to admit something: 30 days of unbroken contentment, of peace of mind, of resilience and, yes, even of optimism, a month of bright light unfiltered by a black veil – that sounded pretty good. If health is happiness in month-long blocks, then suddenly the idea that unhappiness is a curable disease didn't seem like such a bad one.

I ducked inside a restaurant. I wasn't hungry, but I ordered a sandwich anyway. And a glass of water. I gulped down my six golden pills. I waited for my month to begin.

Was George Papakostas thinking of the placebo effect when he asked me that question? I don't think so. But maybe he should have been.

Placebos trouble doctors. There's too much magic in them and not enough science. They highlight a subject that most physicians would prefer to avoid: that they may not entirely deserve the power that they wield. The word itself, which is Latin for I will please, contains more than a hint of condescension, as if the doctor is merely tossing a pill at whiners, and as if the reason that the placebo effect persists is that people are too credulous (or perhaps too dumb) to get well by virtue of science alone.

It is, though, possible to specify how a placebo will affect its taker. Especially when it comes to psychoactive drugs, you can fool many of the people a great deal of the time. You can, for instance, give people fake alcohol (without, of course, telling them that it only tastes like the real thing) and put them in a crowd of socialising drinkers and watch them get "drunk". You can give them fake morphine and hear them sigh in relief as their pain goes away. You can tell one group of subjects that caffeine will impede their co-ordination, another group that it will improve it, give both groups decaf, and observe as everyone behaves accordingly.

Psychologists have had a great deal of fun investigating this phenomenon, and while they disagree about much of it, they have been able to arrive at the not-so-startling conclusion that when it comes to mind-altering drugs, expectation shapes response. People given fake alcohol already know how to be drunk, knowledge they have acquired from experience, perhaps, or from observing others – in short, from what Norman Zinberg, a drug researcher of the 1960s and 1970s, called the "setting" of drug use. Setting, Zinberg argued, was only one of three interacting factors that determined the nature of drug experience. The other two were the biochemistry of the drug and the mindset of the user – his psychological makeup, his expectations and desires and motivations for taking the drug in the first place. The effects of drugs, Zinberg said, had to be understood in all three dimensions – drug, set and setting.

Zinberg cited all kinds of evidence for the importance of this trinity. He found, for instance, that the effects of marijuana had changed over time. Research in the 1950s and 1960s showed that people had to smoke pot two or three times before they could get high on the drug – an effect thought to be the result of some kind of neurochemical process. But by the late 1970s, this was no longer the case. "As a result of accumulated knowledge about the effects of marijuana use," he wrote, "even first-time users are prepared to experience the high and therefore many have done so."

Pot use had become so widespread that virtually no one, not even a pot virgin, could be naive to its effects – and this change in setting changed the effect of the drug.

Zinberg, who died in 1989, never wrote about antidepressants like Prozac. But there is an obvious connection between his theory and the magic-bullet ideas behind them. After all, if pain goes away when people think they are taking morphine, then it doesn't make much sense to talk about psychiatric drugs as compounds that merely straighten out the twisted molecules that give rise to psychic suffering – at least not without giving due consideration to the expectations the doctor hands the patient along with the prescription.

And it really doesn't make sense to pretend that what happens between doctor and patient doesn't matter, that when he asks you about your sleep and your appetite and your sex drive, or about that elusive 30 days, he is only assessing your symptoms, and that when he tells you you are getting better he is only reporting the facts. He's also loading the dice, helping his drug give you a particular experience by telling you what to look for.

The first drug touted as an antidepressant was amphetamine. An ad that ran in a 1945 issue of the *American Journal of Psychiatry* featured a photograph of a man in a business suit, hands on hips, smile on his face, eyes on the horizon as if he is glimpsing the good fortune that awaits him there. Looming behind him, barely distinguished from the background, is a close-up of his face in a different mood – brow furrowed, eyes downcast, mouth curling into a frown. "If the individual is depressed or anhedonic, you can change his attitude by physical means," the ad copy reads. Doctors, it continues, have known this for at least 20 years, but only in the last decade has the "agent of cure" been available: Benzedrine, "a therapeutic weapon capable of alleviating depression."

Smith Kline & French, maker of Benzedrine, wasn't suggesting that doctors give amphetamine to psychotic manic-depressives – people who would be hospitalised and for whom the cure of choice was still the shock therapies – but to outpatients with what were then thought of as reactive or neurotic depressions. And amphetamine often pulled such patients out of their funks. Its problems – chiefly that it was addictive and its effects unstable – were soon obvious, however, and it fell into disfavour (until it was resurrected in the 1960s as a cure for attention deficit disorder, an indication that was worth \$1.5bn in sales of various stimulants in 2008).

In 1955, Wallace Laboratories, an arm of the company that made Carter's Little Liver Pills, came up with an alternate treatment for neurotic depression: meprobamate, which the company named Miltown. Full-page ads in medical journals told doctors of the "outstanding effectiveness ... with which Miltown relieves ... anxious depression". And, perhaps most important, patients loved it. Within a few years of its introduction, people were "miltowning": turning on with a "Miltown cocktail" – a pill washed down with a bloody mary – and then tuning in to "Miltown" [comedian Milton] Berle in such large numbers that drugstores often had to hang out "No Miltown today" signs.

By 1965, Wallace had sold 14bn of its little brain pills to 100 million satisfied customers. The only limit on Miltown's sales was another group of minor tranquillisers – the benzodiazepines, which included Valium and Librium, both

invented in the early 1960s by Hoffman-La Roche. The industry pushed the minor tranquillisers hard – not only to psychiatrists but also to general practitioners, the doctors most likely to see the "minorly" depressed.

Valium eventually took up more medical journal advertising pages than any other pharmaceutical drug, and by 1972, it was the most commonly prescribed drug in the world – a position it occupied until the end of the decade.

The minor tranquillisers' success wasn't all hype. In 1972, David Wheatley, one of the earliest antidepressant researchers in the UK, reported on a series of trials testing antidepressants against minor tranquillisers and concluded that the latter were better at treating neurotic depression – a finding echoed in studies that appeared in the *New England Journal of Medicine* and the *Journal of the American Medical Association (JAMA)*.

But the real boon to the drug industry was not so much the drugs themselves as the emergence of a vast new market: people whose suffering wasn't bad enough to warrant a visit to a psychiatrist's office but who would confess it to their family doctor and then gladly take Miltown or Valium. Miltown, according to medical historians Christopher Callahan and German Berrios, was the first "product of the pharmaceutical industry (rather than academia) [that] responded to consumer demand", and the success of the minor tranquillisers capitalised on this response. It's impossible to know how much patients' newfound willingness to talk about their discontents was due to their knowledge that it might be rewarded with a Miltown buzz, but industry executives didn't need to consider that. What they knew was that patients were now convinced that the whole world, including them, could be insane, that the insanity could be treated with a minor tranquilliser, and that family doctors, and not psychiatrists, held the keys to the Valium kingdom.

In the years since – years in which sales of the family of drugs including Prozac have superseded Valium as the magic bullets of choice – doctors were ready to give their patients a pitch: that they had a disease, that it was no different from any other disease (except perhaps for how widespread it is), and that the cure was waiting for them at the chemist. They were ready, in other words, to change the setting in which antidepressant use takes place, to name their patients' pain and create expectation for its cure, to mobilise, whether or not they meant to, the placebo effect.

And it wasn't only the doctors. The drug industry had help from a news media more than willing to report breathlessly on the new wonder drug (within a couple of years of its introduction, Prozac was featured on the covers of both *Newsweek* and *Time*).

And when the *JAMA* reported in early 1997 that still only 10% of the depressed were getting treatment, it seemed that the rising tide was capable of floating as many boats as the drug companies could launch. It was in that year that Lilly, the makers of Prozac, hired the Leo Burnett agency, to launch an ad campaign for Prozac.

According to a Burnett vice-president, "This is one of the most serious assignments we've ever had", and its mission was clear: to inform the public that, as Mike Grossman, Burnett's director of public relations, put it, "[Depression] isn't just feeling down. It's a real illness with real causes." Lilly spent \$22m in the last six

months of 1997 – nearly two-thirds of its entire advertising budget for the year – "assisting people in their depressed stupor," as Grossman put it, "to raise their hand for help."

The first ad was a three-page spread: a drawing of a rain cloud over the caption "Depression Hurts", a sun shining on the slogan "Prozac Can Help" and, on the last page, the fine print about side effects. It turned out that you didn't need to be in a depressed stupor at all, but merely under the weather, to have the "real illness" that "doctors believe" may be caused by "an imbalance of serotonin in your body". The copy under the cloud suggested: "You may have trouble sleeping. Feel unusually sad or irritable. Find it hard to concentrate. Lose your appetite. Lack energy. Or have trouble feeling pleasure."

And when people feel this way, the reader discovered, just before moving to the sunny side, "the medicine doctors now prescribe most often is Prozac."

You have to admire the economy of ads like these. They distil a century and a half of medical history into the simple message that if you are suffering, you may very well be sick, that your sickness is internal and biological, that it can be cured with a precision-targeted medicine and, above all else, that anyone can be depressed, that indeed the whole world can be insane.

Some critics worried that it just wasn't fair to deploy the techniques of consumer advertising – which, as the *British Medical Journal* put it in an editorial decrying the practice, is "the science of arresting the human intelligence long enough to get money from it" – on vulnerable people. Adam Block, an independent researcher at Harvard, estimated in 2007 that in America more than a half million doctors' office visits were inspired every year by consumer advertising of antidepressants. Using epidemiological data, he estimated that only one in 15 of those patients was likely to be depressed, but using statistics derived from other studies, he determined that more than half of them would get a prescription, which meant, he said, that only "6 percent of the increase in antidepressant use due to [direct-to-consumer] advertising is by people who are clinically depressed."

If you go to the Myths and Facts page of Pfizer's website you find the assertion that "Depression doesn't mean you have something wrong with your character. It doesn't mean you aren't strong enough emotionally. It is a real medical condition, like diabetes or arthritis." It's easy to see why the depression doctors want to make that comparison. Diabetes provides a classic magic-bullet scenario: your pancreas stops producing insulin (or, in the case of type 2 diabetes, your cells lose their ability to absorb insulin), and the deficiency is treated with regular medication. No one would be ignorant or insensitive enough to suggest that your illness is related to your character or your emotional strength. No one would blame the victim or imply that a diabetic is weak for taking his medicine. A depressed person who thinks of himself this way, in other words, is a loyal patient for life.

But doctors don't have to convince their diabetic patients that they have a "real illness". The symptoms generally speak for themselves. The doctor takes a urine sample and does a blood test. He doesn't have to talk about chemical imbalances that he knows aren't really the problem or contend with package inserts that say, in plain black and white, that the drug makers have no idea at all why their drug works.

And above all else, the diabetes doctor doesn't have to tell the patient that he is getting better. Which is what they kept telling me at Mass General. At the end of my fourth visit, George Papakostas finished jotting in his notebook and told me that my Hamilton score had dropped to 14, from my baseline of 18. This was the week after he had asked me about the 30 days of symptom-free living that I'd apparently been missing out on because of my disease. Had I heard him right? I asked. How long did he say I should be feeling good?

"For at least a month," he said.

Then I asked him why he wanted to know.

"People, when they're depressed," he answered, "they get a sort of recall bias. They tend to feel that their past is all depressed."

Which meant, I wanted to point out, that depression is more like an ideology than an illness, more false consciousness than disease, and that telling me I was getting better was like dispatching propaganda from a new regime.

But this wasn't the only way in which Papakostas was telling me what my disease consisted of or what health would be like. He also did it through the tests. They asked me about my sleep and appetite; they asked me if I thought my life had been a continuous process of learning, changing and growth.

They gave me zero points for seeing myself "as equally worthwhile and deserving as other people" and three for "thinking almost constantly about major and minor defects in myself". You don't have to be a weatherman to know which way that wind is blowing.

When Papakostas added up my Hamilton numbers and concluded that I was getting better, he didn't have to say in what way that was true. It was already in the air. And when he asked me, "Are you content with the amount of happiness that you get doing things that you like or being with people that you like?" he didn't have to tell me outright that this was the whole point: that to be healthy, to be back to yourself, was to be content. Which is a deep philosophical statement, and one that seems at odds with a consumer society and an economy that depends on our never being content, at least not too content to think that there is always some other happiness you could be pursuing at the mall. But he didn't make this claim as a philosopher.

He made it as a doctor. So we didn't have to talk about any of that.

On my last visit to Mass General I was seen not by Papakostas but by a woman named Christine Dording. She just had to look in the binder, riffle the pages, pause and then smile. "Look at your scores. Nice response."

I wasn't sure whom she was congratulating, but there wasn't any question who – or what – was responsible for my improved mental health. Or so I found out when she started talking about my next visit.

"Next visit?" I asked. "I thought this was the last."

"You're not coming in for the follow-up?" She seemed surprised and hurt and a little incredulous, as if no one with such a nice response would pass up the opportunity to get even better. I asked her if the follow-up would be any different from what we'd been doing. It wouldn't, she said. So I declined.

But she wasn't done with the subject. By then we'd adjourned to an examination room, where she was performing a cursory physical.

"I think you've done very well," she said as she looked into my eyes with a scope. "You're much improved."

But if the treatment made me better, I wanted to know, then why did I need any more follow-up? And for that matter, how did she know I wasn't on the placebo?

"I don't think we unblind the study," she told me, looking again through my binder.

"No, not in this one. No unblinding."

I protested. "I don't get to find out?" Was it possible that being much improved could have no other meaning than that the drug had worked its magic? Wasn't that what the study was supposed to find out?

"No," she said. "But you had a good response."

I didn't see the point in arguing, but a few months later, I called the doctor in charge of the study. I asked him why Dording had offered to keep me on the drugs when she didn't know if I'd been on them in the first place, and why neither of us was allowed to find out. He explained that clinical trials remain blinded so that researchers don't get tipped off by associating certain patterns of response with certain outcomes and thus start behaving differently toward patients whose condition they have deduced. But, he told me, seemingly unaware that he was contradicting himself, it is common practice for the doctors to "take their best guess" and offer follow-up accordingly.

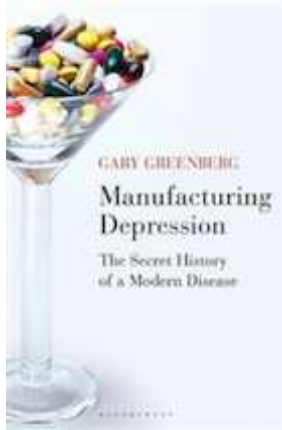
I wasn't going to let this mystery stand. I didn't know if I was really better. Some days I thought so. I wasn't feeling content exactly. But sometimes, on some days, there was some ineffable feeling, a flicker of belief, a floor beneath me that kept me from plunging into darkness, where I could stand and catch and hold love and goodness, dwell with it and feel, if just for a moment, that life wasn't only cruel and stupid. And maybe it was the pills that were making me feel that way.

Or maybe not.

I had some extra capsules. I sent them off to a commercial lab.

The report came back a couple of weeks later. I'd been on the placebo.

Extracted from Manufacturing Depression by Gary Greenberg, published by Bloomsbury on Tuesday, price £20.



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