The New York Review of Books

‘The Illusions of Psychiatry’: An Exchange

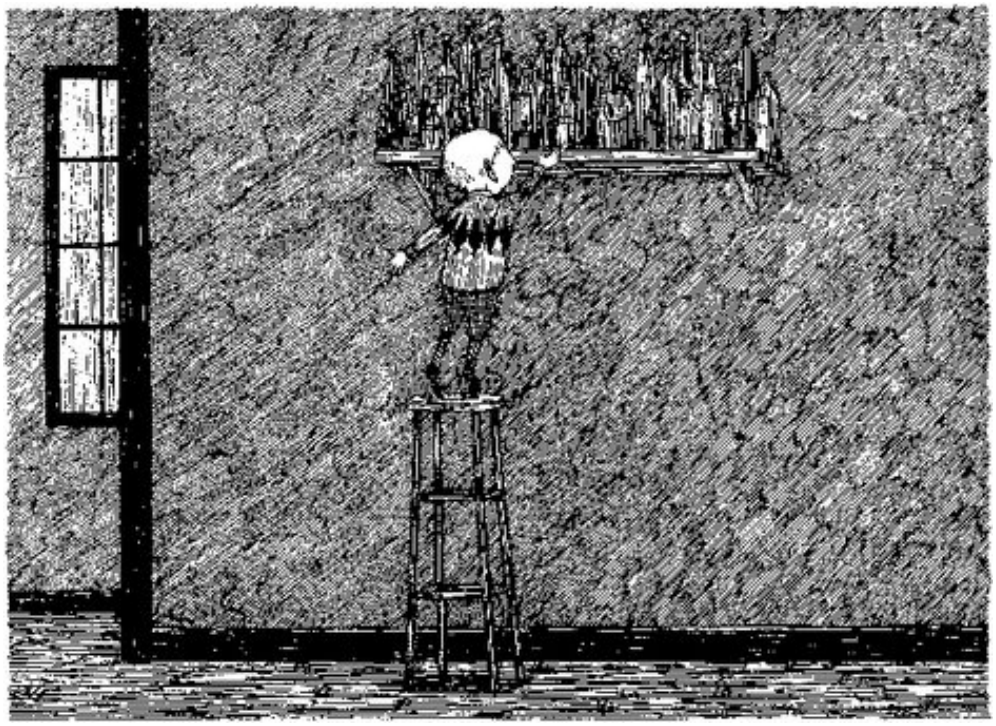
AUGUST 18, 2011

John Oldham, Daniel Carlat, Richard Friedman, and Andrew Nierenberg, reply by Marcia Angell

IN RESPONSE TO:

The Illusions of Psychiatry from the July 14, 2011 issue

The Epidemic of Mental Illness: Why? from the June 23, 2011 issue



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To the Editors:

In its June 23 edition, *The New York Review* chose to review three books that are highly critical of modern psychiatry. We regret that a more balanced approach was not taken.

Dr. Marcia Angell writes of a “raging epidemic” in mental illness, citing the fact that there are more individuals receiving disability payments for mental illnesses than ever before. While this is accurate, her article suggests that this is a false crisis that owes its existence to

the discovery of psychotropic drugs starting in the 1950s. This creates the impression that Americans are overtreated for mental illnesses. Nothing could be further from the truth. The National Institute of Mental Health reports that currently only 36 percent of those who suffer from mental illnesses actually seek and receive treatment. This is especially concerning given the fact that comprehensive, biopsychosocial treatment of mental illnesses is increasingly effective, comparable to or at times greater than the effectiveness of treatment for many other medical disorders, such as heart disease and diabetes.

Dr. Angell and the authors she reviews also suggest that psychiatry, in general, regards mental illnesses through the reductionist lens of an imbalance of chemicals in the brain. Although psychotropic medications have been found to alter the balance of neurotransmitters in the brain, there is no consensus on whether these imbalances are causes of mental disorders or symptoms of them. The bottom line is that these medications often relieve the patient's suffering, and this is why doctors prescribe them. It does not mean, as Dr. Angell suggests, that mental disorders were invented in order to create a market for psychotropic drugs. The disorders that these medications (and other therapies) treat have been around for all of recorded history. The difference is that today, thanks to medical and therapeutic advances, there is real help for those who suffer the devastating effects of mental illness.

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To the Editors:

In her two articles, "The Epidemic of Mental Illness: Why?" [*NYR*, June 23] and "The Illusions of Psychiatry" [*NYR*, July 14], Marcia Angell takes aim at modern American psychiatry, and finds plenty of shortcomings. Her argument is correct in its essentials. Psychiatrists often overdiagnose disorders of questionable scientific validity, they have become overly fixated on medication solutions to life's problems, and many have accepted a steady flow of drug industry money, creating so many conflicts of interest that it is impossible to know who we can trust.

But missing from her review is an unequivocal if perplexing truth about psychiatric drugs —on the whole, they *work*. Antipsychotics for schizophrenia, stimulants for ADHD, hypnotics for insomnia, benzodiazepines and SSRIs for anxiety disorders—in all these cases, drugs are robustly more effective than placebos in double-blind controlled trials. Even Robert Whitaker, in his *Anatomy of an Epidemic*, concedes that these drugs are

effective in the short term—it is the potential long-term effects that he discusses. Whitaker makes the argument that used long-term, all psychiatric drugs are essentially poisonous to the brain and have led directly to skyrocketing rates of psychiatric disability. While his arguments are intriguing, I agree with Dr. Angell that there are significant weaknesses in the evidence he marshals.

Dr. Angell makes much of the fact that we do not understand the mechanism of mental illness, nor of the drugs we use to treat it. While this is true, it does not mean that the drugs are ineffective—only that as psychiatrists, we should stop overselling ourselves as possessors of a sophisticated neurochemical knowledge of our craft.

My chief criticism of Dr. Angell's review is an uncritical acceptance of the premises in Irving Kirsch's book, *The Emperor's New Drugs.* Dr. Kirsch, in reviewing his lifetime of research on antidepressant efficacy, concludes that antidepressants are no more effective than placebo pills for depression. But his actual research demonstrates quite the opposite. In his meta-analysis of six drugs, he found that active drugs were, in fact, significantly more effective than placebo. Kirsch then dismisses this statistical difference as having no "clinical significance," with which Dr. Angell concurs.

Other researchers disagree. For example, Erick Turner and colleagues (with no industry funding) conducted an even larger analysis, examining all available data, published and unpublished, on twelve of the most commonly used antidepressants. They found an almost identical benefit of drug over placebo as did Kirsch. While acknowledging that drug companies had boosted the apparent effectiveness of antidepressants by selective publication, they still found that, even including the negative data, all twelve antidepressants were statistically superior to placebo. Furthermore, in an editorial, they pointed out that Dr. Kirsch's judgment about the lack of "clinical" significance was based on an arbitrary cut-off point suggested by the UK's National Institute for Health and Clinical Excellence, a cut-off point with little if any scientific validity.

There is no question that among the medical professions, psychiatry is the most scientifically primitive. We have no more than the most rudimentary understanding of the pathophysiology of mental illness and we have resorted to tenuous and ever-shifting theories of how our treatments work. Dr. Angell's review highlights these truths well, but at the same time gives short shrift to the very real benefits that we still provide our patients.

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To the Editors:

Marcia Angell's review "The Epidemic of Mental Illness: Why?" contains serious factual and conceptual errors about the nature and treatment of psychiatric illness and it uncritically repeats the false assertions about the safety and efficacy of psychotropic drugs.

To start, psychiatric illnesses are diagnosed on the basis of signs and symptoms. With the exception of substance-induced disorders, we do not know the cause of most mental disorders. But medicine is no different; aside from infectious diseases, the cause of diseases like cancer, hypertension, and arthritis is unknown.

This hasn't stopped physicians from relieving the suffering of arthritis with anti-inflammatory drugs like Advil or treating hypertension with drugs that lower blood pressure.

Likewise, psychotropic drugs relieve symptoms like depression, anxiety, and psychosis, not by targeting the root cause of these disorders, but by affecting neuronal function to bring relief.

Angell uses an outdated and disproven chemical imbalance theory of depression (i.e., serotonin deficiency) as a straw man to deny that depression has any biological basis at all and, by extension, doesn't even qualify as a disease. Angell appears unaware of recent advances in neuroscience research that demonstrate that depression is not a disease of a single neurotransmitter system or brain region but probably a disorder that involves multiple neural circuits and neurotransmitters. For example, Helen Mayberg has shown that directly stimulating the subgenual cingulate cortex can reverse depressive symptoms in patients who have failed to respond to multiple anti- depressants and electroconvulsive therapy.

Angell's dismissal of the biological basis for psychiatric illness is hard to fathom given our clear understanding of how recreational drugs affect the brain to change mood and thinking. Surely anyone who's ever had a drink knows that there must be a biological substrate to mental states and, by extension, that you cannot have a credible model of the mind, whether healthy or afflicted, without understanding the function of the brain.

What of Angell's claim that antidepressants are no better than placebo? The evidence she cites comes mainly from the psychologist Irving Kirsch who published a meta-analysis of forty-two clinical trials. Kirsch reported an average difference between drug and placebo of 1.8 points on the HAM-D, a scale of depressive severity. However, a subsequent reanalysis

by Konstantinos Fontoulakis showed that Kirsch's meta-analysis was flawed: he miscalculated the mean drug-placebo difference (it is actually 2.68, not 1.8) and overstated his conclusions.

It is true that antidepressants are only modestly effective in acute depression. But Angell does not tell readers that response rates to antidepressants are roughly equivalent to the effect size observed in psychotherapy studies. Nor does she mention the critically important fact that depression is frequently a chronic recurring illness and that antidepressants are highly effective in preventing relapse. A recent meta-analysis by John Geddes in 2003 of thirty-one long-term relapse prevention studies found a relapse rate of 41 percent for placebo but only 18 percent for antidepressant.

What about the inflammatory claim that psychiatric drugs increase the rates of psychiatric disorders? If so, one would expect to see a steady increase in the prevalence of mental disorders in the population. But the epidemiologic evidence shows otherwise. As Ronald Kessler reported in *The New England Journal of Medicine* (June 16, 2005), data from the National Comorbidity Survey show that the prevalence of anxiety, mood, and substance disorders has been stable: it was 29.4 percent in 1991 and 30.5 percent in 2003. This is hardly a "raging epidemic of mental illness," as Angell calls it. What did increase during this period was the number of people receiving treatment: from 20 percent in 1991 to 32 percent in 2003, meaning the vast majority of mentally ill Americans did not receive any treatment. These are people with life-threatening illnesses at high risk of suicide who have impaired functioning. And they are the patients for whom psychotropic drugs can be life-saving.

This does not seem to bother Angell, who instead cites tragic anecdotes about the dangers of off-label use of psychotropic medication, like the young girl with ADHD who died from a combination of Clonidine and Depakote. Of course, such a case is heartbreaking, but it hardly proves that there is an epidemic of harmful off-label use of psychotropic medication.

Angell is right that we should follow the dictum "first, do no harm," but she has distorted the potential adverse effects of psychotropic drugs with anecdotes and flawed data and downplayed the devastating consequences of untreated psychiatric illness. It would be sad —and harmful—if any patients were discouraged from seeking safe and effective psychopharmacological treatment on the basis of Angell's uncritical and biased review.

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Financial Disclosures: Dr. Friedman receives no support from the pharmaceutical industry. Dr. Nierenberg is a full-time employee of the Massachusetts General Hospital (MGH) and has disclosed all external sources of revenue to Harvard Medical School and Partners Health care to the best of his knowledge and in accordance with current regulations. External activities were limited to no more than eight hours per week. In the past thirty-six months (as of July 6, 2010) he has served as a consultant to: Appliance Computing Inc. (Mindsite), Brain Cells, Inc., Brandeis University, Bristol Myers Squibb, Clintara, Dianippon Sumitomo (Now Sunovion), Eli Lilly and Company, EpiQ, Novartis, PamLabs, PGx Health, Shire, Schering-Plough, Takeda Pharmaceuticals, and Targacept. He has consulted through the MGH Clinical Trials Network and Institute (CTNI): Astra Zeneca, Brain Cells, Inc., Dianippon Sumitomo/Sepracor, Johnson and Johnson, Labopharm, Merck, Methylation Science, Novartis, PGx Health, Shire, Schering-Plough, Targacept, and Takeda/Lundbeck Pharmaceuticals. He has received grant/research support through MGH from AHRQ, Cephalon, NIMH, PamLabs, Pfizer Pharmaceuticals, and Shire.

Dr. Nierenberg received honoraria or travel expenses including CME activities from: APSARD, Belvoir Publishing, University of Texas Southwestern Dallas, Hillside Hospital, American Drug Utilization Review, American Society for Clinical Psychopharmacology, Bayamon Region Psychiatric Society, San Juan, Puerto Rico, Baystate Medical Center, Canadian Psychiatric Association, Columbia University, Douglas Hospital/McGill University, IMEDEX, International Society for Bipolar Disorders, Israel Society for Biological Psychiatry, John Hopkins University, MJ Consulting, New York State, Massachusetts Association of College Counselors, Medscape, MBL Publishing, Physicians Postgraduate Press, Slack Publishing, SUNY Buffalo, University of Florida, University of Miami, University of Wisconsin, University of Pisa, and SciMed.

Dr. Nierenberg is a presenter for the Massachusetts General Hospital Psychiatry Academy (MGHPA). The education programs conducted by the MGHPA were supported through

Independent Medical Education (IME) grants from the following pharmaceutical companies in 2008: Astra Zeneca, Eli Lilly, and Janssen Pharmaceuticals; in 2009 Astra Zeneca, Eli Lilly, and Bristol-Myers Squibb. No speaker bureaus or boards since 2003. Dr. Nierenberg owns stock options in Appliance Computing, Inc. and Brain Cells, Inc. Additional income is possible from Infomedic.com depending on overall revenues of the company but no revenue has been received to date. Through MGH, Dr. Nierenberg is named for copyrights to: the Clinical Positive Affect Scale and the MGH Structured Clinical Interview for the Montgomery Asberg Depression Scale exclusively licensed to the MGH Clinical Trials Network and Institute (CTNI).

Marcia Angell *replies*:

All three of these letters simply assume that psychoactive drugs are highly beneficial, but none of them provides references that would substantiate that belief. Our differences stem from the fact that I make no such assumption. Any treatment should be regarded with skepticism until its benefits, both short-term and long-term, have been proven in well-designed clinical trials, and those benefits have been shown to outweigh its harms. I question whether that is so for many psychoactive drugs now in widespread use. I have spent most of my professional life evaluating the quality of clinical research, and I believe it is especially poor in psychiatry.

The industry-sponsored studies usually cited to support psychoactive drugs—and they are the ones that are selectively published—tend to be short-term, designed to favor the drug, and show benefits so small that they are unlikely to outweigh the long-term harms. The problem with relapse studies, like that of John Geddes, which is cited by Friedman and Nierenberg, is that they don't distinguish between a true relapse and withdrawal symptoms that result from the abrupt cessation of drugs.

Both the pharmaceutical industry and the psychiatry profession have strong financial interests in convincing the public that drug treatment is safe and the most effective treatment for mental illnesses, and they also have an interest in expanding the definitions of mental illness. Even Dr. Carlat, whose excellent book I reviewed, admitted that he and other psychiatrists make nearly twice as much money prescribing drugs as providing talk therapy. In his letter, which seems somewhat inconsistent, he states that the "unequivocal, if perplexing truth about psychiatric drugs" is that "they *work*" (his italics), and that all the major psychoactive drugs "are robustly more effective than placebos in double-blind controlled trials." (In fact, the trials yield varying outcomes, many of which fall far short of robustness.) But elsewhere in the letter, he says, "There is no question that among the medical professions, psychiatry is the most scientifically primitive," and in his book, although he claims anti- depressants work, he comes close to Kirsch in concluding that

"much of this response is undoubtedly due to the placebo effect."

Carlat mischaracterizes Kirsch's work by suggesting that he contradicted himself. Kirsch did indeed find that the six antidepressants he studied were more effective than placebos, but the difference was very small (similar to the difference found by Turner and his colleagues, in the study cited by Carlat). Kirsch then speculated that even this small effect might not be real, because patients who received the antidepressant instead of an inert placebo would experience side effects that might enable them to guess that they were receiving an active drug, and therefore might make them more likely to report an improvement in their depression. In support of this hypothesis, Kirsch pointed to a few trials employing placebos that themselves had side effects, where no differences were found between drug and placebo. But despite the persuasiveness of his theory, Kirsch acknowledged that it remains to be proven.

The UK's National Institute for Health and Clinical Excellence (NICE) develops treatment guidelines for the National Health Service on the basis of benefits and costs. It concluded that because improvements in the 51-point Hamilton Depression Score (HAM-D) of less than three points are not clinically discernible, antidepressants that on average fail to provide at least that level of improvement could not be recommended. While that cut-off is indeed arbitrary, as Carlat says, so are many other conventions in medicine, e.g., the number of symptoms required for a diagnosis of a major depressive episode or the accepted standard (P less than 0.5) for statistical significance. The NICE cut-off strikes me as eminently reasonable. Friedman and Nierenberg point out that a reanalysis found a 2.68 point difference instead of a 1.8 difference, but that is still below NICE's threshold for clinical significance.

Contrary to Dr. Oldham, I did not say that mental disorders were invented in order to create a market for psychotropic drugs. What I did say is that the boundaries of mental illness are being stretched for a variety of reasons—to increase drug company sales, to enhance the income and status of the psychiatry profession, and to get insurance coverage or disability benefits for troubled families. It may be that, as Oldham says, the disorders that these medications treat have been around for all of recorded history, but they weren't necessarily considered "disorders," rather, simply emotional states or personality traits. Just as a cigar is sometimes only a cigar, unhappiness might have been considered just that, not a medical condition.

The letter by Drs. Friedman and Nierenberg is filled with inaccuracies and assertions masquerading as fact. They are simply wrong in asserting that psychiatry, in using drugs to treat signs and symptoms of illness without understanding the cause of the illness or how

the drugs work, is no different from other medical specialties. First, mental illness is diagnosed on the basis of symptoms (medically defined as subjective manifestations of disease, such as pain) and behaviors, not signs (defined as objective manifestations, such as swelling of a joint). Most diseases in other specialties produce physical signs and abnormal lab tests or radiologic findings, in addition to symptoms.

Moreover, even if the underlying causes of other diseases are unknown, the mechanisms by which they produce illness usually are, and the treatments usually target those mechanisms. For example, we may not know what causes arthritis, but we do understand a great deal about the mechanism, and we know how anti-inflammatory agents work. Even when there are only symptoms, such as nausea or headache, other medical specialists, unlike psychiatrists, would be very reluctant to offer long-term symptomatic treatment without knowing what lies behind the symptoms.

Contrary to Friedman and Nierenberg, I do not "deny that depression has any biological basis at all." I know very well that all thoughts, emotions, and behaviors have their origin in the brain. But it is a great leap from recognizing the obvious fact that mental states arise in the brain to knowing why and how they arise. Friedman and Nierenberg make much over recent advances in neuroscience research, but so far this research hasn't produced much improvement in diagnosis and treatment.

In fact, Allen Frances, the chairman of the task force that wrote the current version of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), opposed undertaking the ongoing revision because he thought there had not been sufficient new data on the biological causes of mental illness to justify a new edition. As for the chemical imbalance theory of depression being a straw man, I still hear it invoked frequently. Even Oldham seems to entertain it in his letter, saying "…there is no consensus on whether these imbalances are causes of mental disorders or symptoms of them."

Friedman and Nierenberg are right that the National Comorbidity Survey showed very little change in the prevalence of three particular types of mental disorders in adults between 1991 and 2003, although the increase in the percentage of people treated was dramatic. But the frequency of some diagnoses, such as bipolar disease and autism, has soared. Moreover, the survey showed a prevalence of mental illness of about 30 percent, which surely represents either a major epidemic or rampant overdiagnosis. One of the most remarkable findings was that 20 percent of randomly selected adults were undergoing treatment for emotional disorders at the time of the later survey, about half of whom did not even meet the DSM-IV criteria for a mental disorder.

Friedman and Nierenberg refer to the death of Rebecca Riley, who was diagnosed with bipolar disorder as well as ADHD when she was just two years old, as a "tragic anecdote." While that is true, I believe it should also be seen in the context of the extraordinary epidemic of juvenile bipolar disease that was stimulated largely by the teachings of some of Dr. Nierenberg's colleagues at the Massachusetts General Hospital. Three of them were recently disciplined by the hospital for not having disclosed some of their hefty payments from drug companies.

If readers check the *NYR* website, they will see that Dr. Nierenberg discloses his external sources of income, which include consulting arrangements with some of the major manufacturers of psychoactive drugs. While I am not in a position to, and will not, comment on Dr. Nierenberg's consulting work, it seems to me that in general, one of the risks of close collaborations with industry is that even the best of physicians might develop an insufficiently critical attitude toward a company and its products, as well as to pharmacologic treatment generally.

Dr. Friedman seems to agree. In a review of a book by Alison Bass, published in *The New England Journal of Medicine* (June 26, 2008), he refers to the handsome payments by drug companies to physician researchers who test their drugs, and goes on to say, "Bass's riveting and well-researched account of these disturbing ties should be widely read by members of the medical profession, many of whom continue to believe, despite all evidence to the contrary, that they are immune to the influence of drug companies."

Finally, Friedman and Nierenberg accuse me of downplaying the devastating consequences of untreated psychiatric illness. I do no such thing. But it is no favor to desperate and vulnerable patients to treat them with drugs that have serious side effects unless it is clear that the benefits outweigh the harms.