COMMENTARY

THE LIMITS OF BIOLOGICAL PSYCHIATRY

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Psychoanalysts have struggled for decades with the issue of psychiatric medications. Despite Freud's predictions of future biologic treatments (Freud 1940), psychoanalysts were reluctant, generally speaking, to accept the use of medications because it was assumed that medicines treated symptoms only, and did nothing to cure the underlying problems. Medications were believed to actually be counterproductive to analysis because by relieving symptoms, they would take away the patient's motivation for working in analysis (Marmor, 1981).

More recently, psychoanalysts have by and large taken a more pragmatic approach. If prescribing a pill works, prescribe it. If it helps, use it. To some degree, analysts have had to adopt this approach because the biologic revolution has had such sweeping momentum that analysts were in danger of losing business or becoming irrelevant. Medications seem to bring about relief far more quickly and inexpensively than analysis. Third-party payers often only pay for treatment if medication is prescribed. Psychiatric medications are believed by many to be the standard of care, which causes many therapists and analysts to fear that they are placing themselves in legal jeopardy by not prescribing or referring for medications.

A recent issue of *Psychoanalytic Inquiry* (*18* [No 5], 1998) was entirely devoted to the subject of psychiatric medications and it typified the current level of discussion among psychoanalysts as they debate how to integrate (or not) biologic and psychoanalytic models. The issue has also been a renewed topic of interest at psychoanalytic meetings. Underlying all sides of the discussion is the assumption that psychiatric medications are effective. This assumption, however, needs to be challenged. I will limit the scope of this challenge to antidepressant medicines, because 90% of the medicines prescribed for patients undergoing psychoanalysis are antidepressants (Roose and Johannet, 1998).

From a historical perspective, it should be noted that nearly every civilization has had effective medicinal treatments for depression. The list of reputed antidepressants would be several pages long. Probably

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the dominant cure for over 2000 years of Western and Greek culture was Galen's theriac. It even appeared in the German and French pharmacopoeias as late as 1872, and was occasionally prescribed in Europe as recently as 50 years ago, with strong testimonials to its effectiveness (Shapiro and Shapiro, 1997).

The first antidepressant of the modern era was iproniazid. Newspapers reported in 1952 that tuberculosis patients treated with iproniazid were dancing with joy in the hospital corridors. Initially this was considered an annoying side effect, but soon iproniazid had a widespread market as an antidepressant. By 1959 it had been prescribed for 400,000 patients, despite the fact that the only two placebo-controlled trials of iproniazid at that time showed it to be no more effective than placebo (Valenstein, 1998). It did, however, occasionally cause a toxic manic psychosis, which apparently was enough to perpetuate the myth of its effectiveness as an antidepressant.

Within just a few years several tricyclics were serendipitously discovered and placed on the market as antidepressants. At about the same time norepinephrine and serotonin were discovered to be neurotransmitters and the old theory of electrical communication between brain cells began to give way to a theory of chemical transmission. The tricyclics were all found to increase serotonin and norepinephrine levels to varying degrees. This led to the monoamine hypothesis of depression: If antidepressants boost serotonin and norepinephrine transmission, then perhaps depression was caused by low levels of those neurotransmitters. Without further evidence, this "chemical imbalance" theory was promoted vigorously, and still is the predominant theory of depression today. Efforts to prove the theory, however, have had confusing and contradictory results. One study, for example, found that CSF 5-HIAA levels were abnormally low in about 25% of depressed patients, but within the normal range for 50% of patients, and actually above the normal limits for the remaining 25%. But rather than admit that their hypothesis of a chemical imbalance causing depression was not supported, the authors did whay biopsychiatrists often do in such situations—they claimed that their hypothesis appeared to be true for a subset of patients (Valenstein, 1998).

To date, "no biochemical, anatomical, or functional signs have been found that reliably distinguish the brains of mental patients" (Valenstein, 1998, p. 125). Nonetheless, our knowledge of brain functioning has expanded. We know that there are over 100 neurotransmitters. Still, mostly out of ignorance of other neurotransmitter systems, the serotonin system remains the favored theoretical mechanism of antidepressant action, and the favorite target of new antidepressant development. We have

learned that there are 15 serotonin receptor types with multiple subtypes. We have learned that serotonin functions in multiple neuronal and non-neuronal (including endocrine) pathways. Serotonin can function as a neurotransmitter, a neuromodulator, or a neurohormone and can have differential effects in different parts of the brain (Murphy et al., 1998). Each manipulation of serotonin receptors sets into effect an almost infinite series of complex reactions.

Pharmaceutical companies market serotonin drugs as acting on this or that specific receptor subtype, but in fact, those simplistic explanations cannot be true. For example, antidepressants have their effects on receptors almost immediately for every person who takes the drug, but the antidepressant effect occurs in only 60% to 70% of patients, and then only after a delay of days to weeks. Obviously more complex mechanisms are at work. Murphy et al. (1998), after a thorough review of the literature on serotonin systems, concluded "even partial understanding of the final mechanisms involved in the therapeutic effects of drugs like the SSRI antidepressants continues to be elusive" (p. 10). The only known chemical changes brought about by antidepressants are those that are associated with impairments in brain functioning (Breggin, 1997). The idea that we can bathe the brain in a foreign chemical and have it improve brain functioning in any way is naïve; as naïve as trying to fix a computer glitch by spraying chemicals onto the mother board. But more than that, we are expected to believe, without evidence, that the drug can precisely correct a hypothetical imbalance without doing significant damage to the remaining vast and complex systems of the brain.

Even if we do someday identify an underlying chemical imbalance or other biologic marker of depression, we would still be a long way off from establishing the biologic model of depression. Specifically, it would not establish causation. We know that brain anatomy, chemistry, and functioning are plastic and influenced by environmental factors—including psychotherapy. An example would be the finding that patients who commit suicide have low 5-hydroxyindole acetic acid (5-HIAA) levels in their spinal fluids. This particular example is pertinent because fear of a patient's suicide drives many therapists to prescribe or refer for medications in a desperate attempt to leave no stone unturned, and limit liabilities. However, the low cerebrospinal fluid (CSF) 5-HIAA in suicide subjects, though statistically significant, is not specific. Furthermore, there is considerable overlap between subjects and normal controls. It could well be that the lower levels were a result of high levels of stress in the moments prior to suicide. Animal models have shown that stress lowers CSF 5-HIAA levels (Valenstein, 1998). Even if we were to concede that low CSF 5-HIAA levels had a causal relationship

with suicide (rather than being merely correlational), it is still not established that antidepressants are of any value. To date, no study has demonstrated that antidepressants lower suicide rates (although some have shown a decrease in suicidal thinking). Patients in research protocols are as likely to commit suicide if they are in the antidepressant group as they are in the placebo group. The huge expansion in antidepressant use in this country over the last few decades has not been accompanied by a decrease in suicide rates (Fisher and Greenberg, 1997).

A pragmatist would have little interest in this discussion of biologic mechanisms. The question remains: Do antidepressants help depressed patients feel better? Undoubtedly they do. There are millions of testimonials to life-changing effects of antidepressants. Even theriac had its enthusiastic supporters for thousands of years. But as a matter of pragmatics, how helpful are antidepressants? Meta-analyses of controlled studies usually put the success rate at about 60%–70%. That is, about 60%–70% of patients in controlled studies improve on antidepressants (Fisher and Greenberg, 1989, 1997). This should be tempered by the understanding that "improvement" does not mean cure. Usually it means a 50% reduction in Hamilton-D scores. One meta-analysis found that the low mean Hamilton-D score was 9.8 and ranged up to 16.2, even among those who met criteria for successful treatment in antidepressant studies. Unfortunately, those ranges still indicated significant impairment in work function as demonstrated by absenteeism, poor work performance, and/or significant interpersonal conflict (Fawcett and Barkin, 1997). If you ask what percentage of patients on antidepressants improve to the point of no longer being impaired, the answer is probably about 30% (Nemeroff, 1998).

More significant is the fact that the 60%–70% improvement rate is only marginally better than the 30%–40% achieved with placebo (Fisher and Greenberg, 1989, 1997). This means one would have to give the medication to three patients to achieve results better than placebo in one patient. The actual picture may be bleaker yet, because antidepressant trials using inert placebo (sugar pills) are not truly blind. Most research subjects are able to correctly "guess" whether they are being given an active agent or a placebo. This biases the study in favor of the active agent. Shapiro and Shapiro (1997) found that 93% of physicians conducting antidepressant research were able to correctly guess which patients were being given the active agent, as were 73% of the patients. The rate for crossover studies was 100% and 93%, respectively, presumably because the crossover design allowed participants to compare effects of active agent and placebo. This breaking of the blind conditions may perhaps have been forgivable if it had been based on effec-

tiveness of the active agent, but it was not. Adverse effects, but not improvement, were associated with correct guessing. In other words, patients and physicians are able to tell which patients are on the active agent based on adverse effects or so-called "side effects."

Howard et al. (1982) did a thorough investigation of the blindness of a study of the prophylactic use of aspirin for heart attacks. They found that 95 of their 271 subjects had taken measures to test whether they were being given aspirin or placebo, including tasting and smelling the capsule contents, testing the physiologic effects, doing acid tests, having the capsule analyzed professionally, evaluating the bleeding time, and checking blood aspirin levels.

Fisher and Greenberg (1989) report on efforts, seven studies in all, to try to safeguard the blindness of an antidepressant study by using an active placebo (atropine) rather than sugar. The results were the elimination of the difference in outcomes between antidepressant and placebo in all but one study. Apparently all that is really important for a good antidepressant response is that the medication produce some sort of physical effect in the context of the expectation of an antidepressant effect. This fits Dinnerstein and colleagues' (1966) concept that, "Rather than producing direct and unambiguous pharmacologic effects on a subject's pain or anxiety, drugs act primarily as amplifiers or inhibitors of the placebo effects" (p. 104).

Kirsch and Sapirstein (1998) did an elaborate statistical analysis of all 19 double-blind placebo-controlled studies (2318 patients) of antidepressants for which adequate data were available to determine within-condition effect sizes. They found that placebo was fairly consistently able to produce about 75% of the response of the active medication. What was especially interesting about their analysis was that the correlation between placebo effect and drug effect was 0.90. In other words, virtually all the variation between studies in the effectiveness of the antidepressant was a result of the placebo characteristics of the study. Additionally, effect sizes for medications not regarded as antidepressants (amylobarbitone, lithium, liothyronine, and adinazolam) were as large as for those classified as antidepressants. In all cases, inactive placebos produced improvement that was about 75% of the effect of the active drug, and "active placebos" matched the effects of the active drug. Kirscsh and Sapirstein (1998) conclude that antidepressants might function as "active placebos," in which the "side effects amplify the placebo effect by convincing patients that they are receiving a potent drug."

To say that antidepressants are active placebos is different from saying they are inert placebos. Antidepressants do have real chemical effects on the brain, though those effects are poorly understood. Most

patients—as many as 68% (Basco and Rush, 1995)—drop out of antidepressant treatment, primarily because of adverse effects. New information about the possibility of a form of medication dependence is an ominous development. Antidepressant withdrawal syndromes, including depression relapse, are being increasingly recognized (Haddad et al., 1998). Michael Thase reported to the New Clinical Drug Evaluation Unit sponsored by the National Institutes of Health that the rate of recurrence of depression after discontinuation of antidepressant medication is about 10 times higher than would be expected based on the natural history of the disease (cited in Sherman, 1997). This strongly suggests a real chemical-withdrawal effect. But to be consistent, I should consider that it may be a placebo-like effect. After all, patients may naturally expect that stopping an antidepressant may lead to depression, especially because psychiatrists commonly tell their patients that depression is a lifelong illness and medications may be necessary for life. But it is not unreasonable to attribute the high relapse rate to a physiologic process of the brain adapting to the discontinuation of the medication as withdrawal from nearly any psychoactive substance can cause dysphoria.

Take lithium as an example. It is not widely believed to be an antidepressant, but it has made headlines recently for its supposed ability to prevent suicide. Indeed, the study that this claim is based on (Tondo, 1998) showed a small drop in suicide rates in bipolar patients when placed on lithium. However, this small drop was not the basis of the claim of suicide reduction (wouldn't we expect the suicide rate to go down as time goes by?). Rather, lithium advocates point to the fact that suicide rates increased nearly tenfold in the year following lithium withdrawal (it then returned to about the prelithium level after a year). They claim this proves lithium prevents suicide, but a more straightforward interpretation of the data would be that lithium withdrawal raises suicide rates. Saying lithium prevents suicide is like saying alcohol prevents delirium tremens. Giving a suicidal patient lithium may be the worst thing we could do because very few people can tolerate taking it long term. Likewise, rather than telling patients they will need an antidepressant for life, we should tell them that once they start an antidepressant it may be very difficult for them to stop it.

Unfortunately, most psychiatrists would interpret withdrawal-induced relapse as a reemergence of the underlying biologic illness and proof that the patient needs continued medication, rather than recognizing it as a withdrawal effect. Patients deserve to be warned prior to starting an antidepressant that withdrawal may be difficult. Even slowly tapering the medicine leaves more than half of patients with some sort of significant withdrawal reaction (Antonuccio, 1999).

At this point, there is no evidence to counter Breggin's (1997) argument that antidepressants "work" by impairing brain functioning, for example, making the recipient less in touch with his or her emotions and less empathetic to others. Settle (1998) describes a syndrome with newer antidepressants, which he says is "common and increasingly appreciated," consisting of apathy and lethargy. He says it "resembles frontal lobe dysfunction due to the degree of indifference and apathy involved" (Settle, 1998, p. 26). He leaves unexplained how to distinguish drug-induced apathy from the supposedly therapeutic effect of reduced sadness, guilt, and suicidal despair. Antidepressants—especially SSRIs—have also been described as causing increased energy, even to the point of aggressiveness, which again may be very difficult to distinguish from supposed therapeutic effects. Kelly (1988), in his case report of the supposedly successful use of an antidepressant in psychoanalysis, described how the patient learned to titrate the dose of fluoxetine between a low dose, which left him in his baseline state of being timid, and a higher dose that went "too far in the direction of disinhibiting his aggression" (p. 727).

What does all this mean to the practice of psychoanalysis? For one, it means that when we prescribe antidepressants, we should recognize that we are essentially functioning as placebologists. We would do well to study the art of placebology. A vast literature exists on the placebo both from a psychoanalytic perspective and from psychodynamic perspectives in general. The placebo effect, although a real physiologic effect, falls within the domain of psychodynamics and can be explored and understood in a psychoanalytic context. The exact meaning of the placebo can vary widely from person to person and situation to situation. We must also remember we are dealing with "active placebos" so caution is in order with respect to adverse effects and withdrawal effects.

Psychoanalysts ought to free themselves of the burden of feeling they must prescribe antidepressants to their depressed patients in order to keep up with the standard of care. We can set aside the distracting fear that the patient may have some chemical imbalance that cannot be reached through human relationships (such as psychoanalysis), and be free to listen to all the patient's communications as potentially meaningful and analyzable.

This leaves unanswered, however, specific questions of how issues of medication ought to be handled in the clinical situation. My own practice has evolved dramatically over recent years and undoubtedly will evolve further. Currently, I am never the first to raise the issue of medications with patients. Most of my patients progress well in therapy and the issue of medications simply never comes up. Those who don't get better often drop out of treatment and move on of their own accord—

sometimes to a different provider who prescribes medications. I have had many patients express surprise and appreciation that I don't automatically prescribe medications.

The difficult issues arise when a patient requests a medication. It is difficult to make hard and fast rules about how to handle it, but generally speaking, I find it is better to remain in an analytic posture. To put it differently, it is best to remain interpretive, rather than to take an educational approach. In most of my cases the issue of medication simply goes away as the patient and I work to understand the meaning of the request. Let us consider a case example.

John, who has been seeing me for weekly therapy for about 2 months now, began this week's session by saying he has been feeling tired and unmotivated. He had been talking to a friend who suggested he try an antidepressant. He asked me what I thought. I replied that perhaps it would help him feel better. He agreed but went on to say that in some ways he thinks it would be taking a lazy way out, kind of like the way he would always turn to street drugs or alcohol in previous years. As he was talking I imagined him to be like a baby wanting to curl up on his mother's lap and suck on her breast to obtain sweet comfort and rest. The fact that John's mother abandoned him at an early age gave my fantasy some dimension. John went on to say that he has nearly daily fantasies of winning the lottery. Winning the lottery would relieve him from all his debts, and allow him to not have to work. He could just lie on the couch all day and read books or sleep. I then commented that he seemed to need to rest. He agreed and said that this session felt different to him because he didn't feel as much pressure as usual to work hard and say important things, but he was allowing himself to just relax more. He then announced that he didn't want an "energizer pill" after all.

Other patients bring up medications and are more persistent and unable to be patient and reflective. In such cases, I now am likely to prescribe the medicine they request, provided it is medically reasonable. I try to choose a less toxic medication and keep the dose small out of the principle of *primum non nocere*. I have some patients who have continued happily on medications for years, plus or minus psychotherapy. But I would say that the majority of such cases end up disillusioned with the medication or choose for some other reason to discontinue it. Another case example from my practice this week is typical.

Holly is a 22-year-old woman who began missing a lot of work because she was having overwhelming panic attacks. She responded quickly to psychotherapy and the panic attacks abated. However, several weeks into what was

proving to be very painful weekly psychotherapy for her, she was becoming anxious and deeply depressed. She requested an antidepressant. I prescribed sertraline 50 mg a day. I had the strong sense that attempting to be interpretive in that moment would have been unresponsive to the clear and specific request she was making of me. By the next session (this week) she was feeling dramatically better, which she attributed to the medication. I added, "It must feel better just to know we are doing something concrete to help you since you have said that you're not sure talking about your problems can help." She agreed, but added that she actually feels good talking to me, and a calm feeling comes over her during our sessions. But it quickly leaves when she leaves my office. She felt that somehow taking the pill helped her to take that calm feeling with her. This led us to a discussion of how her mother was never able to see, let alone meet, her emotional needs. We discussed her profound fears that I will not see how frightened and hurt she feels, or that I will see her as silly. I said, "So maybe when I prescribed the medicine for you, it let you know that I took you seriously." She agreed, but then blushed and admitted that she actually only took the first dose of the medicine then decided it was enough for her simply to know it was there if she needed it.

Of course, this would have to be considered an enactment. The point is not to avoid enactments altogether, but to manage them wisely when they occur. The giving and taking of antidepressants, and the responses to them, must all be viewed psychodynamically. Only then do they begin to really make sense.

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