Thinking About Prozac

Samuel H. Barondes

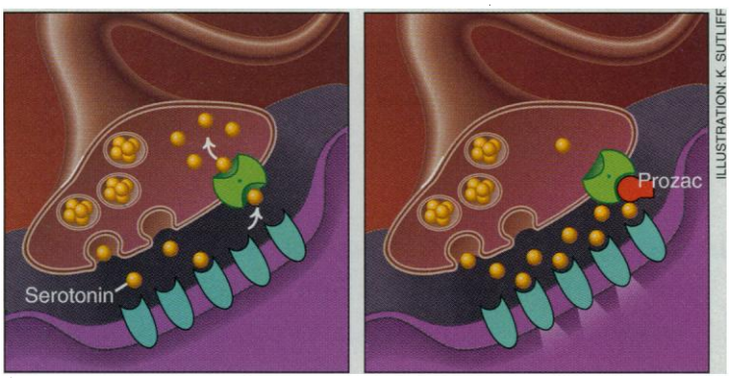
Modern psychopharmacology was born in the 1950s with the introduction of two drugs still in wide use today. First chlorpromazine, originally an antihistamine, was unexpectedly found to alleviate symptoms of schizophrenia (*1*). Then imipramine, initially considered an alternative to chlorpromazine, was observed to alter the course of major depression (*2*). Both drugs interact with proteins that bind to specific amine neurotransmitters in the brain, thereby providing molecular targets for new drugs with superior properties and different applications. Among these is a descendant of imipramine, fluoxetine (marketed as Prozac by Eli Lilly), which is now widely prescribed not only for depression but also to help people cope with a range of less serious but highly prevalent behavioral symptoms (*3*). The value of Prozac and other drugs for problems that had previously been viewed as best suited for psychological treatments has, in turn, stimulated a rethinking of fundamental assumptions in psychiatry.

These developments are traceable to the early discovery that imipramine acts on membrane transporters that remove the neurotransmitters norepinephrine or serotonin from the synaptic cleft, thereby terminating their action. We now know that each of the neurotransmitters interacts with a specific transporter and that imipramine blocks both. This finding provided pharmaceutical companies with a strategy for the development of alternative drugs in order to compete in the huge market that imipramine opened. Eventually, compounds were found that selectively blocked the serotonin (but not the norepinephrine) transporter and yet were equally effective in alleviating major depression. The advantage of these new drugs [called selective serotonin reuptake inhibitors (SSRIs)] is that they lack some of the undesirable side effects of imipramine, such as dry mouth and abnormal heart rhythms. Members of this class of drugs, now available for prescription, include sertraline, paroxetine, fluvoxamine, and the current big winner—Prozac.

The author is in the Center for Neurobiology and Psychiatry, Department of Psychiatry, University of California, San Francisco, CA 94143–0984, USA.

Prozac was introduced for clinical use in 1986 and has already been prescribed for more than 10 million people. Its popularity as an antidepressant derives not from its efficacy, which is no greater than that of imipramine (*4*), but instead from its less objectionable side effects. Not only are patients more willing to take Prozac, but it is also much less toxic than imipramine in large doses and therefore poses less danger as a potential instrument for suicide.

But the impact of Prozac has been even greater than these advantages imply. Like imipramine, which is also helpful in preventing the severe anxiety attacks of patients with panic disorder (*5*) and the repetitive intrusive thoughts and uncontrollable rituals of patients with obsessive-compulsive disorder (*6*), Prozac has been used in the treatment of conditions other than major depression. The fact that Prozac's side effects are more tolerable encouraged its prescription for other symptoms, including some that had been considered the exclusive province of psychotherapy. These have included excessive sensitivity to criticism, fear of rejection, lack of self-esteem, and a deficiency in the ability to experience pleasure. When people with these complaints sought professional help in the past, they turned to a psychological treatment—ranging from psychoanalysis and psychodynamic psychotherapy to cognitive-behavioral therapy and group therapy. But now, many patients with these complaints respond, often dramatically, to Prozac.



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How Prozac works. Prozac blocks the serotonin transporter in the membrane of nerve terminals. The resulting increase in the duration of action of released serotonin is, after several weeks, somehow translated into multiple therapeutic effects.

The major messenger of the news about Prozac is Peter Kramer, a psychiatrist whose earlier practice had focused on psychotherapy and who has also written extensively about psychotherapy both as a columnist in a trade publication, *Psychiatric Times*, and as the author of a popular book (*7*). Now Kramer has written a best seller, *Listening to Prozac* (*3*), in which he reveals his enthusiasm for the use of this drug to transform people's behavior more efficiently and, often, far more effectively than prolonged psychological treatment.

The widespread prescription of Prozac and related SSRIs for problems other than major depression, and the public and professional interest in Kramer's book, signal a major attitudinal change in American psychiatry. For many years the theoretical basis of the field derived from the writings of Sigmund Freud and his successors who emphasized the importance of childhood experiences in the generation of psychopathology—and the importance of insight in its amelioration. Although the education of psychiatrists also included training in the management of the seriously mentally ill and, since the 1950s, the use of psychopharmacological agents, the soul of the field continued to be Freudian. Of course Freud repeatedly predicted a time when chemistry and biology would also fruitfully inform psychiatry (*8*). Kramer's conversion reflects the growing consensus among clinical psychiatrists that this time has come.

But Freud might have been disappointed to learn that clinical psychopharmacology, like psychoanalysis, is not yet based on a deep mechanistic understanding. It had, in fact, been Freud's hope that ultimately studies of synaptic function would lead to an understanding of psychopathology (*8*). Yet even today advances in clinical psychopharmacology have not come about by elegant deduction from an understanding of how the brain controls behavior but instead by chance discoveries based on fragments of information. The development of Prozac depended on the accidental discovery of the antidepressant affect of imipramine; the initial isolation of serotonin from blood serum; the finding that imipramine blocks serotonin's reuptake; and a trial-and-error search for SSRIs. This is science at an early stage, and such bits of knowledge could not have predicted the value of this drug for so much of psychiatry.

Nor do these bits of knowledge reveal the mechanism of Prozac's clinical effects. How, in fact, does an agent whose primary action is to block serotonin reuptake produce sustained and coherent effects on behavior? There are, after all, already 14 different serotonin receptors identified in the brain (*9*), many with distinctive distribu-

tions. Assuming that the duration of action of serotonin at all of these receptors is regulated by reuptake, Prozac would be expected to affect them all. How does that lead to a reduction in the despondence of the depressed, alleviate anxiety in the fearful, and change the outlook of those who are sensitive to rejection? Perhaps selectivity comes because Prozac, by blocking reuptake, only augments the action of serotonin at those brain synapses where it is already being released. Does it, in this way, selectively strengthen already ongoing restorative mechanisms?

The problem is even more complicated, because the therapeutic effect of Prozac depends on adaptive changes in the brain that apparently take weeks to develop. This is suggested by the lag of up to a month before Prozac, imipramine, or many other chemically distinct antidepressants (including those that are selective norepinephrine reuptake inhibitors) become effective. Presumably their primary actions in prolonging neurotransmitter effects set into motion a series of molecular changes in the brain that may mitigate depression, alleviate anxiety, or alter temperament. But are these different psychological phenomena all alternative manifestations of the same underlying problem? Or are different adaptive changes put in motion in different underlying disorders? Explaining this chain of events is the most challenging current problem in psychopharmacology.

There are pressing clinical problems as well. Are the personality changes reported by Kramer and other clinicians really due to Prozac's pharmacological effects, or is the drug just an expensive placebo? Are the effects attributable solely to the drug or rather to its combination with some form of psychotherapy? Are the changes lasting? Must the drug be taken forever? Controlled clinical trials are needed, but both the critical therapeutic variables and the behavioral changes may be subtle and difficult to measure. And, since pharmaceutical companies are often reluctant to test such secondary applications, financial support for work of this type may be difficult to obtain. Yet there is a critical need to formally evaluate what are for now only persuasive, but unverified, clinical impressions about Prozac's efficacy.

But most important is the impact of these developments on the overall field of psychiatry. When chlorpromazine and imipramine were first introduced, they were initially popular only with a small subgroup of psychiatrists who called themselves biological psychiatrists and who tended to focus on serious mental illness, leaving other more common and less severe problems to those who specialized in psychotherapy. Now it is becoming generally appreciated that modern psychopharmacology, genetics, and other offshoots of biology are also relevant to an understanding of the less serious behavioral disorders. The fact that new enthusiasts for this position include Kramer and many others who had viewed themselves as being primarily psychotherapists signals a shift in the intellectual mainstream of this field. Whether Prozac ultimately proves to be of value in altering rejection sensitivity or low self-esteem, the new openness to biological treatment will have profound effects on the way we educate the next generation of psychiatrists and on our ability to attract the interest of biological scientists in psychiatric problems. In thinking about Prozac, we have been led to reevaluate our basic assumptions about behavioral disorders and how we approach them.

References and Notes

1. P. Deniker, in *Discoveries in Biological Psychiatry*, F. J. Ayd and B. Blackwell, Eds. (Lippincott, Philadelphia, PA, 1970), pp 155–164.
2. R. Kuhn, *ibid.*, pp. 205–217
3. P D Kramer, *Listening to Prozac. A Psychiatrist Explores Antidepressant Drugs and the Remaking of the Self* (Viking, New York, 1993)
4. P. Stark and C. D. Hardison, *J. Clin. Psychiatry* **46**, 58 (1985).
5 D F. Klein, *Psychopharmacologia* **5**, 397 (1964).
6. J. L. Rapoport, *The Boy Who Couldn't Stop Washing* (New American Library, New York, 1989).
7 P D. Kramer, *Moments of Engagement· Intimate Psychotherapy in a Technological Age* (Norton, New York, 1989).
8. S. H. Barondes, *Molecules and Mental Illness* (Scientific American Library, New York, 1993), pp. 3–11 and 199–201
9. L. H. Tecott and D. Julius, *Curr. Opin. Neurobiol.* **3**, 310 (1993); Y Shen *et al.*, *J. Biol. Chem.* **268**, 18200 (1993); F. J. Monsma *et al.*, *Mol. Pharmacol.* **43**, 320 (1993).
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Duality of TBP, the Universal Transcription Factor

Kevin Struhl

Transcription in eukaryotic organisms is extraordinarily complex. Three nuclear RNA polymerases are responsible for the synthesis of ribosomal (Pol I), messenger (Pol II), transfer (Pol III), and small nuclear (Pol II and Pol III) RNAs. These RNA polymerases act as structurally distinct promoters, and they function as part of macromolecular complexes composed of distinct sets of basic transcription factors. The Pol II machinery responds to numerous activator and repressor proteins, whose regulated action largely accounts for the diversity in gene expression patterns. Remarkably, there is a universal transcription factor, the TATA-binding protein (TBP), that is central to the expression of all eukaryotic genes. However, it appears that TBP does not play a common role in all transcription but rather has an inherent duality.

TBP is the most highly conserved eukaryotic transcription factor, with its functional domain showing greater than 80% sequence identity in a wide variety of species (*1*). It interacts specifically with TATA DNA sequences and with many proteins and carries out an impressive array of functions. First, TBP interacts with associated factors (TAFs) to form distinct multiprotein complexes, SL1 (*2*), TFIID (*3*), and TFIIIB (*4*), that, respectively, are specific for transcription by Pol I, Pol II, and Pol III. The relative ability of TBP to form these complexes is likely to regulate the balance of the various classes of RNAs in vivo (*5*). Second, for most Pol II promoters, specific binding of TBP to the TATA element initiates the assembly of an active transcription complex (*6*, *7*). In the course of this assembly process, promoter-bound TBP interacts with TFIIA and TFIIB, which are basic components of the Pol II transcription machinery. Third, TBP can interact in vitro with transcriptional activators (*8*) and general negative regulators (*9*), and it is likely to be a mechanistically relevant target of these and other transcriptional regulatory proteins in vivo. Fourth, TBP is a subunit of the SNAPc complex, which binds specifically to the proximal sequence element (PSE) of small nuclear RNA Pol II and Pol III promoters (*10*). Amazingly, all of these TBP functions are carried out by a single structural domain of only 180 amino acid residues.

As revealed by x-ray crystallography, TBP is an intramolecular dimer of related, but not identical, 90-residue subdomains (*11*). It has been described as a saddle consisting of a curved 10-stranded, antiparallel β sheet, with four α helices lying on its upper surface. Structural, biochemical, and mutational analyses indicate that the concave underside of the saddle binds to DNA, whereas the α helices and the convex surface of the saddle are likely to bind to other

The author is in the Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA.