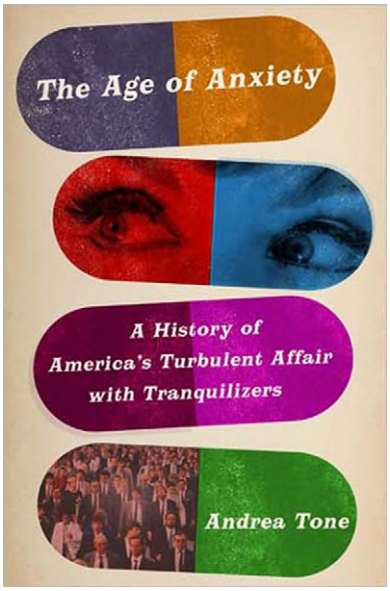
Neuron
Book Review

The Trouble with Chill Pills



The Age of Anxiety

Andrea Tone
Basic Books (2008)
320 pp., $26.95 hardcover.

In the early 1960s Hoffman La-Roche, a Swiss pharmaceutical company, introduced Librium (chlordiazepoxide) and Valium (diazepam) for the treatment of anxiety. Members of a new class of drugs named benzodiazepines, they were immediate best-sellers. In *The Age of Anxiety* Andrea Tone (2008), a Professor of the Social History of Medicine at McGill, describes the people, the companies, and the cultural forces that brought us these medications and considers their societal impact. In telling these stories Tone also helps us anticipate the reaction to the new drugs for anxiety that are on the way.

Benzodiazepines were not the first antianxiety drugs to enjoy an enthusiastic reception. Tone starts the book by describing Wallace Laboratories' discovery of their immediate predecessor, meprobamate (Miltown), which was introduced in 1955 and revealed the unexpected demand for what the public called chill pills. Eager for a share of this huge new market, other drug companies rushed to compete. Some tried to make patentable knock-offs of meprobamate, a me-too approach that remains popular, but they didn't get very far. Roche decided to take a much riskier approach by asking their chemists to hunt for something truly novel by trial and error.

The leading advocate of the trial and error approach was Leo Sternbach, a chemist whom Roche had rescued from the Nazis and who had established himself as a gifted innovator. Having no idea what kind of chemicals might reduce anxiety, Sternbach decided to make a series of derivatives of a synthetic dye that he had studied in the past and submitted them for behavioral testing in mice. Amazingly, one of them worked: mice treated with the new compound were much easier to handle, a sign of decreased anxiety, yet were not as sedated as those who took meprobamate. The same was true in more sophisticated behavioral tests in animals and in anxious patients. Furthermore this drug, which became Librium, had very little toxicity. Tone describes how its usefulness was then quickly established in clinical trials that were far less stringent than those that are required today, and how its superiority to Miltown was subsequently confirmed.

Having discovered the value of this new compound, Sternbach continued his tinkering. He soon made Valium, which was much more potent than Librium and became an even bigger blockbuster. Over the years other popular benzodiazepines such as Klonopin (clonazepam) flowed from his lab and their clinical values were established by the rigorous criteria that the FDA had by then put in place.

Benzodiazepines were not only helpful for patients. They also turned out to be valuable tools for basic neurobiological research. The first breakthrough came in 1975 with the discovery that benzodiazepines work by augmenting the actions of GABA, which made them useful for studying inhibitory neurotransmission. Subsequent studies showed that these actions are somewhat selective because they only bind to regulatory sites on certain forms of the GABA-A receptor, and this opened up many productive lines of investigation.

While these exciting discoveries were being made, the dark side of benzodiazepines was also becoming apparent, as Tone describes in considerable detail. One of their troublesome features is that the dose required to relieve anxiety also produces some sedation and slowing of cognition. They also have a much bigger drawback: all of them are potentially habit forming. Although most people can be taught to use these valuable drugs without getting into trouble, some become physically and psychologically dependent on them and may even become addicted.

Despite these drawbacks sales boomed. Fueled by a vigorous advertising and marketing campaign that was an early example of those that are now all too familiar, physicians began prescribing Valium for any sign of emotional distress and it became the number one prescription drug for a decade. Stay-at-home moms were Valium's major consumers, but men also began to rely on it to help them deal with the pressures of their jobs. For some it proved very helpful. For those who were simply swept up by this latest fad it did more harm than good.

Eventually there was public criticism of the overuse of these medications. Tone's most memorable example is the Rolling Stones' hit song, *Mother's Little Helper*, which lamented a housewife's dependence on her little yellow pill. Public advocacy groups also joined in the attack and condemned what they considered to be overzealous promotion of drugs to people who don't really need them. Their case was greatly strengthened by stories of the abuse of benzodiazepines by public figures such as President Gerald Ford's wife, Betty Ford.

All this negative publicity took its toll. Tone explains how the outcry led to the FDA's classification of benzodiazepines as controlled substances, which constrained their marketing and

their prescription. She ends her book by pointing out that, despite this constraint, benzodiazepines are still the most widely prescribed drugs for anxiety even though dependence and other side effects remain a problem.

But there is more to the story of these medications that Tone does not cover—because it is going on behind the closed laboratory doors of several major drug companies. Recognizing the drawbacks of the existing medications, scientists at these companies continue to look for ways to improve them, and much of this work is based on a growing understanding of GABA-A receptors (Barondes, 2003). We now know that these receptors are made by combining various alpha, beta, and gamma subunits to give complex structures including four subtypes—alpha 1-, 2-, 3-, and 5-containing—that have benzodiazepine-binding sites. Furthermore, pharmacological experiments have shown that binding to different subtypes has different behavioral effects: selective agonists for the benzodiazepine-binding site of the alpha 1 subtype cause sleepiness, those for alpha 2 and 3 reduce anxiety, and those for alpha 5 impair cognition and memory.

Many of these selective agonists are not members of the benzodiazepine family. A notable example is Ambien (zolpidem), a nonbenzodiazepine that is selective for alpha 1 and has become an extremely popular sleeping pill. But the most tantalizing goal of this research program is a pill that reduces anxiety without causing sleepiness or cognitive impairment and that is also—a big also—not addictive. This is the challenge that several companies have accepted.

So far Merck has published most extensively about subtype-selective GABA-A modulators such as L-838,417 and TPA-023 (also known as MK-0777) (Atack, 2008). L-838,417 is a partial agonist at alpha 2, 3, and 5 and an antagonist at alpha 1, and it reduces anxiety with few sedative and cognitive effects. TPA-023, which has one less fluorine and one more methyl, looks even more promising. It too is a partial agonist at alpha 2 and 3 but not at alpha 5, raising the possibility that it would have even fewer undesirable side effects. Furthermore, the fact that these compounds are only partial rather than full agonists at alpha 2 and 3 raises the hope that they may not be addictive.

But there are many potholes on the road to drug development, and Merck's compounds aren't yet on the way to approval as treatments for anxiety. Roche's scientists are also exploring this area but are keeping their findings close to their chests. To the best of my knowledge, only AstraZeneca has a GABA-A receptor subtype partial agonist (AZD7325) in clinical trials for anxiety disorders, although details about its properties have not been made public. Drugs that influence other potential targets in anxiety-generating brain circuits are also being evaluated by a number of companies.

Should nonsedating and nonaddicting medications make it to the clinic, they will be extremely valuable for patients with disabling anxiety. Yet they, too, will not be trouble-free. As Tone and others (Elliott, 2003; President's Council on Bioethics, 2003) remind us, all medications that affect the mind are frequently prescribed for people who don't need them and can also be diverted for illegal misuse. It's not hard to imagine the misuse of any drug that can reduce anxiety below the level required for effective psychological functioning: chilling out may be wonderful, but only up to a point.

Nevertheless it seems likely that the personal and societal downside of such new pharmaceuticals will be considerably less than that of their predecessors. It is a prediction that I hope we will see tested in the not-too-distant future.

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