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EDITORIAL

The rise and fall and rise of benzodiazepines: a return of the stigmatized and repressed

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Those who do not remember the past are condemned to repeat it.
(George Santayana)

The path of discovery has varied for various psychotropic medications, at times beginning with serendipitous findings by keen observers (e.g., the discovery of imipramine's antidepressant properties by Roland Kuhn), followed by more targeted research to expand the armamentarium with similar medications. In the mid-1940s, Frank Berger observed that mephenesin had calming, yet not sedating, properties in rodents. This compound had several disadvantages, such as very short duration of action and weak activity. Thus, Berger with a colleague at Carter-Wallace, a small pharmaceutical company, later synthetized meprobamate, overcoming the shortcomings of mephenesin. By the mid-1950s meprobamate became a blockbuster drug under the name of Miltown, in spite of not performing better than placebo in clinical trials.[1] Berger wanted to call it a sedative but was persuaded by others that it provided tranquil feelings, thus tranquilizers (and, later, minor tranquilizers) were "born."

Given heavy sales, other pharmaceutical companies wanted to enter the tranquilizer market. Roche Pharmaceuticals tasked Leo Sternbach to develop a meprobamate-like "me-too" drug. Sternbach, however, following another serendipitous observation, examined a group of azo dyes and in the mid-1950s synthesized the first benzodiazepine, chlordiazepoxide. He later synthetized, among other drugs, several other benzodiazepines, e.g., diazepam, flunitrazepam, and clonazepam.

By 1977, benzodiazepines became the most prescribed medications worldwide. They were appreciated not just for their anxiolytic properties, but also for their usefulness in insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a surgical premedication.

The efficacy of benzodiazepines in various anxiety disorders and other diagnostic entities (e.g., anxious depression[2]) was established through clinical trials from the 1960s through 1990s. Then the new antidepressants – selective serotonin reuptake inhibitors (SSRIs) arrived during the 1990s. They were originally approved by regulatory agencies for depressive disorders, but the pharmaceutical companies began seeking additional approval for SSRIs to be used in anxiety disorders.

As the number of SSRI indications grew for anxiety disorders and some psychiatrists were historically apprehensive about prescribing benzodiazepines (mainly for fear of abuse), benzodiazepine prescriptions for anxiety disorders decreased, especially among psychiatrists. Thus, benzodiazepines were gradually replaced by SSRIs for these indications. Interestingly, this happened without solid evidence that SSRIs were superior to benzodiazepines.[3]

One may ask why psychiatrists would prefer SSRIs over benzodiazepines in anxiety disorders without sufficient evidence of better efficacy and tolerability. It seems to us that benzodiazepines were exposed to an almost perfect storm of several factors that worked against them.

First, due to historical circumstances, regulatory agency approval was disadvantageous for benzodiazepines. Most of them were approved prior to the arrival of the DSM-III, when there were just 3 anxiety disorder diagnoses available – anxiety neurosis, phobic neurosis, and obsessive-compulsive neurosis. DSM-III established new anxiety disorder diagnoses, e.g., panic disorder, generalized anxiety disorder, social phobia, post-traumatic stress disorder, etc., and SSRIs were approved for many of those diagnoses. In contrast, benzodiazepines were not approved for

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these indications, since they were mostly off-patent and their manufacturers were not willing to spend money on new clinical trials. The exception was alprazolam, which was investigated and approved for panic disorder. Clonazepam was also later approved for panic disorder. Many psychiatrists have been trained to use medications only for approved indications and many insurance companies have been paying for medication use only for approved indications.

Second, SSRIs were welcomed with much enthusiasm, while many of their disadvantages, such as high placebo response rates in clinical trials and their adverse effects, were either unknown or overlooked. For instance, the originally reported frequency of sexual dysfunction associated with fluoxetine was 1.8% (based on spontaneous reporting). We now know that the incidence of sexual dysfunction associated with SSRIs is much higher. Moreover, when SSRIs were introduced, a discontinuation syndrome upon their cessation was not mentioned at all, which was considered a significant advantage over benzodiazepine discontinuation symptoms that were often portrayed as dangerous.

Third, the pharmaceutical industry has done a marvelous job promoting SSRIs while subtly mentioning the disadvantageous properties of benzodiazepines, in spite of the fact that benzodiazepines are comparably or more efficacious and have fewer side effects than older antidepressants in the management of generalized anxiety disorder,[3] or that SSRIs have a less favorable side effect profile than benzodiazepines in acute treatment of panic disorder.[4]

Fourth, benzodiazepines have been constantly stigmatized by claims of substance abuse and withdrawal syndrome despite a lack of evidence that they are abused when properly prescribed to patients not already abusing substances, and despite the evidence that they are almost always abused in the context of misuse and abuse of other substances.[5] Interestingly, withdrawal syndromes were termed discontinuation syndromes in the mainstream literature on antidepressants, but not for benzodiazepines. That, in a way, was one key to make clinicians believe that benzodiazepines cause dependence while antidepressants do not.

Fifth, with cognitive-behavior therapy gaining prominence in anxiety disorder treatment, psychiatrists have been bombarded with suggestions (based on hardly any evidence) that it is detrimental to combine cognitive-behavior therapy with benzodiazepines, whereas combining cognitive-behavior therapy with antidepressants might be beneficial.

Despite these factors, benzodiazepines continue to be frequently prescribed worldwide. The rates at which they are prescribed vary from one country to another, but reports suggest that these rates are steady or even increasing. For example, benzodiazepine prescriptions to older adults in the USA increased between 2003 and 2012.[6]

There are several reasons for the ongoing popularity of benzodiazepines and their "resurrection." Although they are not considered first-line medications in anxiety disorders, they provide quick relief of anxiety and other disorders. Their efficacy is comparable to, if not better than, that of antidepressants in anxiety disorders. They also work well in anxious depression.[2] When used in anxiety disorders, their side effect profile seems better than that of SSRIs and other antidepressants. Benzodiazepines are versatile agents that could be used intermittently, for short-term treatment, long-term treatment and perhaps even indefinitely if properly prescribed and managed.

The time has come to properly re-evaluate the place of benzodiazepines in psychiatry's armamentarium. We should not deprive our patients of efficacious and well tolerated medications because of historical mishaps, personal and specialty biases, and negative marketing propaganda. The tale of the rise and fall of benzodiazepines and their stigmatization and suppression should be a warning to other classes of psychotropic medications, and the field in general.

Disclosure

The authors report no conflicts of interest.

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