The expanding role of benzodiazepines in neurology: an historical overview

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THE BENZODIAZEPINES have been an important part of the neurologist's armamentarium since the 1960s and, as new compounds become available, their therapeutic role continues to expand. Sleep disorders, movement disorders, epilepsy, and psychiatric conditions are among the problems for which benzodiazepines may be helpful. The purpose of this volume is to focus attention on the rational use of these medications in this diverse group of disorders.

FIGURE 1. The "father" of the benzodiazepines: Dr. Leo H. Sternbach, Director of Medicinal Chemistry Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey (1941 to present).

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The "father" of the benzodiazepines is Dr. Leo H. Sternbach of the Medicinal Chemistry Research Department of Hoffmann-La Roche Incorporated in Nutley, New Jersey (*Figure 1*). Dr. Sternbach began his research on the parent group of compounds—a class of heterocycles (*Figure 2*)—at the University of Cracow in Poland in 1933.[1] He stated that he was attracted to these compounds, known since 1891, because of their relative accessibility, easy crystallization, and the expectation that they would lend themselves to many variations and transformations.[1] Dr. Sternbach's investigations were interrupted by World War II; but when resumed in 1955 with Hoffmann-La Roche, they were extremely fruitful.

In a retrospective of his work, Dr. Sternbach explained that his initial experiments, adding basic side chains, resulted in compounds with "uninteresting"

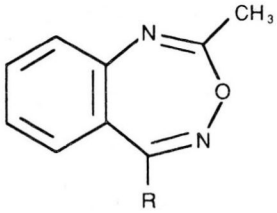

FIGURE 2. The parent group of the benzodiazepines, a class of heterocycles, was identified in Germany in 1891 by Auwers and von Meyenburg. This and the other diagrams of chemical structure in figures 3-5 were modified from Sternbach[1] with permission from the author and the publisher.

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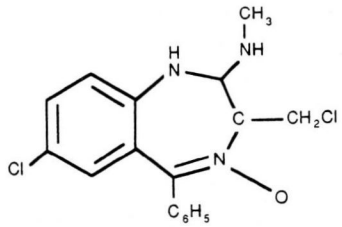

FIGURE 3. "Methylamino derivative II," a compound undergoing clinical trials in 1957 at Hoffmann-La Roche.

pharmacologic properties.[1] However, treatment with methylamine produced compounds with muscle-relaxant, taming, sedative, and anticonvulsant effects. Further experimentation resulted in the so-called "methylamino derivative II" (*Figure 3*), which progressed in 1957 toward clinical trials as an anxiolytic. In 1960, Dr. Sternbach simplified this derivative compound for enhanced pharmacologic properties and reduced bitterness, thus introducing the drug chlordiazepoxide (Librium) (*Figure 4*).

With the discovery of chlordiazepoxide, a new class of medications became clinically available. Modifications of these compounds resulted in an ever-widening spectrum of benzodiazepines with different pharmacologic properties (*Figure 5*). As of 1990, 13 benzodiazepines are available by prescription in the United States, with efficacy against a wide variety of disorders.

In this volume we will explore the use of these medications in the treatment of neurologic disorders. I extend my thanks to the authors of this publication for sharing with us their expert clinical experience.

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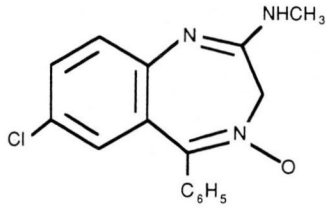

FIGURE 4. Chlordiazepoxide (Librium), introduced in 1960, was the first benzodiazepine to be marketed clinically as an anxiolytic.

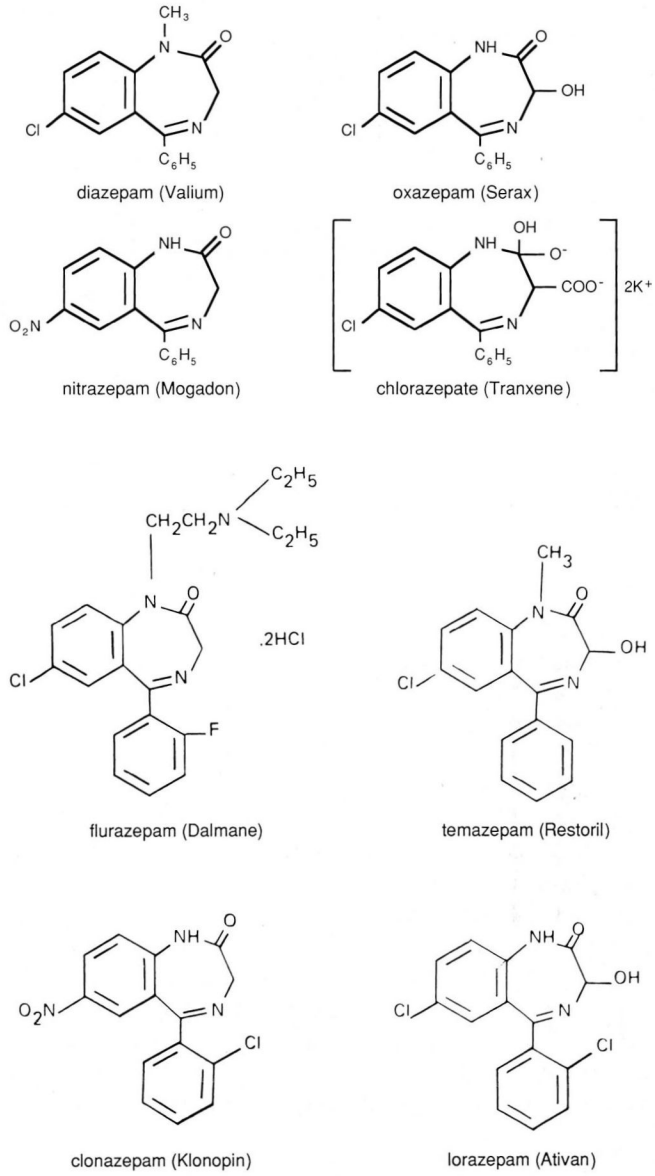

FIGURE 5. The later benzodiazepines provide efficacy in diverse clinical settings such as sleep disorders, movement disorders, epilepsy, and psychiatric conditions.

REFERENCE

1. Sternbach LH. Chemistry of the 1,4-benzodiazepines and some aspects of the structure-activity relationship. [In] S Garratini, E Mussini, LO Randall. The Benzodiazepines. New York, Raven Press, 1973, pp. 1–26.

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