Chapter 5

1,4-Benzodiazepines and New Derivatives: Description, Analysis, and Organic Synthesis

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Additional information is available at the end of the chapter

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Abstract

Benzodiazepines are widely used drugs for several indications. This study provides, on the other hand, a global vision of the family starting for their fortuitous discovery, the synthesis of their derivatives, their mechanism of action widely known nowadays, the actual classification according to the chemical structure and pharmacokinetic properties, and their uses and indications, the traditional and the new ones. On the other hand,the study is focused in the mainly problems of benzodiazepines, depedence, and tolerance, many times led by a misuse of the patient, wrong prescriptions, or extended treatments. A withdrawal program is proposed that includes the important factors or criteria to success, with a slow and gradual reduction of these drugs, avoiding relapse or severe adverse effects. New lines of research related to benzodiazepines are taken into account, which not only include the new therapeutic uses but also the adverse effects in short and long term. They are also analyzed the new discoveries concerning the nonbenzodiazepine drugs due to the close relation they have with benzodiazepines.

Keywords: benzodiazepines, withdrawal program, nonbenzodiazepine drugs, biological activities, side effects

1. Discovery and history

Many of the drugs that had represented a great advance in many therapeutic approaches were not a result of a rational design but of a consequence of casual observations, fortuitous discoveries, or serendipity. Way back then, a rational design did not guarantee the exit because the knowledge of the biological systems was not clear or complete. That happened in the beginning of the past century, and many of the drugs used nowadays come from this type of

discovery, from the curiosity of many investigators that decided to study the reason why they were not achieving their goals.

Discovery starts with chemist Leo Sternbach and his research group, working in the Hoffmann-La Roche laboratories in Nutley, New Jersey. They were trying to find new tranquilizers, but due to the limited knowledge of the processes occurring in the brain, they were taking an empirical approach: to search for a new class of drugs purely guided by modifications in the known chemical synthesis [1]. In 1957, they serendipitously identified the first benzodiazepine (BZD), *chlordiazepoxide*, while they were studying the activity of *quinazoline oxide*. They saw that the compound obtained was not a quinazoline-N^3-oxide but a benzodiazepine-N^4-oxide. With a posterior investigation, Sternbach himself managed to explain what happened [2].

By 1960, Hoffmann-La Roche introduced the *chlordiazepoxide* in clinical treatment under the brand name Librium®, and it pursued molecular modifications to improve its activity. By the time of its introduction, it was felt that an explanation of the BZDs mechanism of action might be really helpful to understand the basis of anxiety. *Diazepam* (Valium®) followed in 1963, which was considered for a long time as head of the family.

An important improvement was their lack of respiratory depression, a safety concern they had with barbiturates [3].

Medical professionals accepted benzodiazepines enthusiastically at first, increasing their popularity and patient demand. BZDs were prescribed frequently and often long term for various conditions. Soon they became the pharmacological family *par excellence* in the treatment of anxiety disorders and so initiating "the benzodiazepine saga" [4].

It took 15 years for the researchers to associate benzodiazepines and their effect with their high-affinity receptor complex as a mechanism of action. They did it in 1977, and it was the major turning point in the research [2].

1.1. Benzodiazepines (BZDs)

Benzodiazepines are a structural class of compounds that are used as hypnotics, anxiolytics, anticonvulsants, and muscle relaxants. Their core chemical structure is formed by the fusion of a benzene ring and a diazepine ring (**Figure 1**). Different compounds have different side groups attached to this central structure in position 1, 2, 5, or 7. The different side groups affect the binding of the molecule to the $GABA_A$ receptor and so can modulate the pharmacological properties, the potency of the effect, and the pharmacokinetic conditions (duration of the effect, distribution, etc.).

BZDs have proven to be excellent drugs for the known pharmacological properties they present, as shown in **Table 1**.

In humans, benzodiazepines are also recognized to have anterograde amnestic effects, providing amnesia for events that occur subsequent to the administration of the drug [6]. Another important use they have is in alcohol withdrawal syndrome (AWS). They are generally considered to provide no analgesia.

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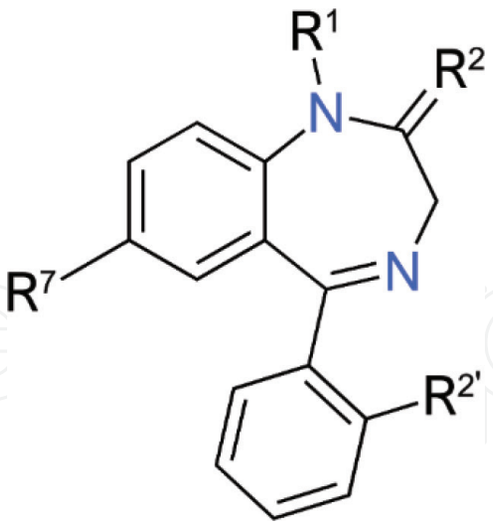

Figure 1. BZD structure.

Action	Clinical uses
Anxiolytic	Anxiety and panic/phobias, alcohol withdrawal
Hypnotic	Insomnia
Muscle relaxant	Muscle spasms, spasticity caused by CNS pathologies
Anticonvulsive	Attacks caused by drug intoxications, some forms of epilepsy
Amnesic	Intraoperatively or pre-surgery medication

Table 1. Principal actions and uses of BZDs [5].

It is important to note that the variation of the dose changes the effects: a hypnotic BZD administered in low doses produces anxiety-relieving effects, whereas a BZD marketed as an antianxiety drug at higher doses induces sleep.

1.2. Mechanism of action

To understand their mechanism of action, it is necessary to know the physiology and function of the *gamma*-aminobutyric acid (GABA) neurotransmitter. They are neurotransmitters in the central nervous system (CNS) that increment or decrease the excitability of neurons and so regulate the brain activity. GABA functions as the principal inhibitory neurotransmitter, and BZDs potentiate that function.

The GABAA receptor is a protein complex located in the synapses of neurons. It belongs to a family of receptors associated to ionic channels, formed by combinations of protein subunits with high selectivity for chloride ion (Cl^-). They conduct chloride ions across neuronal cell membranes. The receptor is formed by five subunits arranged around the central chloride: two alphas, two betas, and one gamma. There are also multiple isoforms of each subunit: six

alpha subtypes ($\alpha_{1,2,3,4,5,6}$), four beta ($\beta_{1,2,3,4}$), three gamma ($\gamma_{1,2,3}$), and one delta (δ). These receptors are heterogeneous and can consist of different mixtures of different polypeptide classes (alpha, beta, gamma, etc.)

There are two GABA binding sites in the receptor and a single binding site for the BZDs which is located in the pairing (interphase) between an α subunit and a β subunit (**Figure 2**).

The binding of a BZD to its binding site cause an increment of the GABA affinity for its own binding site. They act as a **positive allosteric modulator**: the union of the BZD to the receptor does not alter the GABA union, but it increases the total conduction of chloride ions across the neuronal cell membrane. This increment of chloride ions leads to a hyperpolarization of the neuron and, as a result, a decrease of the neuronal activity [8].

The advantage of the BZDs comparing to other drugs that act in the same receptor and decrease the activity of neurons is that BZDs are the only drugs that give GABA more affinity for its receptor and act as an allosteric modulator. For the same reason, BZDs are not able to provide a higher activation than GABA itself, and this is what explains the elevated therapeutic index (toxic/therapeutic dose ratio), superior than barbiturates.

This last group, barbiturates, in low doses helps to maintain the chloride channel opened by acting in the GABA. However, in high doses they open directly the chloride cannel, which can lead to toxicity.

1.3. Specific BZD receptors

The BZD receptor has been classified into different types, based on α subunit isoforms and clinical effects related to each type [8, 9]. In addition, each BZD has different affinity to the $GABA_A$ receptor and its subunits:

- The BZ_1 receptor contains the α1 subunit isoform, which represents approximately the 60% of the $GABA_A$ receptors. This receptor is highly concentrated in the cortex, thalamus, and cerebellum, and it is responsible for sedative effects and anterograde amnesia, explaining this frequent side effect in the most of the BZDs.
- The BZ_2 receptor contains the α_2 isoform, and the BZ_3 contains the α_3 isoform. Although the BZ_2 is a widespread receptor, it is believed that those located in the spinal cord and motor neurons largely mediate myorelaxant effect, such as BZ_3 receptor, and those located in the limbic system are responsible for the anxiolytic effect.

The different effects of the BZDs are explained by their interaction and binding with the different receptors (the isoform, the affinity of the binding, and the location of the receptor in the CNS). According to this, all the effects should be expected for those BZDs that interact indiscriminately with all the receptors. Others, nonbenzodiazepines or Z-drugs, for example, only interact with one type of receptor (BZ1 in this case) so they are going to be used with more specificity.

1.4. Chemical structure and structure-activity relationship (SAR)

As introduced before, BZDs have a cyclic structure that includes one benzene cycle (*benzo*) plus a heterocycle where two atoms are nitrogen (–*diaza*-) normally in 1 and 4 positions but which

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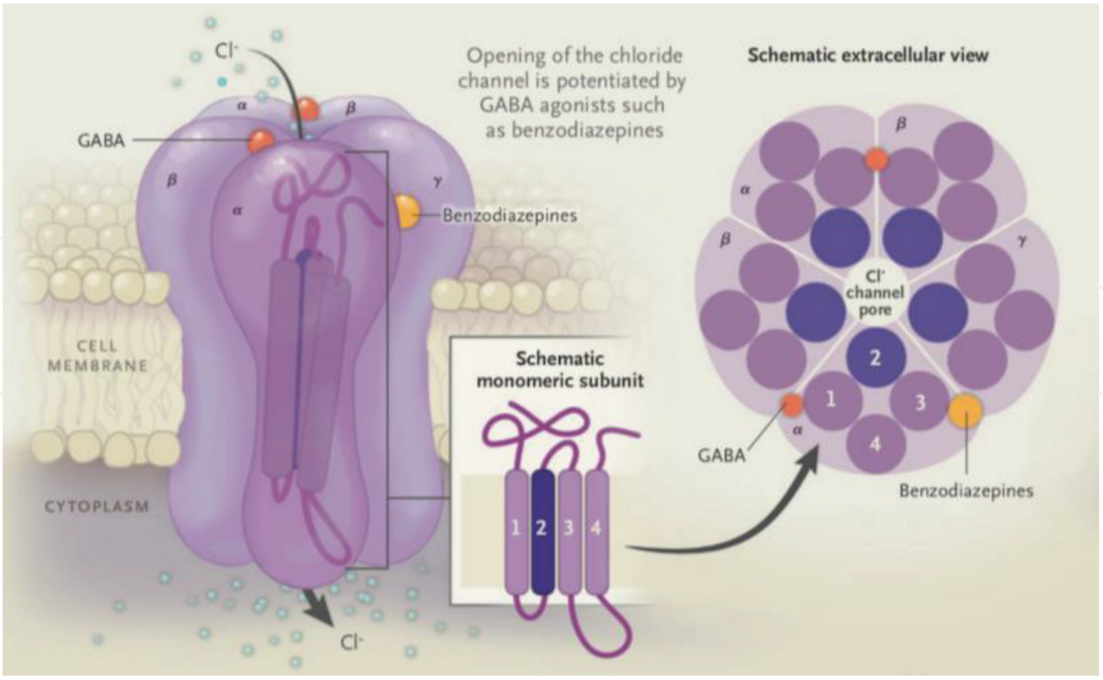


Figure 2. The $GABA_A$ receptor. On the left, a side complete view of the receptor: the subunits and the chloride ion channel, with the BZDs binding sites. On the right, a top view of the receptor, illustrating the most common combination of α, β, and γ subunits [7].

can also be in 1,5 or 2,3. Normally the benzodiazepines used in clinical are 1,4-dinitrogenated systems.

By analyzing the structure, we can see the substitutions at the different positions of and the consequences that have on the activity:

- Substitution at position 1: ↑ Activity by alkylation (prodrug). Example: *diazepam*
- Substitution at position 2: Electronegative atom

  (O or N) derived from carboxyl → first generation of BZDs. Although it can also be non-substituted. Example: medazepam
- Substitution at position 3: If it is not substituted or has an –OH: ↑ polarity → glucuronidation → faster elimination. Example: lorazepam
- Benzene ring at position 5: Optimal for activity.
  - Substituted in *ortho* by **Cl, F**: ↑ activity (electron-attracting group). Example: *flurazepam* (F) and *clonazepam* (Cl).
  - Replaced by another cycle. Example: cyclohexenyl (tetrazepam).
- Substitution at position 7: Establish the potency.

  Favorable position to ↑ activity, specially by an electron-attracting group: CF_3 > NO_2 > Br > Cl > OCH_3 > R.
  - NO_2: Hypnotic action.

Example: clonazepam, nitrazepam, and lormetazepam.

- X: Anxiolytic action. Example: lorazepam and alprazolam.

Any substitution on the other positions (6, 8, and 9) may decrease the activity. There are others who are fused with triazole or imidazole ring and so producing *triazolobenzodiazepines* or *imidazolobenzodiazepine* (or diazolobenzodiazepines), respectively [10]. From a chemical structure point of view, BZDs can be divided in three groups (**Figures 3** and **4**).

1.5. Pharmacokinetics and pharmacodynamics

Some of the pharmacokinetics properties change in function of the side groups (R) of each BZD. That will be decisive when prescribing them. Normally this family of drugs is taken by oral administration due to its good absorption. The intravenous administration presents a quick distribution to the brain and central nervous system, but it is reserved for emergencies like acute seizures.

BZDs and their metabolites are highly protein bound (90% union with albumin). These compounds are widely distributed in the body and preferentially accumulated in lipid-rich areas

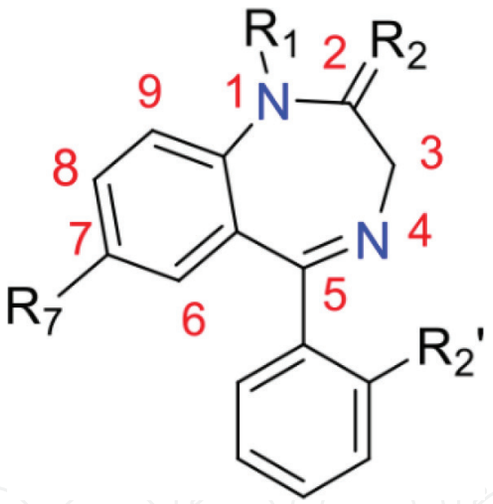


Figure 3. Compound numbering.

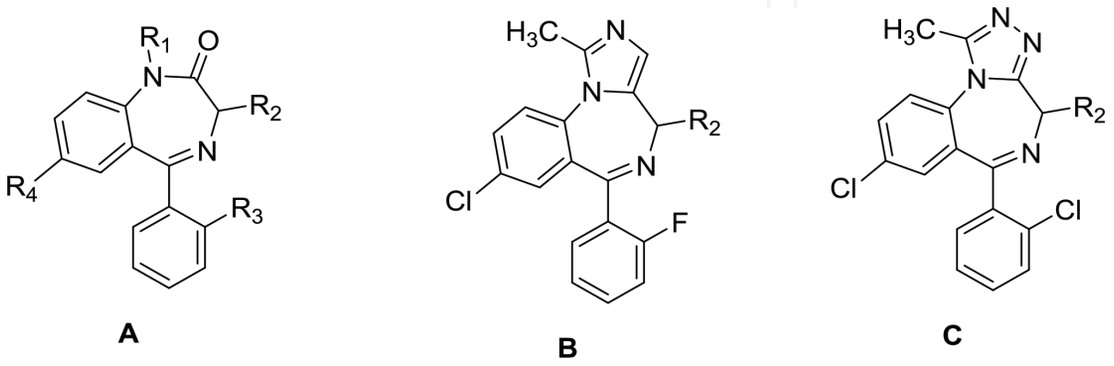


Figure 4. General structure of various BZDs: (A) 5-Aryl-1,4-benzodiazepine; (B) *midazolam*, a diazolobenzodiazepine; and (C) *triazolam*, a triazolobenzodiazepine [11].

such as the central nervous system and adipose tissue. It is important to mention that the major factor in predicting amnesia risk is lipid solubility: the greater the lipid solubility, the greater the risk of amnesia. BZDs with high lipid solubility have higher absorption rates and faster onset of clinical effects than BZDs with low lipid solubility [8]. Most BZDs are metabolized by the cytochrome P450 enzymes (phase I) by oxidation, hydroxylation, or dealkylation and after conjugated with glucuronide or sulfate (phase II). At the end, the urine excretes them almost entirely.

Some BZDs produce active metabolites during the process, as they are administered in a prodrug form. This supposes an important consideration when prescribing these agents. For example, *diazepam*, a long-acting BZD, produces the active metabolites *oxazepam*, *desmethyldiazepam*, and *temazepam.* A classification of the BZDs exists in basis of their half-live time for elimination, an estimation of the time needed to reduce the drug concentration in the plasma by half. After 5–7 h post-administration, a drug is eliminated from the body [8].

These previous reasons should be considered when administering BZDs in the elderly and in the patients with preexisting hepatic diseases: the metabolites further increase the duration of drug action, which can also have variations in the elimination half-life.

2. Classification of BZDs

BZDs are classified in terms of their elimination half-life in short-acting, intermediate-acting, or long-acting (**Figure 5**):

- Short-acting. Elimination half-life <5 h (*midazolam* and *triazolam*). Mainly used as hypnotic for their quick sleep onset. They have few residual effects and can cause rebound insomnia when disruption, as well as amnesia and dependence problems.
- Intermediate-acting. Elimination half-life 5–24 h, normally they are used for anxiety purposes. Might have next-day residual effects if used as hypnotic (alprazolam, lorazepam, lormetazepam).
- Long-acting. Elimination half-life >24 h, arriving to 100 h in diazepam. They present risk of accumulation, especially in the elderly or patients with metabolism disease (diazepam, clorazepate).

A huge number of BZDs have been synthetized over the years, but only a few had shown improved efficacy and are actually used in clinical. Today, approximately 35 benzodiazepine derivatives exist, 21 of which have been approved internationally by clinical use [7].

2.1. Abuse and dependence: problem presentation

BZDs became one of the most frequently prescribed drugs in the world around the 1970s, even though the potential abuse and dependence was quickly detected. As a result of many concerns about misuse, BZDs were placed on the Food and Drug Administration (FDA) restricted drug list in 1975. It was not until the 1980s that the dependence occurring with these drugs was confirmed, after several clinical trials and after many declarations coming from not only patients but also from clinicians. Despite recommendations of a treatment no longer than 4 weeks, many of

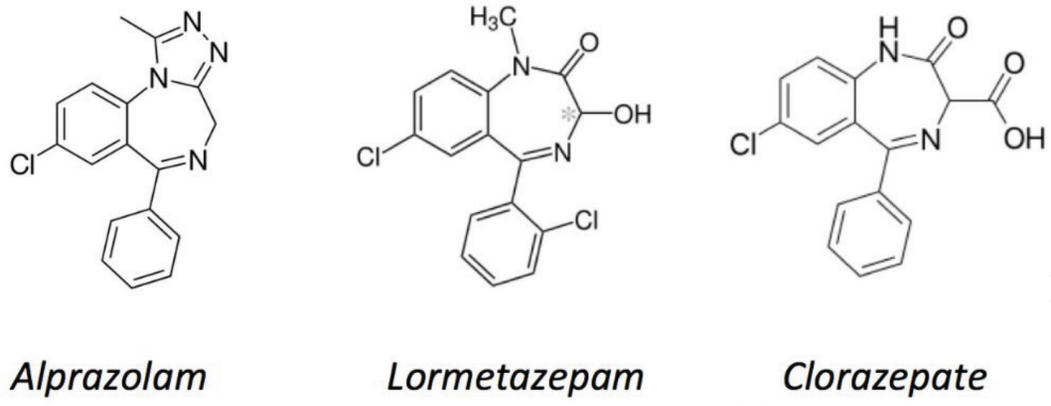


Figure 5. Examples of 1,4-benzodiazepines.

them continued to prescribe them for months or even years. Their use gradually declined after the mid-1980s as a result of growing information and concerns, and also with the discovery of other antianxiety medications like the selective serotonin reuptake inhibitors (SSRIs), which proved to be safer and more effective than BZDs. In fact, the total BZD use increased from 1999 to 2014, mainly caused by the augmentation of the long-term inappropriate users [12].

Intentional abusers of BZD usually have other substance abuse problems. Benzodiazepines are usually a secondary drug of abuse, used mainly to augment the "high" received from another drug or to offset the adverse effects of other drugs. Few cases of addiction originated from legitimate use of benzodiazepines. On August 31, 2016, FDA issued a drug safety communication about serious risks, including death, when opioid pain or cough medicines are combined with benzodiazepines. The safety announcement warned that "health care professionals should limit prescribing opioid pain medicines with benzodiazepines... only to patients for whom alternative treatment options are inadequate" [13].

The pharmacological dependence derived from a BZD, which is normally manifested in withdrawal symptoms when the treatment is suddenly interrupted, can happen even from a legitimate use. This response, caused by the constant action of drug after a long time, can be avoided, for example, with dose tapering and/or medication switching [14].

2.2. Adverse effects

In general, BZD are well-tolerated drugs if the use and administration are correct. The toxicological profile of BZDs is similar between compounds, although the frequency and gravity of the reactions can be different. In most of the cases, adverse reactions are a prolongation of the pharmacological action that affects the CNS.

- Frequent: somnolence (half of the patients experiment it during the first days of treatment), sedation, ataxia (especially in the elderly), fatigue, and anterograde amnesia (difficulty to remember recent facts)
- Occasionally: dizziness, headache, depression, confusion, and dysphasia
- Exceptionally: rush or urticaria, pruritus, and visual and/or audition alterations

They can also produce problems in psychomotor performances (driving, incoordination, sometimes causing falls). There is sufficient evidence from epidemiologic and experimental studies to establish a strong causal connection between benzodiazepine and also Z-drug use to motor vehicle accidents, falls, and fractures as a consequence of psychomotor impairment [15]. In addition, taking into account their pharmacological properties, benzodiazepines can cause muscular hypotonia and respiratory difficulties, especially in patients presenting a respiratory deficiency.

The intensity of the effects depends on the doses and is worst in patients with hepatic alterations and in the elderly. The physiological changes of aging in the liver result in prolonged clearance of drugs: by decreasing the metabolism, the half-life elimination increases. BZDs are eliminated slowly from the body, so repeated doses over a prolonged period can result in significant accumulation in fatty tissues. Thus, some symptoms of overmedication (impaired thinking, disorientation, confusion, slurred speech) can appear over time [8].

The side effects of BZDs are increased when paired with other drugs such as barbiturates, alcohol, narcotics, or tranquilizers. BZDs potentiate the sedative effects of opioids and are the most common combination in polydrug users, along with alcohol [6]. The risk of fatality via respiratory or nervous system depression from BZD overdose is barely inexistent, but if they are involved with other agents known to cause CNS and respiratory depressions, especially alcohol or opioids, the risk of harm substantially increases.

Over the past few years, biomedical literature has emerged raising a tentative link between benzodiazepine and/or Z-drug exposure with adverse outcomes such as respiratory disease exacerbation, infections, dementia, pancreatitis, and cancer. Doubt persists in the biomedical community regarding this relatively new safety accusation against these drugs by pharmacoepidemiologic researchers.

Based on the Hill criteria for causation, a list of the possible adverse outcome associations is indicated in **Table 2**.

	Traffic accidents	**Falls leading to fractures**	**Dementia**	**Infections**	**Pancreatitis**	**Respiratory worsening**	**Cancer**
Consistency	+	+	±	±	±	–	±
Strength	+	+	+	±	+	±	±
Temporality	+	+	–	+	–	–	–
Specificity	–	–	–	–	–	–	–
Dose–response	+	+	±	–	±	–	±
Coherence	+	+	±	±	–	±	–
Experimental evidence	+	+	–	±	–	±	–
Analogy	+	+	–	–	±	+	–

+ criteria fulfilled, ± criteria partially fulfilled or arguable either way, – criteria not fulfilled.

Table 2. Criteria for BZD/Z-drug adverse events [16].

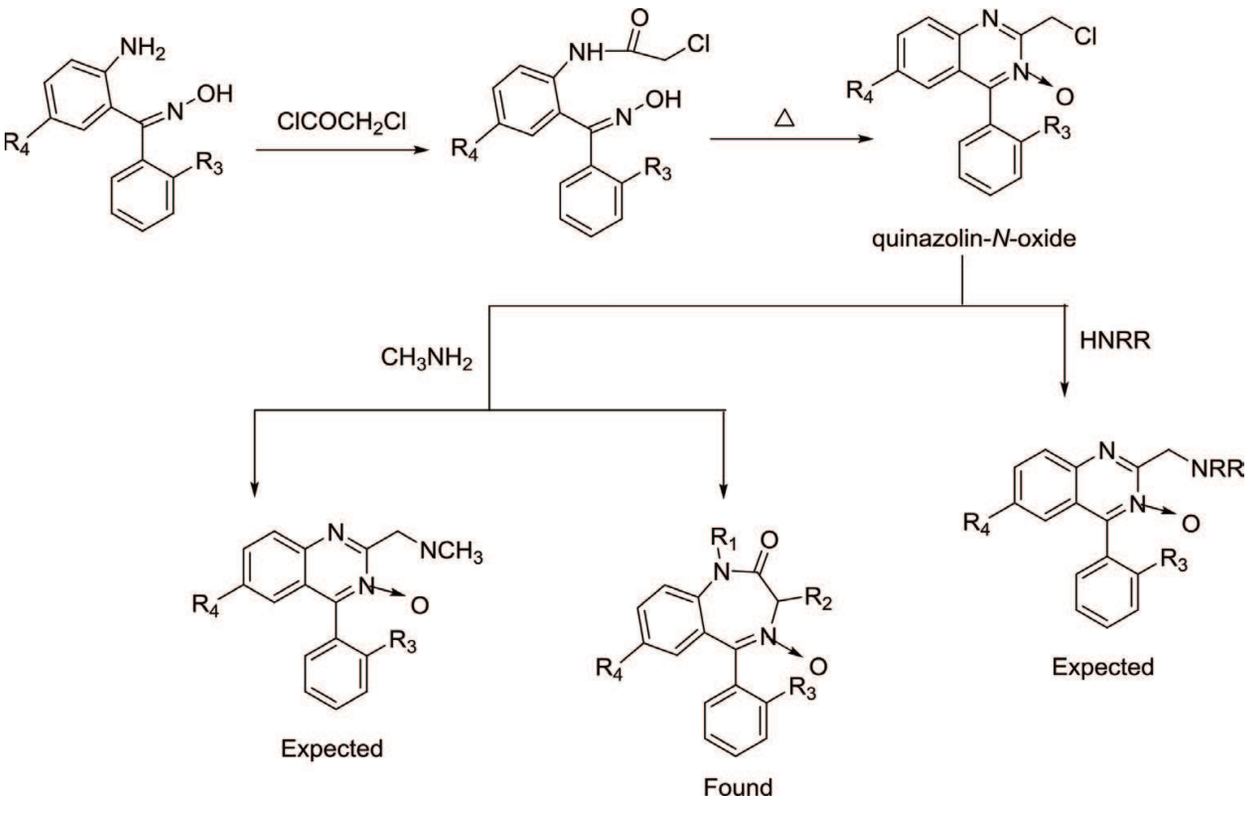
There is a lack of evidence to prove causality between BZD and Z-drugs to any of these conditions due to insufficient and conflicting evidence from both epidemiologic and experimental studies, except for fall leading to fractures, which has already been proved [15]. Anyway, there are reasons to associate them: there are clinical studies that are in process to verify it or that are proposed for future research about the subject.

3. Synthesis of benzodiazepines

The first BZD, serendipitously founded, was *chlordiazepoxide*, and its synthesis started after the synthesis of the *quinazoline-N-oxide*3 as indicated in **Scheme 1**. From the 2-aminobenzophenone, the synthesis of BZDs can be raised as indicated below:

The 2-aminobenzophenone is treated with hydroxylamine to obtain the oxime **1**. The oxime can exist in the form of two stereoisomers *Z* and *E*, the stereoisomer *E* being the most stable due to steric problems. The reaction of this compound with *chloroacetylchloride* gives the chloroacetamide, which by treatment with NaOH leads to the found benzodiazepine-*N*-oxide **5**. The intramolecular cyclization reaction proceeds through the nitrogen atom of the oxime. The resulting *N*-oxide function can be reduced by treatment with PCl_3.

By treating this *quinazoline-N-oxide* with secondary amines (HNRR), a tertiary amine was obtained as an expected compound for the nucleophilic substitution (**6**). However, by treating it with a primary amine: *methylamine* (CH_3NH_2), the result was an unexpected compound



Scheme 1. Synthesis of [1, 4]-benzodiazepines [2].

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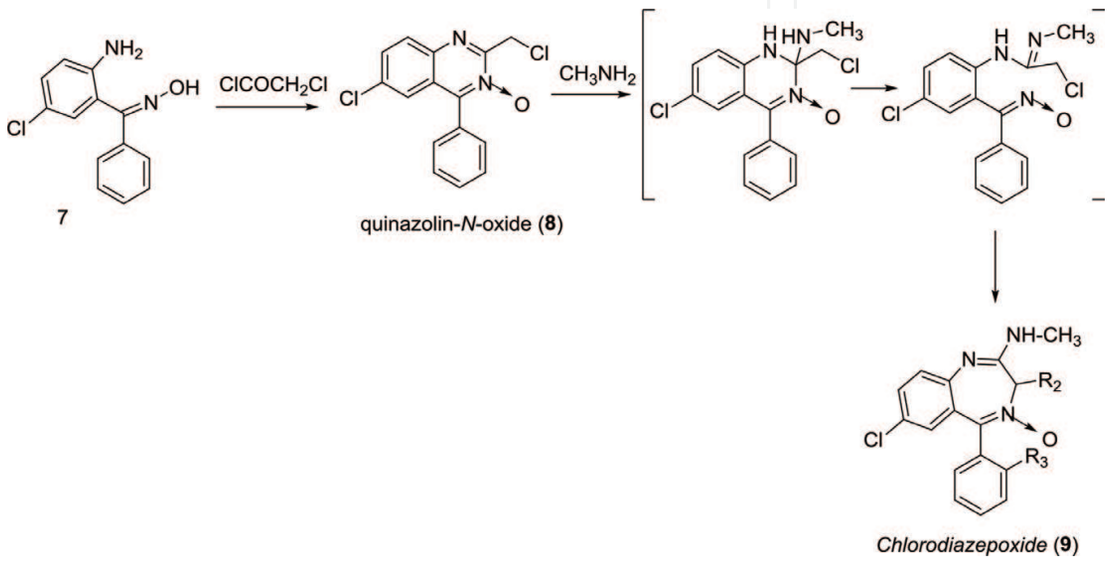
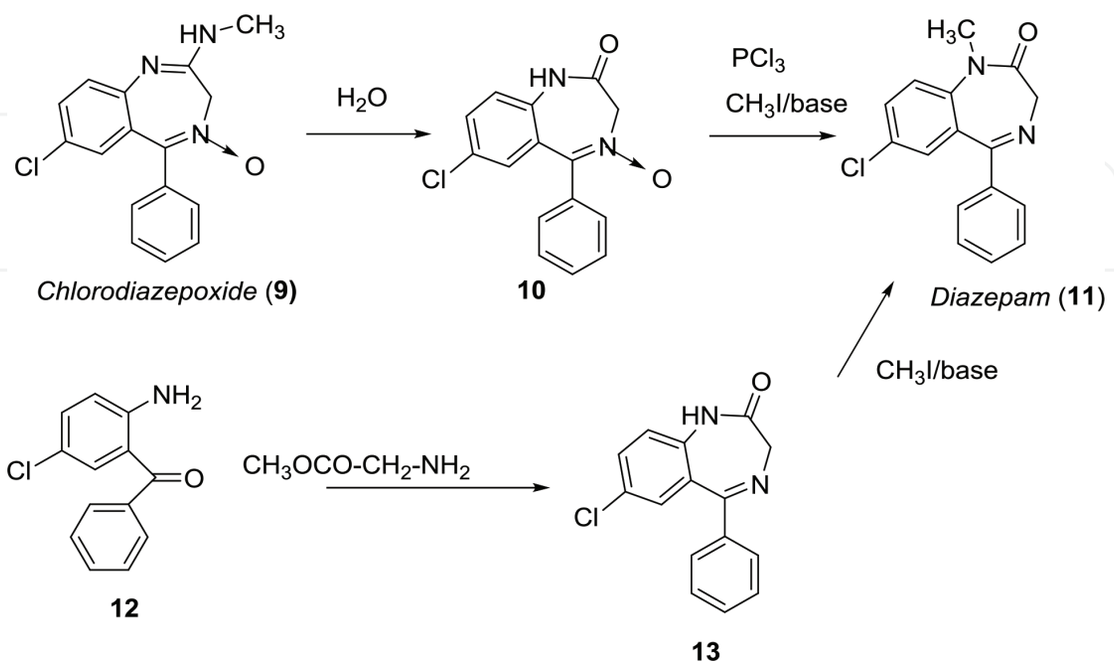
considered a derivative from *1,4-benzodiazepine-N^4-oxide (9)*. An addition reaction in the carbon C-2 of the quinazoline was produced, with a rearrangement of the 6-atom ring (quinazoline) to a 7-atom ring (benzodiazepine) as a consequence (**Scheme 2**).

The reaction was generalized for other primary amines, but none of the new obtained products was better than *chlordiazepoxide* after all. Later they found that *N*-oxide group was not essential for the biological action.

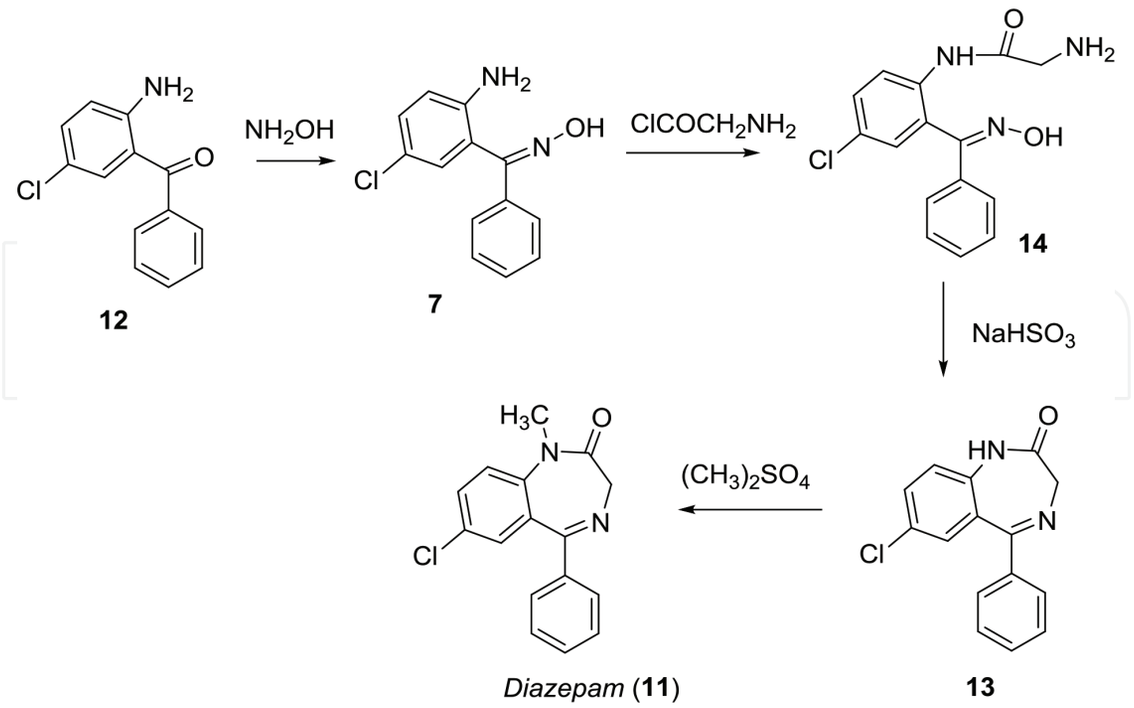
Thus, new anxiolytic drugs such as *diazepam*, *bromazepam*, *or nitrazepam* were found, widely used nowadays.



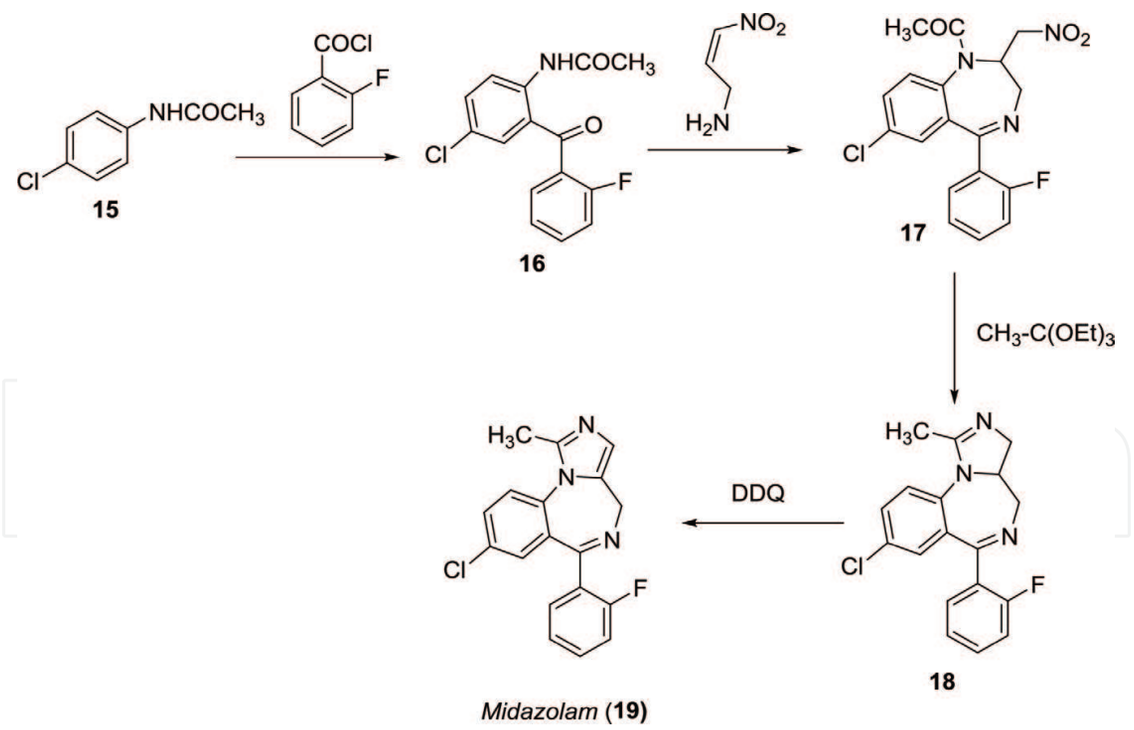
Scheme 2. Mechanism preparation of *chlordiazepoxide* [17].



Scheme 3. Metabolism and synthesis of *diazepam* [2].



Scheme 4. Alternative synthesis of *diazepam* [17].



Scheme 5. Synthesis of *midazolam* [18].

In the first line of the previous scheme, we can see how *diazepam* is formed by metabolism of *chlordiazepoxide* (**9**) (**Scheme 3**). The first step is an oxidative deamination then the reduction of *N*-oxide **10** with PCl_3 following with *N*-alkylation using CH_3I/base, which introduces a methyl group by nucleophilic substitution, obtaining the metabolite *diazepam*.

Scheme 3 shows also an alternative synthesis for *diazepam* from ketone **12**, starting with a cyclization of the corresponding keto-aniline with methyl 2-aminoacetate. Then with CH_3-I/base again the introduction of a methyl group in the nitrogen of the amide leads to *diazepam*.

However, d*iazepam* has other alternative synthesis (**Scheme 4**). Starting with the 2-amino-5-chlorobenzophenone **12** and reacting with NH_2OH, we obtain the oxime **7**. Then by reacting with $ClCOCH_2NH_2$, this group is introduced by addition of the amino group to the carbonyl, ready for the next steps: a cyclization by dehydration with $NaHSO_3$ and the introduction of a methyl group to obtain the *diazepam* (**11**).

The last scheme is midazolam's synthesis, as an example of a *diazolobenzodiazepine*.

Midazolam can be prepared from 4-chloroacetanilide (**15**) by treatment with 2-fluorobenzoyl chloride. The obtained ketone **16** is treated with 3-nitro-2-propanamine to obtain the intermediate benzodiazepine **17**. Next, the nitro derivative **17** is reduced, and ethyl orthoformate is added to obtain the tricyclic system **18**. Finally, the oxidation of **18** with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) leads to *midazolam* (**Scheme 5**).

4. Traditional uses and new discoveries

When research scientists could finally give an explanation for the mechanism of action to understand the results they were obtaining with BZDs, a breakthrough happened, not only in the knowledge of anxiety but also in other central phenomena such as sleep problems or seizures.

An important advance was concerning the barbiturates. Barbiturate abuse—both prescription and illicit—peaked in the 1970s, but by the late 1980s, barbiturates had been largely replaced by benzodiazepines for treatment of anxiety and insomnia due to safety issues [19]. BZDs proved to be effective for the same purposes but with a superior therapeutic index and lower risk to cause respiration depression, the principal serious adverse effect that made barbiturates a dangerous drug with restricted uses.

Generally, it can be considered that all BZDs that are actually used in clinical are anxiolytics in low doses and hypnotic in high doses. Pharmacokinetic properties are what differentiate each compound and what define the use. Furthermore, all the treatments with BZDs should be short term due to their probability to cause tolerance and dependence problems.

4.1. Anxiolitics

Back then, the explanation of BZDs' mechanism of action supposed an important discovery in the knowledge of anxiety, which the biological basis was not completely clear.

BZDs should be seen as a symptom treatment for this condition, to facilitate the patients' adaptation or reaction to a difficult situation in their everyday life but not as a first-choice anxiety treatment. Treating anxiety should be a personalized combination of drugs and psychotherapy during the period of time the patient need, and BZDs should be only used for sporadic moments.

Nowadays there are other drugs as a first choice for anxiety treatment that does not present any long-term use problem and that show good results (SSRIs or SNRIs). Anyway, BZDs are

indicated in several anxieties for short-term management of anxiety. They can be also used as an adjunct in treatment for panic disorders (PD), generalized anxiety disorders (GAD), and social anxiety disorders (SAD) as adjuncts to SSRIs for treatment of obsessive–compulsive disorder or as adjuncts to antipsychotics for treatment of acute mania or agitation [8, 20].

The BZDs used for relieving anxiety are the ones with long half-lives, which are converted in other active metabolites that also have long half-lives. According to this, we achieve continuous drug concentrations and therefore a long duration of action and effects. Some of these drugs are *alprazolam*, *bromazepam*, *oxazepam*, *clorazepate*, *diazepam*, and *lorazepam*.

It is important to note that even if the different compounds are in the same family and are used for the same objectives, they have different potencies, and the doses can notably range between compounds. For example, alprazolam is presented in 0.25, 0.5, 1, and 2 mg doses; a dose of 0.5 mg of alprazolam is equivalent to 10 mg of diazepam. That can lead to administration mistakes if there is a change between these two BZDs, for example.

4.2. Hypnotics

The quality of a hypnotic drug is not judged only on sleep but also on the state of the subject on awakening and during day, somnolence or not, on the possibility of adverse effects, etc. BZDs are used for hypnotic purposes because they increase the total sleep time by decreasing the time to fall asleep and the number of awakenings. However, the architecture of sleep is significantly altered [21]: it is composed by four non-REM stages (of which the 1 and 2 are considered light-sleep phases, while 3 and 4 phases are associated with deep sleep) and a REM stage. BZDs reduce the 3 and 4 stages and decrease the REM sleep stage, known as "the most restful phase of sleep" [22]. That could be translated, in a long-term, as a worsening of sleep quality [23].

They are useful for treating occasional insomnia, in short treatments (they must be used only for 2–4 weeks) or with an intermittent use. The most used for this objective are *lormetazepam*, *triazolam*, *nitrazepam*, *loprazolam*, *flunitrazepam*, and *estazolam*.

Either short-acting or long-acting, BZDs can be used:

- To treat insomnia characterized by a difficulty of falling sleep, this BZD will have a rapid onset and a short duration of action, with the objective to quickly achieve higher concentrations. Among hypnotic benzodiazepines, triazolam is one, which has the fastest effect, but it also causes adverse effects such as amnesia and dependence problems.
- In other cases, when the patient tends to awake in the middle of the night and is not able to continue sleeping, intermediate or long action BZD is more useful.

The duration of the action must be adapted to the sleep period: if it is too short, it might be insufficient, and if it is too long, the patient can have residual insomnia on the next day.

In many cases, there is no need of pharmacological treatment for insomnia. The following recommendations are proposed: to change the sleep habits, to avoid caffeine late in the day, or to limit the electronics devices (mobile phone, TV) in the bedroom. Exercise can often help to promote a more restful sleep as well. All these options must be tried before starting a BZD treatment.

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4.3. Muscle relaxant

Benzodiazepines such as *diazepam* may be used short term as muscle relaxants reducing the tone of skeletal muscle. The myorelaxant effect is mediated through α_2-containing receptors (and α_3 in a less extent) in the spinal cord and motor neurons [8]. They can also help relieve the pain of the spasticity caused by other CNS pathologies. High doses are used: 2–10 mg even 4 times a day, depending on the severity and the patient's age, so adverse effects must be considered.

4.4. Anticonvulsive

Clonazepam is the benzodiazepine most frequently used for long-term control and prevention of chronic seizure disorders. For this purpose, it is used at high doses to achieve high brain concentrations. However, in general BZDs are not the first choice for long-term treatment for epilepsy due to the tolerance and dependence problems that they present. Traditional types of seizure treatments should be used in first line for epilepsy.

Despite that, all BZDs have anticonvulsant properties especially for seizures caused by toxic agents or due to alcohol withdrawal syndrome. For most types of acute or prolonged seizures or *status epilepticus*, an intravenous or rectal benzodiazepine would be the treatment of first choice.

4.5. Amnesics

It is important to note that in the perioperative setting, BZDs are used specifically for their amnesic properties, but in nearly all other instances, amnesia is an undesired side effect.

Their use can be advantageous as an adjunct to anesthesia to induce relaxation and amnesia (procedural memory loss) in cases of outpatient surgery or procedure that allows the patient to return home the same day, for example, endoscopy or colonoscopy, which can cause discomfort to the patients.

Intravenous *midazolam* is normally the preference in these cases due to its rapid onset and short duration of action. However, recent researchers have found that sublingual *alprazolam* is as effective and safe as oral midazolam for sedation during esophagogastroduodenoscopy (EGD): *they were similar in reducing procedural anxiety, and patients had similar tolerance and satisfaction with both treatments; however, sublingual alprazolam was accompanied with less pain/discomfort during EGD* [24].

4.6. Other uses

BZDs can be used in patients in the intensive care unit (ICU) in those with mechanical ventilation or those with acute pain, although they should be used carefully because of the possible respiratory depression in some cases.

- They are proved to be first-line choice in AWS treatment. AWS results in people who are dependent on alcohol and either stopped drinking or reduced their alcohol consumption. Severe forms of AWS may be associated with generalized seizures, hallucinations, and delirium tremens, which can be fatal [25]. BZDs have proved to be the best studied and

most effective drugs, especially to prevent severe symptoms and particularly the risk of seizures and delirium tremens. The most used oral BZDs for this pathology are diazepam, chlordiazepoxide, and lorazepam.

- BZDs can be used for abreaction, a technique applied to recover memories.

5. A new discovery: BET inhibitors

A few years ago, BZDs started to be investigated by their possible action as BET protein inhibitors. These families of proteins (bromo- and extra-terminal domain, BET) are epigenetic reader proteins, involved in transcription regulation and chromatin remodeling. Each protein contains two domains (D1 and D2) that bind acetylated lysine on histones H3 and H4. This bind is produced in the hydrophobic pocket of BET by hydrogen bonding, where researchers found high-affinity small molecule ligands that block the binding with the histones. These BET protein inhibitors are the first successful example of inhibition of epigenetic readers, and they offer the opportunity to target cancer drivers, for example, the family of proto-oncogenes *MYC*. Thus, BET inhibitor treatment of cancer cells dependent on the oncogene c-*MYC* can result in significant antiproliferative and cytotoxic effects [25].

In view of the results, at least 10 BET inhibitors are in clinical trials today for the treatment of a range of hematological cancers (including leukemia, lymphoma, and myeloma), certain solid tumors, and atherosclerosis [26]. Most of these molecules are structurally based on the BZD family and have their pharmacological properties.

On November 2017, a new study was published concerning the *design, synthesis, and biological activity of 1,2,3-triazolobenzodiazepines BET inhibitors* [27]. Starting from the previous recent discoveries, they focused in testing if the different molecules had acetyl lysine mimicking activity. Based on the bromodomain-binding framework, they developed a 1,2,3-*triazolobenzodiazepine* with the optimal conditions for hydrogen bounding: a diazepine ring for protection and high affinity with asparagine.

The synthesis of **25** (**Scheme 6**) was carried out in the following way: first formation of the diarylamine **21** from the 1,2-diiodobenzene **20** and the aniline by means of a Buchwald cross-coupling reaction. Then, an introduction of an alkyne under Sonogashira coupling reaction conditions. The acylation of **22** with the 2-chloroacetyl chloride leads to **23**. Subsequently the addition of sodium azide to **23** allows a 1,3-dipolar cycloaddition cascade that leads directly to the *triazolobenzodiazepine* **24** by heating at 150°C. The yield of this step was low (13%). Finally, the reduction of carbonyl group with BH_3 provided **25**.

They assessed this compound by a binding assay (*AlphaScreen*), and it showed good activity against all bromodomains. After that, they optimize it and expand the series, obtaining a range of analogs.

BET inhibitors have been shown to have a remarkable effect on certain primary cells and cell lines, consequently of downregulation of oncogenes like c-*MYC*. From all of the analogs, and after the tests were done, they selected two of these compounds, both with excellent selectivity in BET domains, and tested them against a cancer cell panel to study their antileukemic effects.

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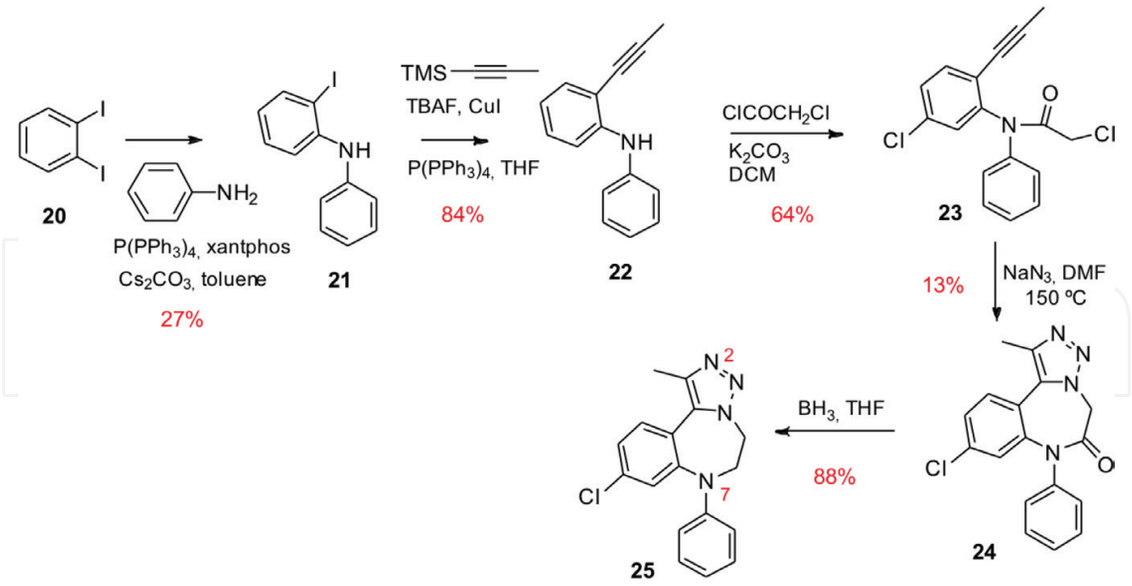

Scheme 6. Synthesis of 7 (1,2,3-*triazolobenzodiazepine*) [27].

They showed potent antiproliferative activity in some specific leukemia and downregulation of oncogene *MYC*. They also tested them on primary mouse osteosarcoma (OS) cells: both compounds inhibited proliferation of primary OS cell types, showing the utility of 1,2,3-*triazolobenzodiazepine* derivatives in cancer studies.

This new line of study shows a different and interesting use for BZDs that needs to continue to be developed according to the actual interest in the different lines of cancer treatment research. It is an example of how drugs that already exists for a determinate purpose can become the main source for a study with very different new indications.

5.1. Analysis of the reasons that lead to abuse and addiction

Nowadays, BZDs are mostly used for symptomatic treatment of anxiety and/or insomnia, anesthesia, and AWS. Many BZDs received FDA approval for the treatment of "anxiety states" or "anxiety disorders." Therefore, BZD treatment represents an off-label use (without FDA disease-specific approval) for most mental disorders.

Serotonergic agents (SSRIs or serotonin and norepinephrine reuptake inhibitors [SNRIs]) are the first-line pharmacologic treatments for anxiety disorders. These antidepressants typically take 4–6 weeks before they exert clinical effect, even more in the treatment of anxiety symptoms. When this treatment is initiated, it is typical to co-administer BZDs [28].

Moreover, antidepressants are not necessarily effective at starting doses. During titration to an effective dose (by increasing it in a gradual way), a patient can remain symptomatic. Consequently, it can be months before anxiety relieves because of the antidepressant treatment. Theoretically, BZDs are commonly used as adjuncts during the first few weeks of starting a serotonergic agent with the hopes that once a therapeutic dose is achieved, the BZD can be discontinued.

Unfortunately, there is no evidence to support this practice. This was verified in a cohort's study performed between 2001 and 2004 to patients with recent depression diagnosis and with no

previous treatment. No significant differences were found between the group that only was taking antidepressant and the group that simultaneously started both antidepressant and BZD [29].

Despite conventional knowledge, BZDs do not make SSRIs more effective when prescribed simultaneously. There are no long-term benefits, but there is a long-term risk of physical dependence (tolerance and/or withdrawal) when these drugs are associated at the beginning of the treatment. Moreover, it is frequently for patients to continue BZDs long term in the presence or absence of the antidepressant. Despite many clinicians intending to interrupt them after the 4–6 weeks (when SSRIs begin to have their therapeutic effect), 12% of patients receiving this treatment and trialed at the study previously mentioned to continue BZDs for over 6 months—sometimes in the absence of SSRIs—likely indicating the difficulty of discontinuing BZDs once started [29, 20].

Despite these mentioned factors, the rate of physicians prescribing this way has not stopped growing in the last 25 years [28]. Because of the risks associated with BZD, this practice (simultaneous new use at antidepressant initiation) requires careful consideration.

The only mental disorders—not including alcohol/sedative-hypnotic withdrawal—for which there is an evidence basis for BZD treatment are PD, GAD, social anxiety disorder (SAD), and insomnia. For these four conditions, BZDs have only demonstrated efficacy for short-term durations (less than 2–4 weeks) and for treatment-resistant cases. Even for those conditions, which there are proofs of efficacy, there is no evidence for benefit in long-term treatment [20].

Nevertheless, BZDs are frequently overprescribed for other indications for which there is no evidence of efficacy, to individuals who have contraindicated comorbid conditions, for longer periods than are recommended, and before other first- and second-line treatments are tried or offered.

Apart from these four previously mentioned, there are no other mental disorders with an evidence basis for BZD treatment. To the contrary, this treatment in post-traumatic stress disorders (PTSD) is particularly concerning because BZDs have not proved to possess preventative value and may actually increase the risk in 2–5 times of developing PTSD among the patients with trauma. Moreover, PTSD is commonly comorbid with conditions that are contraindicated for BZDs (substance use disorders, traumatic brain injury, depression, etc.), and BZDs can inhibit trauma-focused psychotherapy by inhibiting the cognitive processing, which is extremely necessary for a good recovery [30].

It is common in many disorders to find patients receiving treatment not supported by evidence-based clinical practice guidelines (CPGs). Though the only FDA-approved medications for PTSD are *sertraline* and *paroxetine* (both antidepressants), of PTSD patients receiving pharmacotherapy: 65–90% receive antidepressants, 37–74% receive sedative-hypnotics (including BZDs), and 21–34% receive antipsychotics [20]. In fact, most of CPGs strongly recommend against the use of BZDs for PTSD, such as the guideline done by the Department of Veterans Affairs/Department of Defense (VA/DOD) [31].

Psychotherapy is the gold standard treatment for anxiety, while medications are generally considered adjunctive: only serotonergic agents (SSRI and SNRI) are considered first-line pharmacologic monotherapies [32]. The evaluation of the recovery should be based on the improvement of the normal functioning and not only based on the results of the sedation, which often does not relate with the patients' improvement. A variety of evidence-based

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treatments might be considered previous to initiating BZD treatment if there is not a strong evidence of efficacy. In many cases of anxiety, psychotherapy or support would be advised, instead of starting a treatment with a high potential of risk.

An other reason that should be considered when talking about possible addiction is, as previously mentioned, the elevated percentage of patients who continue to use BZDs for long term or self-medication. Even when the prescription instructions are followed, these drugs normally present difficulties when discontinued, mostly due to their properties such as the quick onset and relief of the symptoms that are likely to cause addiction.

To help prevent abuse and diversion of BZDs, prescribers should use appropriate precautions, similar to those used when prescribing other controlled substances such as opioids.

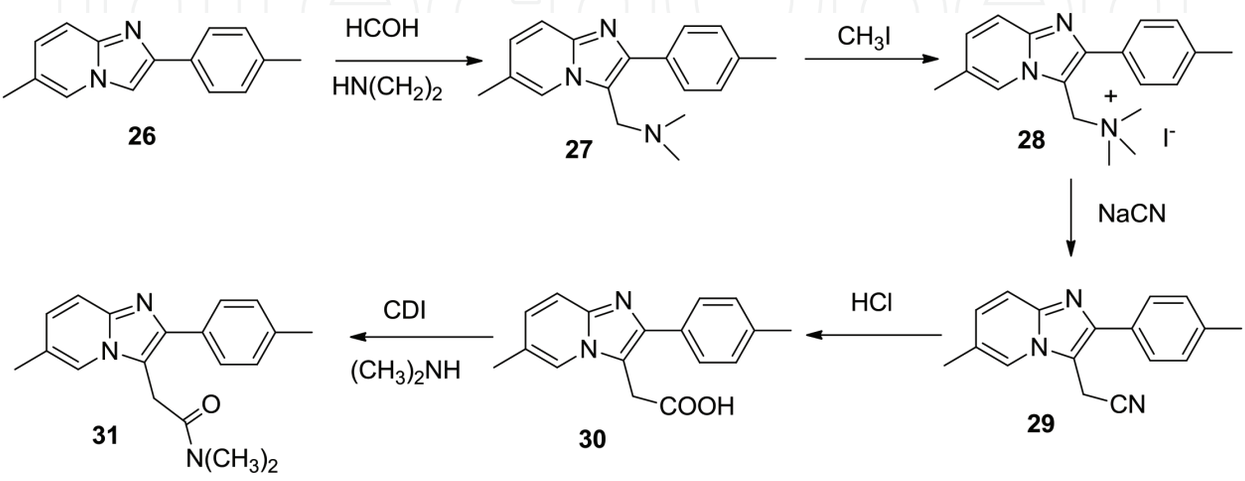
5.2. "Z-drugs" or nonbenzodiazepines

As introduced before, a new type of related drugs appeared in the 1990s specifically for insomnia treatment: nonbenzodiazepines receptor agonists (NBRAs) or Z-drugs.

There are three approved: *zolpidem*, *zopiclone*, (*eszopiclone* as the active enantiomer), and *zaleplon*. They present the same mechanism of action than BZDs (facilitating the inhibitory effect of GABA) but showing more selectivity for BZ1, which affects specifically to sedation and also cause fewer adverse effects [19]. However, they do not have BZD chemical structure, not even the same between them.

The synthesis of zolpidem is proposed in **Scheme 7**. The aminomethylation of the imidazopyridine yields the 3-dimethylamino derivative **27**, which is alkylated with CH_3I to obtain the quaternary ammonium salt **28**, which is then reacted with sodium cyanide to give the corresponding nitrile **29.** The acid hydrolysis of the nitrile yields the carboxylic acid **30**, which is activated with carbonyldiimidazole (CDI) and then treated with dimethylamine excess to obtain the corresponding dimethylamide **31** (*zolpidem*) (**Figures 6** and **7**).

The adverse effects of traditional BZDs (like alteration of the sleep architecture, reduction of deep sleep (REM), and residual effects on daytime lead to dependence, tolerance, and withdrawal) have driven the development of these alternative sedative-hypnotic drugs.



Scheme 7. Chemical structure of the three commercialized Z-drugs.

Figure 6. Synthesis of zolpidem via Mannich aminomethylation [33].

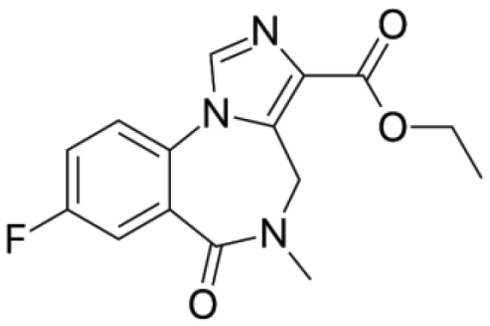


Figure 7. Flumazenil.

Z-drugs have significant hypnotic effects by reducing sleep latency and improving sleep quality, though duration of sleep may not be significantly increased. Their pharmacokinetics properties approach those of the "ideal hypnotic" with rapid onset within 30 min and short half-life (**Table 3**).

Initially clinical trials were promising due to their low adverse effects and improvements, reducing the potential of abuse. They possess short duration of action and half-life, do not disturb sleep architecture, and cause less residual effects during daytime hours, making them more clinically attractive than BZDs [22, 35].

Despite that, there are other kinds of side effects that are common among these drugs. During the first trails, the most reported side effects were nausea, dizziness, malaise, hallucination, nightmares, or agitation. Although *zolpidem* appeared to be well tolerated, there were cases of abuse, withdrawal, or tolerance in cases where the recommended dose of *zolpidem* was exceeded or with patients who had a history of substance abuse and/or a psychiatric disorder.

Later, cases of Z-drug reports causing visual hallucinations and amnesia in people with no history of mental disease appeared. Although the mechanism of action to describe these phenomena is not clear, it is speculated that *GABA receptor (α1 subunit) may be overexpressed, or they may be rapid activation after quick absorption in sensitive individuals* [36]. As seen in the reports, this is especially true for those patients with mental disease such bipolar disorder, borderline

Drug	Onset (min)	Half-life (h)	Duration of action	Insomnia indication
Zolpidem	30	1.4–4.5	Short	Sleep onset
Zolpidem ER	30	1.6–5.5	Intermediate	Sleep onset and sleep maintenance
Zaleplon	20	0.5–1	Ultrashort	Sleep onset
Eszopiclone	30	6–7	Intermediate	Sleep maintenance

ER = extended release. Due to its duration of action, *zaleplon* does not present next-day drowsiness; it can be taken within 4–5 hours of wake time without the risk of hangover effect [34].

Table 3. Principal Z-drugs and properties.

personality disorders, or drug abuse potential, because the sensitization of GABA receptors in some of these patients may predispose to the development of hallucinations [37].

Other symptoms seen in the reports are bizarre and complex behavioral effects like sleep-related complex behaviors [38], proved to be related with Z-drugs, particularly *zolpidem* [39]. There have also been some reports and posterior studies of suicidal attempts by zolpidem. In 2016 a study demonstrated a significant association between using *zolpidem* and suicide or suicide attempt in people with or without comorbid psychiatric illnesses [40].

Reports of incidents related with these drugs had increased over the years, indicating that *zolpidem* and others may not be considered as risk-free and should be carefully prescribed, dispensed, and used [19].

Studies have seen that Z-drugs usually present the same problems that of BZD: they are prescribed for longer use with excessive doses, particularly in the elderly. This fact shows a relation with the high incidence of falls and risk of hip fracture among these patients [15]. There are also studies that support the lack of demonstrable improved efficacy of Z-drugs, which causes similar rates of adverse events compared to benzodiazepines [41].

The last aspect to consider these drugs is their potential recreational use. As what happens with BZD, by mixing high doses of drug with opioids or alcohol, a major CNS depression is obtained, producing euphoric "high" symptoms with anterograde amnesia on the next day. A study carried out in 2011 showed that when *zolpidem* was ingested with other medications or ethanol, admissions to the ICU were highly common. Despite its reported safety, these overdoses often required ICU admissions, which were results of the association with other drugs and/or alcohol [42].

5.3. Tolerance, dependence, and withdrawal syndrome

Despite BZDs' successful use, tolerance was rapidly discovered and studied. A clinical trial in 1985 performed by the Medical College of Ohio showed the regional differences in down-regulation of brain BZD receptors using a quantitative autoradiographic method because of the chronic presence of this drug to its receptor locus [43].

Clinical experience showed that benzodiazepines are frequently used for long-term treatment, and there are many reasons for this: prescribing tradition, patient preference, difficulties

associated with benzodiazepine withdrawal (even in patients taking low doses) because they have a rapid clinical onset of action, and good efficacy with few initial adverse effects. Long-term intake of a drug can induce tolerance of the secondary effects (because increased amounts are needed to achieve intoxication, or the effects are minimized with continued use) and physical dependence, a risk associated even at therapeutic doses [44]. There is no standard definition of long-term use, but the most common is 6–12 months. Tolerance to the sedating effects of benzodiazepines is rapid, but tolerance to the anxiolytic effects develops slowly and to a limited extent.

Symptoms of withdrawal after long-term benzodiazepine use usually develop faster with shorter-acting drugs (within 2–3 days) than with longer-acting drugs (within 5–10 days). This is presented by physical symptoms (spasms, weakness, muscle tension, etc.) and psychological symptoms (anxiety and panic disorders, agitation, mood changes). Seizures are also quite common, especially if the agent is discontinued abruptly. Severe withdrawal symptoms include paranoid thoughts, hallucinations, and delirium [7].

5.3.1. Intoxication and antidote

Generally, BZDs are a safe family of drugs because they present a large therapeutic index. Patients may misuse them by self-medication or by increasing the therapeutic dose for recreational purposes [45]. Real risk comes when patients combine these drugs with other substances: the combined use of alcohol and benzodiazepines increases the risk of a fatal overdose. A similar fatal interaction can occur with opioids: BZDs are often misused by high-risk opioid users and are associated with morbidity and mortality among this group.

Misuse or abuse may lead to intoxication or a withdrawal syndrome, which may be fatal. Differential diagnosis of intoxication by these drugs could be polydrug use (toxicity is highly augmented by combination with other drugs), epilepsy, agitation, alcohol withdrawal delirium or respiratory depression, among others [7].

Fortunately, overdose with benzodiazepines and Z-drugs responds to an antagonist, *flumazenil*, although it has its limitations and potential adverse effects.

This benzodiazepine antagonist, *flumazenil*, is available for the treatment of acute benzodiazepine intoxication and has been shown to reverse also the sedative effects of all three Z-drugs [35]. Actually, it is a BZD with high affinity, which is able to displace other BZDs and has very short half-life, of approximately 1 hour.

It is used for:

- BZDs or Z-drugs intoxications
- To reverse the effects of anesthesia caused by a BZD
- Diagnosis of states of coma, which have an unknown origin

However, it may not completely reverse respiratory depression, and it can provoke withdrawal seizures in patients with benzodiazepine dependence [9].

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5.3.2. Possible treatment of dependence to avoid withdrawal symptoms

Based on several guidelines to avoid withdrawal symptoms, different steps are recommended when patients want to quit a BZD treatment. For the following recommendations, a specific guideline is consulted: *Benzodiazepines: how they work and how to withdraw* or commonly known as *The Ashton Manual* [46]. It is written by Professor C Heather Ashton, a psychopharmacologist from Newcastle, who has dedicated the majority of her career to psychotropic drugs, and especially to BZDs.

Successful withdrawal strategies should combine gradual dosage reduction and sufficient psychological support. The precise rate of withdrawal is an individual matter and should be personalized, depending on many factors including the dose and type of BZD used, the duration of use, and the personality and the will of the patient. For patients without any motivation for withdrawal and those with a severe depressive episode or other major mental disorders, stabilization might be preferable before initiating withdrawal treatment [7].

Various authors suggest optimal times from 6 to 8 weeks to several months for the duration of withdrawal, but some patients may take a year or more if they have taken BZDs in prolonged use. The best results are achieved if the patient himself is in control of the rate of withdrawal and proceeds at whatever rate he finds tolerable.

5.3.2.1. Dose tapering

Sedative withdrawal symptoms can be avoided by slowly tapering down the dose of the BZD over several weeks and by managing the anxiety if needed. Under any circumstances it is recommended to suddenly stop the treatment. Abrupt withdrawal, especially from high doses, can precipitate convulsions, acute psychotic or confusional states, and panic reactions [47]. The ideal situation is one where the patient, with the help of the doctor, decides together the schedule, accepting that there will be readjustments to the time according to his progress. The length of time between each dose reduction should be based on the presence and severity of withdrawal symptoms. The longer the interval between reductions, the more comfortable and safer the withdrawal would be [48].

5.3.2.2. Switching to a long-acting BZD

With short-acting BZDs, it is impossible to achieve a smooth decline in blood and tissue concentrations because of the way they are eliminated quickly from the body. In these cases, it is preferred to switch to a long-acting and slowly metabolized BZD such as *diazepam*. Due to its metabolites and long half-life, it is easy to decrease the concentrations in a smooth and gradual way.

The dose has a very important role: not only it has to be changed by the equivalent in *diazepam* but it also has to contemplate the properties of each BZD (if changed to an anxiolytic for a hypnotic, different symptoms can be expected). *Diazepam* is also good to switch to, because its presentation (2 or 10 mg) makes the dose adaptation easier for every patient.

As indicated before, there is an equivalence of doses between different compounds depending on the active metabolites and the potency (**Table 4**).

Benzodiazepine	Half-life (h) (active metabolite)	Oral dosages (mg)
Alprazolam (Xanax)	6–12	0.5
Clonazepam (Klonopin)	18–50	0.5
Lorazepam (Ativan)	10–20	1
Diazepam (Valium)	20–100	10
Chlordiazepoxide (Librium)	5–30	25
Clorazepate (Tranxene)	36–200	15
Oxazepam (Serax)	4–15	20

Table 4. Half-life and equivalent potencies of BZD anxiolytics [5].

Most potent drugs like *alprazolam*, *clonazepam*, or *lorazepam*, which has 10–20 times more potency that *diazepam*, are highly addictive; dependence develops rapidly, and they are particularly hard to leave. In addition, their dose presentations do not allow a gradual dosage reduction when withdrawal.

6. Conclusions

Concerning the prescriptions, **guidelines have failed** to reduce the prescriptions: clinicians do not always adhere to recommendations to use BZDs as hypnotics and anxiolytics only for short term and only after trying psychological therapies. It has been difficult to accept the high risk and low benefits of the long term in most of the cases.

The **equivalence of doses** between different compounds had presented difficulties, leading to incorrect and excessive dose prescriptions in many situations. Prescriptions of most potent BZDs (as *alprazolam*, *clonazepam*, *or lorazepam*) with excessive dosage are the more problematic, partly of their addictive potential and partly of their dose presentation, that does not allow a gradual dosage reduction when withdrawal.

New lines of study related with BZDs as **BET inhibitor** compounds are an interesting way to change the direction of the therapeutic uses, especially long term. Other new uses, as perioperative, are a valuable way to use an adverse effect derived from the biological activity and apply it with a clinical purpose.

After analyzing the advantages and disadvantages of the **Z-drugs**, it can be concluded that even if they are not exactly as BZD, they must be treated with the same precaution due to the amount of adverse effect reports that had appeared over the recent years.

Despite the amount of biomedical literature on BZDs and Z-drugs, there is still a need to answer vital questions relevant to their effectiveness and safety in society, for example, the possibility of irreversible effects due to extended treatment, especially those associated to new safety accusations [16].

The constant investigation concerning BZDs is an indication that the problems related with these drugs are an actual concern, not only as a medical issue but also as a social concern. On July 11, there is a "World Benzodiazepine Awareness day (W-BAD)," with the objective to educate the population, to offer support to the patients suffering from dependence, and to try to gain global awareness about the dependency this kind of drugs cause if they are not prescribed correctly, among others [49].

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