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BENZODIAZEPINES AND DERIVATIVES

Overview, analysis and synthesis

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Main scope: Pharmaceutical chemistry

Secondary scopes: Pharmacology and therapeutics, Organic Chemistry

INDEX

1. ABSTRACT / RESUM

Benzodiazepines are widely used drugs for several indications. This study provides, on the one hand, a global vision of this family starting for their fortuitous discovery, the synthesis of their derivatives, their mechanism of action which is well known nowadays, the actual classification according to the chemical structure and the pharmacokinetic properties and their uses and indications, including the traditional and the new ones.

On the other hand, the study is focused in the dependence and tolerance derived from their use, many times lead by a misuse of the patient, wrong prescriptions or extended treatments. A withdrawal program is proposed, including the important factors or criteria to success, with a slow and gradual reduction of these drugs to avoid relapse or severe adverse effects.

New lines of research related to benzodiazepines are taken into account, including the new therapeutic uses but also the adverse effects in short and long-term. They are also analyzed the new discoveries concerning the non-benzodiazepinic drugs due to the close relation they have with benzodiazepines.

Les benzodiazepines son medicaments àmpliament utilitzats per nombroses indicacions. Aquest treball proporciona, per una part, una visió global de la família començant pel seu descobriment fortuït, la síntesi dels seus derivats, el seu mecanisme d'acció àmpliament conegut a l'actualitat, la classificació actual segons estructura química i propietats farmacocinètiques i els seus pertinents usos i indicacions, tant els tradicionals com els mes nous.

Per altre part, el estudi es centra en la dependència i tolerància derivada del ús d'aquests medicaments, molt cops per una mala utilització per part del pacient o per prescripcions errònies i/o massa extenses. També es proposa un model de programa de retirada que té en compte tots els factors necessaris per aconseguir reduir gradualment aquests medicaments, sense patir cap recaiguda ni efectes secundaris severs, fins a aconseguir-ho amb èxit.

Es tenen en compte les línies de recerca actuals en relació a benzodiazepines, tant per nous usos terapèutics com per efectes secundaris, ja sigui a curt o llarg termini. També s'analitzen els nous descobriments pel que fa als derivats no benzodiazepínics ja que tenen una estreta relació amb les benzodiazepines.

2. INTEGRATION OF THE DIFFERENTS AREAS

This study here presented is considered to be fundamentally multidisciplinary. The objective is not only to integrate the three specific areas but also to complement it with the knowledge acquired throughout all the career. These three areas are **Pharmacology, toxicology and therapeutic chemistry, Organic chemistry** and **Pharmaceutical chemistry**, being this last the principal.

The main field of this project is Pharmaceutical chemistry, since one of the objectives is to understand the relations between the structure and the biological activity of these compounds. New discoveries in relation with these drugs are analyzed, with the objective of improve their properties and to find new clinical purposes. Organic chemistry has an important role too, concerning the synthesis of benzodiazepines and their chemical structure. The line of approach for the study is mainly between these two chemistries due to their close relation.

Nevertheless, this project contains a wide part of characterization and description of the drug family, their mechanism of action and their biological activity, among others. All these sections can be classified within the framework of pharmacology, toxicology and therapeutic chemistry, as well as the clinical applications.

To do a complete overview of a drug is necessary a global approach, but it is important to know how this three fields connect and participate within this study in particular.

3. INTRODUCTION

3.1 Discovery and history

Many of the drugs that had represented a great advance in many therapeutic approaches were not the result of a rational design but of a consequence of casual observations, fortuitous discovers or serendipity. Way back then, a rational design didn't 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 Hoffman-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 *chlorodiazepoxide*, the first benzodiazepine (BZD), 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 *chlorodiazepoxide* 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 the Head of the family.

Initially, BZDs appeared to be less toxic and less prone to cause dependence than older drugs used for the same purposes as barbiturates. An important improvement compared to barbiturates was their lack of respiratory depression, an important safety concern.[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]

In the mid-to-late 1970s, benzodiazepines became the most commonly prescribed medication in the world, providing treatment for "minor forms" of anxiety. It took 15 years for the researchers to associate benzodiazepines and their effect with their high-affinity receptor complex as the mechanism of action. They did it in 1977 and it was the major turning point in this research.[2]

3.2 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.)

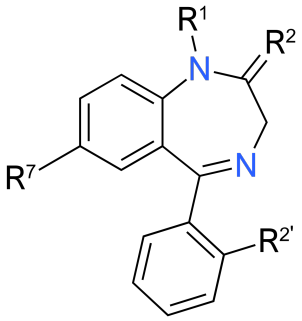


Figure 1. BZD structure

BDZs have proven to be excellent drugs for the several pharmacological properties they present, as shown in the next table:

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

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

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] They are generally considered to not provide analgesia.

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 anti-anxiety drug at higher doses induces sleep.

3.3 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. There are neurotransmitters in the central nervous system (CNS) who increment or decrease the excitability of neurons and so regulate the brain activity. GABA functions as the major inhibitory neurotransmitter and BDZs potentiate that function.

GABA controls the excitability of neurons by binding to the $GABA_A$ receptor. The binding creates a conformational change that hyperpolarize the cell. This effect leads to a minor communication between neurons and, therefore, has a calming effect on many of the functions of the brain. These receptors are located in different areas of the brain (mostly at the cortex and limbic system) and in the spinal cord.

The $GABA_A$ 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 (two alphas, two betas and one gamma) arranged around the central chloride channel. 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 BZDs, which is located in the pairing (interphase) between an α subunit and a ß subunit (Figure 2).

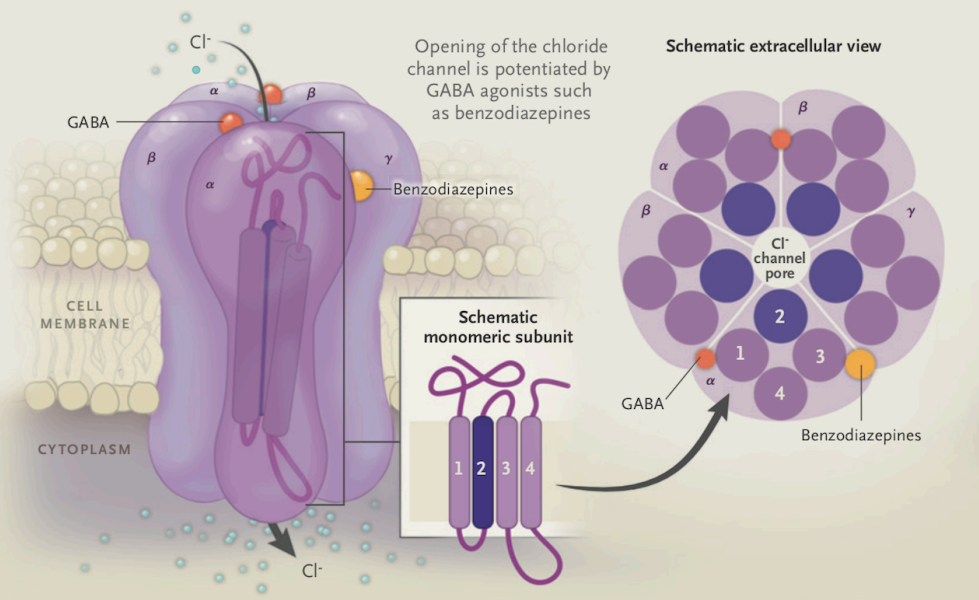


Figure 2: The $GABA_A$ receptor. On the left, a complete view of the receptor, the subunits, the chloride ion channel and the BZDs binding sites. On the right, a top view of the receptor, illustrating the most common combination of α, ß and γ subunits.[7]

The binding of a BZD to his 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 (ethanol, barbiturates, anesthetics…) 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 that GABA itself and this is what explains the elevated therapeutic index (toxic/therapeutic dose ratio), superior than barbiturates. In low doses, barbiturates help 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 a toxicity.

3.4 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 his subunits:

- The BZ1 receptor contains the α1 isoform. This receptor is highly concentrated in the cortex, thalamus and cerebellum, and it is responsible for sedative effects and anterograde amnesia. Sixty percent of $GABA_A$ receptors contain the α1 subunit. Therefore, amnesia is a common side effect of BZD use because the majority of $GABA_A$ receptors contain the BZ1 receptor responsible for amnesia.

- The BZ2 and BZ3 receptors contain the α2 and α3 isoform. BZ2 receptor mediates the anxiolytic and to large extent, the myorelaxant effects, such as does the BZ3 receptor. They are highly concentrated in areas such as the limbic system, motor neurons and the dorsal horn of the spinal cord. The anxiolytic effects of BZDs are believed to be mediated through BZ2 receptors located in the limbic system, and myorelaxant properties are mediated through those in the spinal cord and motor neurons.

Not all BZDs interact with the same type of BZD receptor or with equal affinity to a specific receptor. These differences in a subunit isoform, BZD receptor type affinity, and location within the central nervous system explain the different effects of the various BZDs.[8] Classical BZD interact indiscriminately with all the receptors hence all the range of effects must be expected. However, other drugs interact specifically with one type of receptor, for example Z-drugs, who interact specifically with BZ1.

3.5 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 2 atoms are nitrogen (*diazepine*) normally in 1 and 4 positions, but which 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 and the consequences that have on the activity:

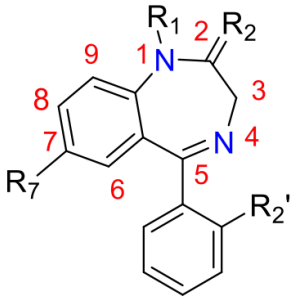


Figure 3. Compound numbering

- **Substitution at the position 1:**
  ↑ activity by alkylation (prodrug). Ex: *diazepam*
- **Substitution at the position in 2:** Electronegative atom (**O** or **N**) derived from carboxyl: first generation of BZDs. It can also be non-substituted. Ex: *medazepam*
- **Substitution at the position 3:** if it is not substituted or has an -OH: ↑ polarity: glucuronoconjugation: faster elimination. Ex: *lorazepam*

- **Benzene ring at the position 5:** optimal for activity.
  - Substituted in *ortho* by **Cl, F**: ↑ activity (Electron-attracting group).
    Ex: *flurazepam* (F), *clonazepam* (Cl)
  - Replaced by another cycle. Ex: Cyclohexenyl (*tetrazepam*)
- **Substitution at the position 7:** Establish the potency. Favorable position to ↑ activity, specially by an electron-attracting group:
  - **NO_2 :** hypnotic action
    Ex*: Clonazepam, nitrazepam*
  - **X**: anxiolytic action
    Ex: *lorazepam, alprazolam*

$CF_3 > NO_2 > Br > Cl > OCH_3 > R$

Any substitution on the other positions (6, 8 and 9) may decrease the activity. There are other compounds who present triazole or imidazole ring fused to the structure and so producing *triazolobenodiazepines* or *imidazolobenzodiazepine* (or diazolobenzodiazepines) respectively.[10]

From a chemical structure point of view, BZDs can be divided in 3 groups:

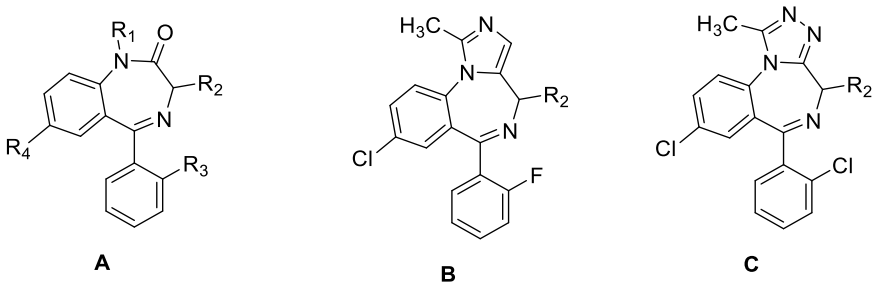


Figure 4. General structure of various BZDs; **A)** 5-Aryl-1,4-benzodiazepine**; B)** *Midazolam*, a diazolobenzodiazepine; **C)** *Triazolam*, a triazolobendodiazepine.[11]

However, the different chemical structures show no relation with the therapeutic uses or effects. The main classification will be depending on the onset and duration of the action.

3.6 Pharmacokinetics and pharmacodynamics

Some of the pharmacokinetics properties, specially solubility and metabolism, change depending on the side groups (R) of each BZD. This fact will be decisive when prescribing them. Normally this family of drugs are 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 such as the CNS 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 suppose an important consideration when prescribing these agents. For example, *diazepam*, a long-acting BZD, produces the active metabolites *oxazepam, desmethyldiazepam,* and *temazepam*.

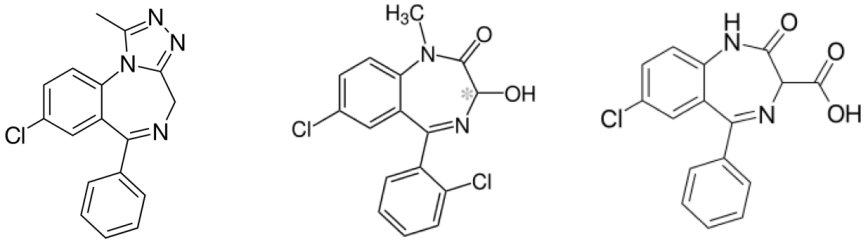
A classification of the BZDs exists in basis of their half-lives time for elimination, an estimation of the time needed to reduce the drug concentration in the plasma by half. After about 5-7 elimination half-lives, a drug is eliminated from the body.[8]

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

3.7 Classification of BZDs

BZDs are classified in terms of their elimination half-life in short acting, intermediate acting or long acting:

- **Short-acting.** Elimination half-life <5 h. Ex: *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. Ex: *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. Ex: *Diazepam, clorazepate*.



Alprazolam *Lormetazepam* *Clorazepate*

Figure 5. Examples of different BZDs

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]

3.8 Abuse and dependence – problem presentation

By the 1970s, BZDs became one the most commonly prescribed medications in the world. Unfortunately, the potential for abuse and dependence was rapidly discovered.

In 1975, BZDs were placed on the Food and Drug Administration (FDA) restricted drug list, reflecting growing concerns about abuse. After years of patients and clinicians reporting tolerance and withdrawal with long-term use, several controlled trials in the 1980s confirmed that BZDs could cause dependence.[12]

With growing data and warnings about BZDs as well as the arrival of safer, more effective anti-anxiety medications like selective serotonin reuptake inhibitors (SSRIs), BZD use slowly declined after the mid-1980s. Despite recommendations against long-term BZD use (more than 2–4 weeks), many providers continued to prescribe them for months or even years, allowing for dependence to occur. Total BZD use actually increased from 1999 to 2014, largely driven by increases in long-term use.[13]

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 are 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*".[14]

Pharmacologic dependence is a predictable and natural adaptation of the body when it is long accustomed to the presence of a drug and may occur even in patients taking therapeutic doses of BZD. However, this dependence, which generally manifests itself in withdrawal symptoms upon the abrupt discontinuation of the medication, may be controlled and ended through dose tapering, medication switching, and/or medication augmentation.[15]

3.9 Adverse effects

Generally, BZD are well tolerated drugs if their 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, dysphasia.
- Exceptionally: rush or urticarial, pruritus, visuals 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 psycho-motor impairment.[16] 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 those 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, increase the half-life elimination. 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 poly-drug 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 depression, specially 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 accusations against these drugs by pharmacoepidemiologic researchers. As shown in the next table (Table 2), and based on the Hill criteria for causation, there is a list of the possible adverse outcome associations.

Table 2. Criteria for BZD/z-drug adverse events.[17]

	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

Nevertheless, 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 have already been proved.[16] Anyway, there are reasons to associate them, so there are several proposed clinical studies for future research and others that are already in process in order to verify this accusations.

4. OBJECTIVES

The main objectives of this study are:

- Study of the discovery, synthesis and design of benzodiazepines and derivatives.
- Presentation of the traditional uses/indications and new discoveries/actual uses.
- Overview of the non-benzodiazepinic related drugs and their adverse effects.
- Analysis of the reasons that lead to abuse or addiction and the relation with the clinicians' prescriptions.
- Proposal of a withdrawal treatment to avoid dependence symptoms.

5. MATERIALS AND METHODES

To elaborate this project, a deep bibliographic research was made with the purpose to find all the information related to this subject. All of the bibliographical information was obtained from several sources, especially scientific articles but also from notes of class, that provided all the necessary knowledge about the subject.

The main databases consulted were the following:

- PubMed (http://www.ncbi.nlm.nih.gov/pubmed), a platform created by NCBI (National Centre for Biotechnology Information)
- Clinical Practices Guidelines
- SchiFinder Scholar

Research criteria consisted in identifying and selecting the most relevant articles, in a chronological order so that the concepts detailed in the project displayed a temporary evolution. Many specific articles of journals of chemical synthesis, pharmacological applications and clinical uses have been used to carry out this work.

Keywords as "benzodiazepine", "benzodiazepine synthesis" and "benzodiazepine derivatives" were used to obtain general information. Otherwise, so as to get information related to precise issues, websites were also consulted.

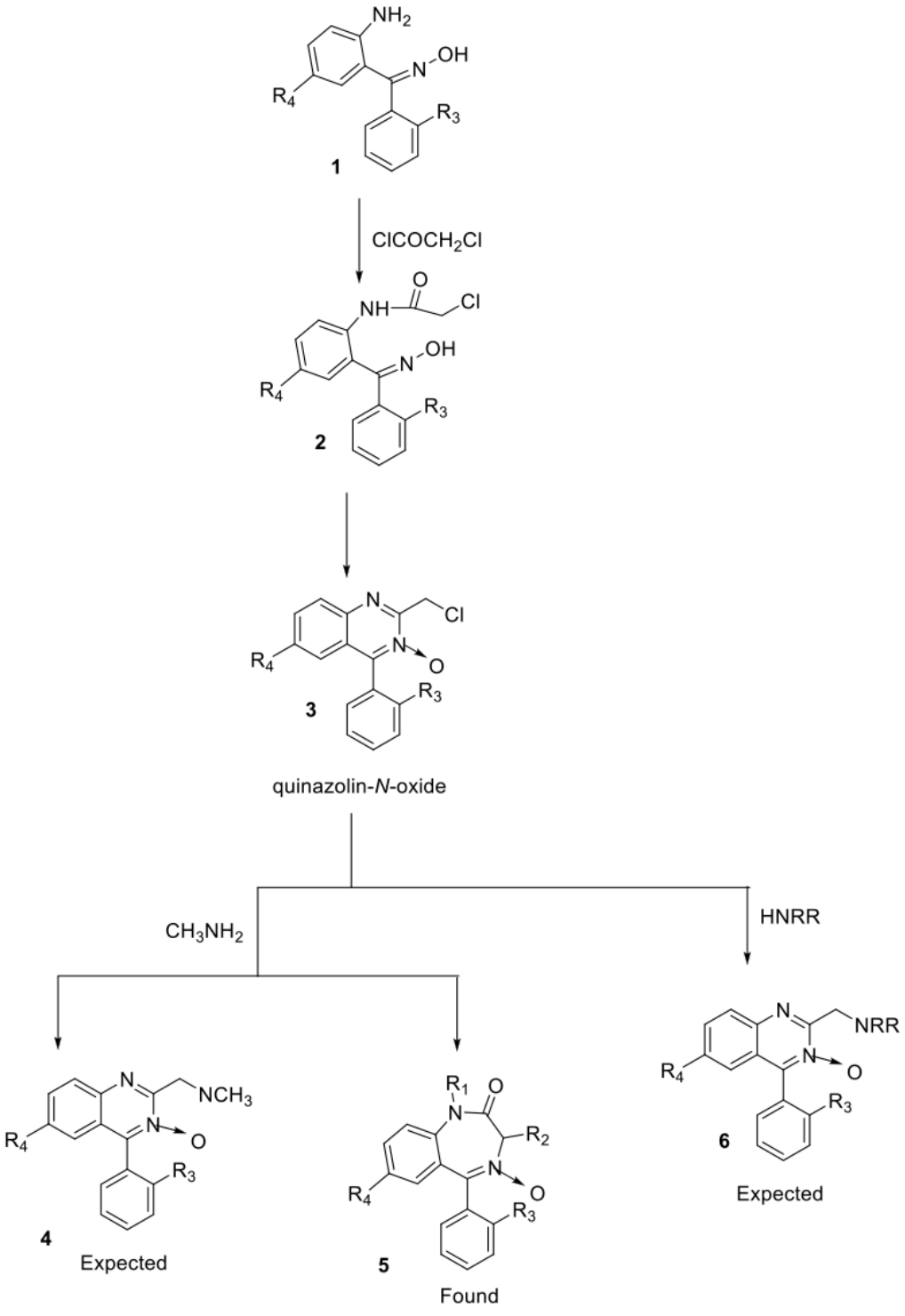
After searching and going through all the above mentioned, the content of this paper was carefully summarized, organized and displayed with the aid of a tutor in order to achieve a logical planning.

Finally, yet importantly, bibliographical references were introduced according the ACS method and were managed and added through Mendeley, an online software used to keep track of any documental consultations and their authors, year of publishing, etc. ChemDraw 16.0 has been used to draw the chemical structures of the compounds and synthesis schemes.

6. RESULTS AND DISCUSSION

6.1 Synthesis of benzodiazepines

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

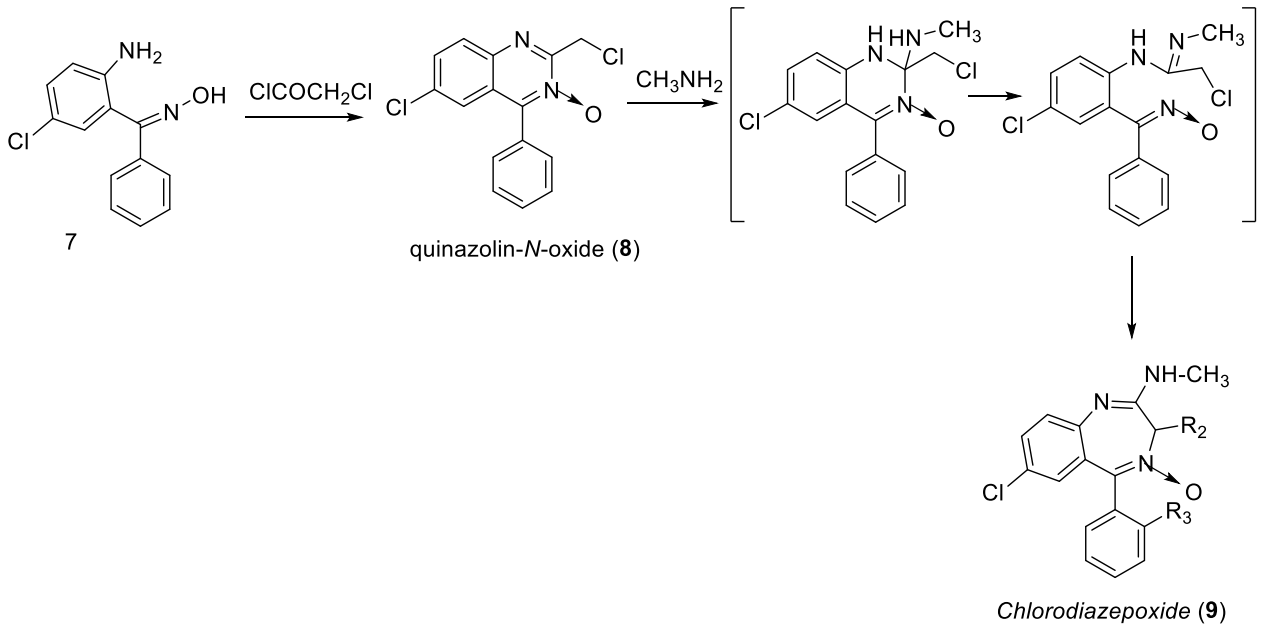


Scheme 1. Synthesis of [1,4]-benzodiazepines.[2]

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 *chloroacetyl chloride* gives the chloroacetamide, which by treatment with NaOH leads to the found *quinazoline-N*-oxide **3**. 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 the *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: *mehylamine* (CH_3NH_2), the result was an unexpected compound considered a derivative from *1,4-benzodiazepine-N^4-oxid* ***(5)***.

An addition reaction in the carbon C-2 of the quinazoline was produced, with a rearrangement of the 6 atoms- ring (quinazoline) to a 7 atoms-ring (benzodiazepine) as a consequence (Scheme 2).



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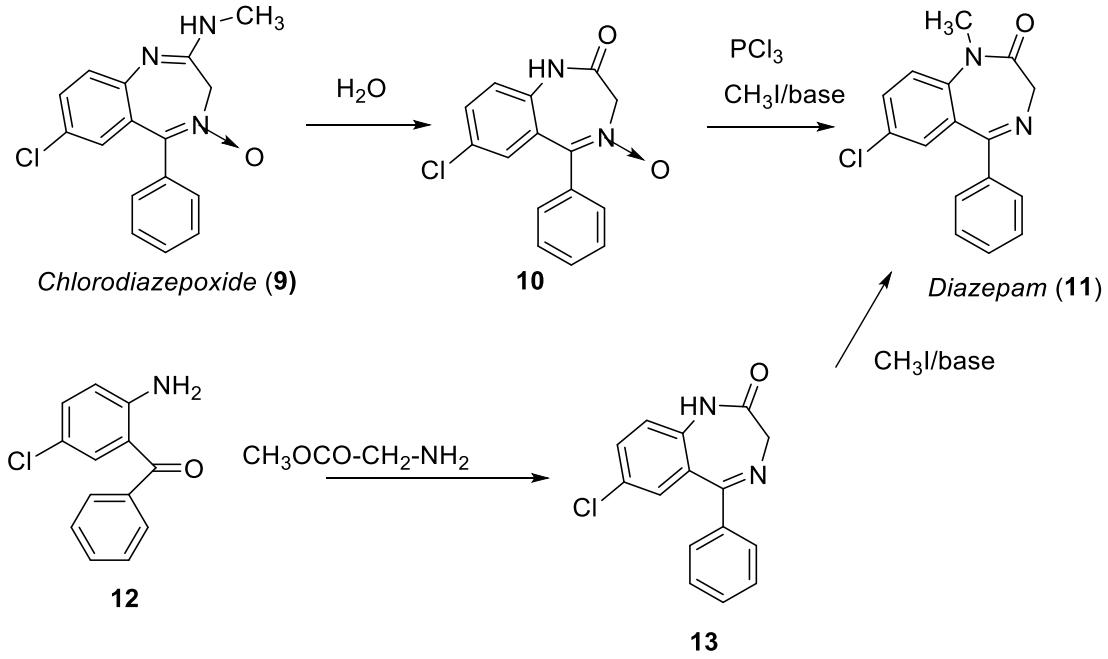
quinazolin-*N*-oxide (**8**)

Chlorodiazepoxide (**9**)

Scheme 2. Mechanism preparation of *chlorodiazepoxide*[18]

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

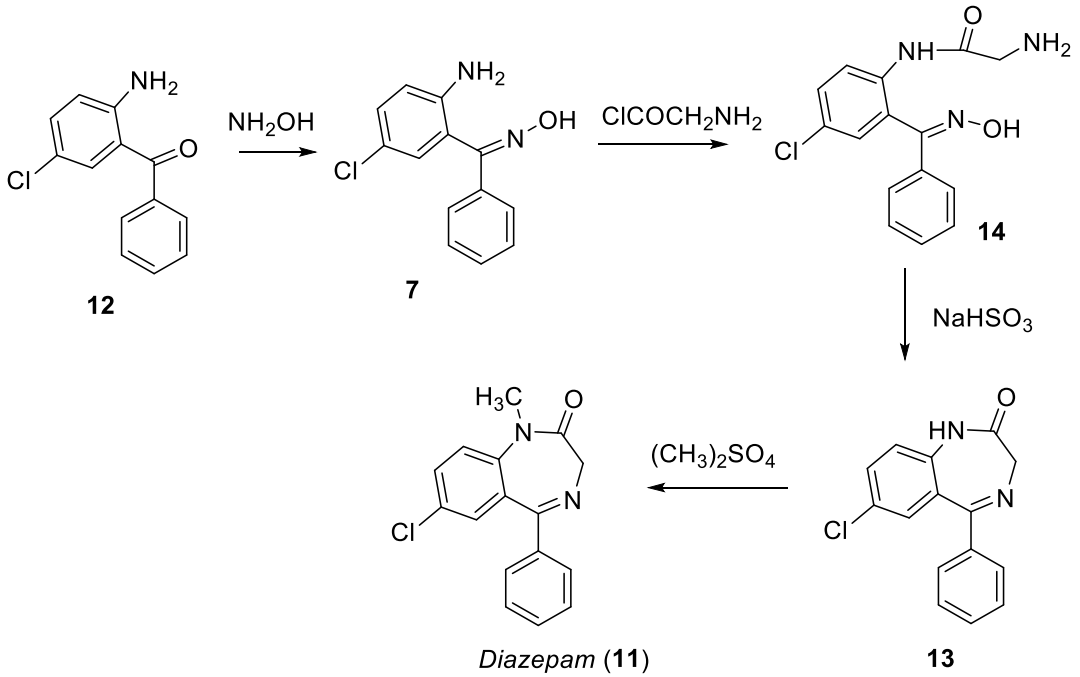
Thus, new anxiolytic drugs as *diazepam, bromazepam or nitrazepam* were found, widely used nowadays.



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

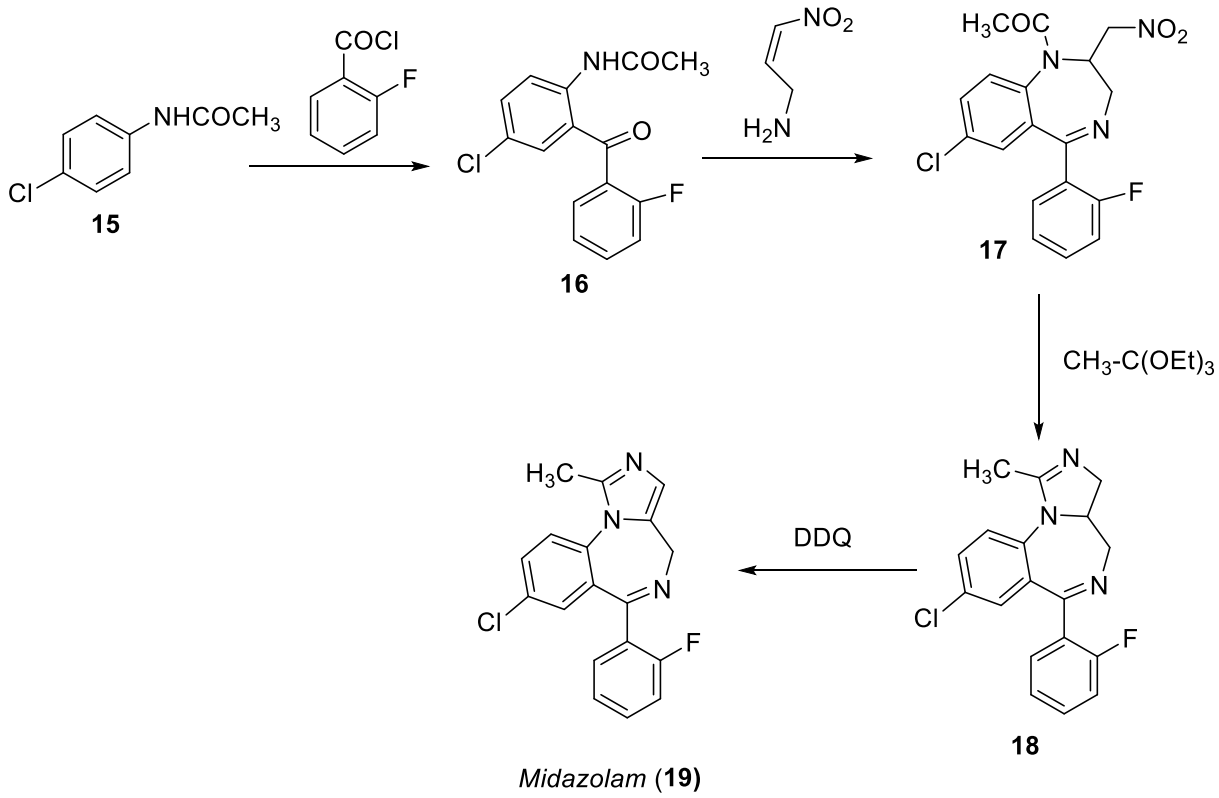
In the first line of the previous scheme, we can see how *diazepam* is formed by metabolism of *chlorodiazepoxide (**9**)* (Scheme 3). First step is an oxidative deamination. Then there is a reduction of *N*-oxide **10** with PCl_3 following with *N*-alkylation using CH_3I/base, which introduce a methyl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

The second line (Scheme 3) shows an alternative synthesis for *diazepam* from the 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, that leads to *diazepam*.



Scheme 4. Alternative synthesis of *diazepam*.[18]

However, d*iazepam* has other alternative synthesis (Scheme 4). Starting with the 2-amino-5-chlorobenzophenona **12** and reacting with NH_2OH we obtain the oxime **7**. Then by reacting with $ClCOCH_2NH_2$, the 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*.



Scheme 5. Synthesis of midazolam.[19]

Last scheme is midazolam's synthesis, as an example of a *diazolobenzodiazepine*. *Midazolam* can be prepared from 4-chloracetanilide (**15**) by treatment with 2-fluorobenzoyl chloride. The obtained ketone **16** is treated with 3-nitro-2-propenamine 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 the *midazolam*.

6.2 Traditional uses and new discoveries

When 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 the anxiety but in other central phenomena 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.[20] BZDs proved to be effectives 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 dangerous drugs 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 must be short-term due to their probability to cause tolerance and dependence problems.

ANXYIOLITCS

Back then, the explanation of benzodiazepines' mechanism of action supposed an important discovery in the knowledge of the 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 as an adjunct in several anxieties for short-term management of anxiety: 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.[8,12]

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, continuous drug concentrations are achieved and therefore, long duration of action and effects.

Some of these drugs are:

- *Alprazolam*
- *Bromazepam*
- *Oxazepam*
- *Clorazepate*
- *Diazepam*
- *Lorazepam*

It is important to note that, even if the different compounds are from the same family and 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 mg, 0.5 mg, 1 mg or 2 mg doses. A dose of 0.5mg of *alprazolam* is equivalent to 10mg of *diazepam*. That can lead to administration mistakes if there is a change between these two BZDs, for example.

Normally they are used by oral administration, by exception of panic attacks, when they can be administrated by intravenous administration.

HYPNOTICS

The quality of a hypnotic drug is not judged only on sleep, but 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. The architecture of sleep is composed by 4 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 significantly alter it:[21] they 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*
- *Estazolam*

Both short-acting or long-acting BZDs can be used:

- BZDs used to treat that kind of insomnia characterized by a difficulty of falling sleep are those with a rapid onset and a short duration of action, with the objective to quickly achieve higher concentrations. Among hypnotic benzodiazepines, *triazolam* is one with a fastest effect, but it also causes adverse effects such as amnesia and dependence problems.
- In other types of sleep disturbances, for example in those when the patient tends to awake in the middle of the night and is not able to continue sleeping, intermediate or long action BZD are more appropriate.

The duration of the action must be adapted to the sleep period: if it is too short it might be insufficient but 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 should be 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.

Nowadays, the benzodiazepines that were initially FDA-approved for insomnia are not used as frequently today due to the availability of the newer non-benzodiazepine drugs (Z-Drugs), who are approved specifically for treatment of insomnia.

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 $\alpha 2$- containing receptors (and $\alpha 3$ in a less extent) in the spinal cord and motor neurons.[8] They can also help relief the pain of the spasticity caused by other CNS pathologies. High doses are used depending on the severity and the patient's age: it can be 2-10 mg even 4 times a day so adverse effects must be considered.

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, BZDs are not generally the first choice for long-term treatment for epilepsy due to the tolerance and dependence problems that they present. More traditional types of seizure treatments should be used in first line for epilepsy.

Despite of 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*, intravenous or rectal benzodiazepine are the first choice treatment.

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 his rapid onset and short duration of action. However, researchers have recently 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] In addition, by changing the administration mode, the monitoring is no longer need and there are no concerns about possible serious hemodynamic events (side effects in heart rate, systolic pressure and/or arterial oxygen saturation) as with *midazolam*.

OTHER USES

- BZDs can be used in patients in 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 alcohol withdrawal syndrome (WAS) treatment. AWS results in people who are dependent on alcohol and either stop drinking or reduce the alcohol consumption. Severe forms of AWS may be associated with generalized seizures, hallucinations and *delirium tremens*, which can be fatal. As indicated in a recent article about WAS: *"The ideal drug for alcohol withdrawal should have a rapid onset and a long duration of action, a wide margin of safety, a metabolism not dependent on liver function, and absence of abuse potential.*[25] BZDs have proved to be the best studied and most effective drugs, especially to prevent sever symptoms and particularly the risk of seizures and *delirium tremens*. The most used oral BZDs for this pathology are *diazepam*, *chlorodiazepoxide* and *lorazepam*.

6.3 A new discovery: BET inhibitors

A few years ago, BZDs started to be investigated by their possible action as BET protein inhibitors. This family 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

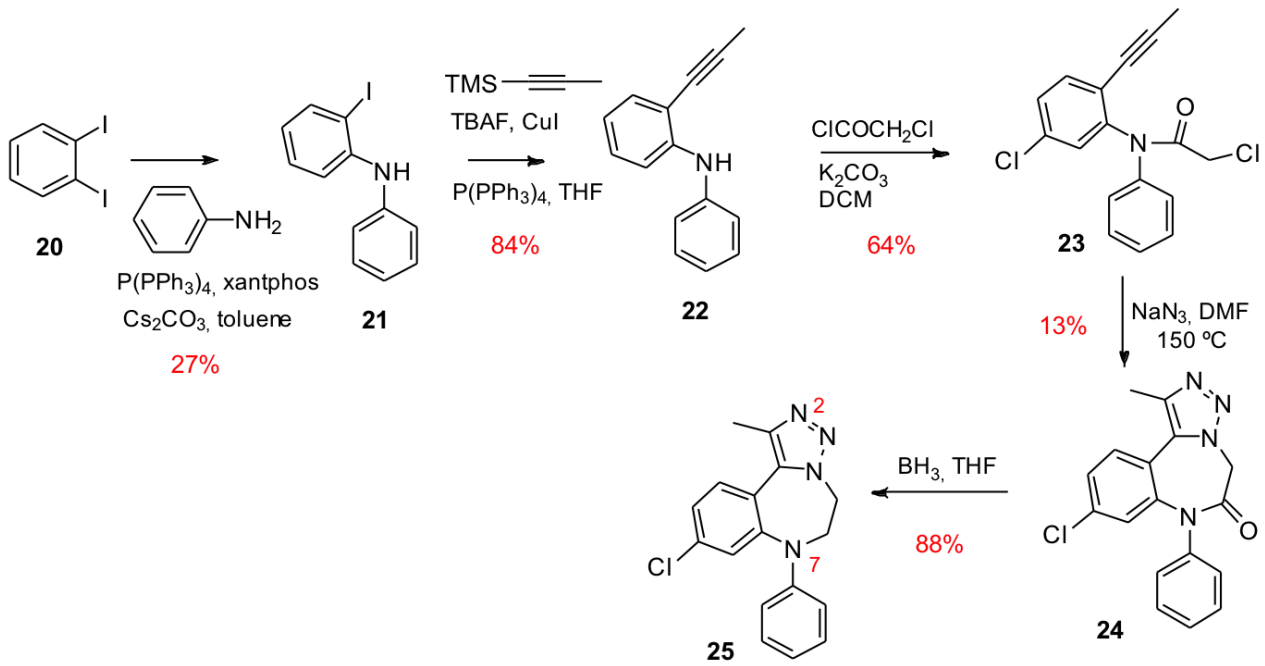
H4. This bind is produced in the hydrophobic pocket of BET by hydrogen bonding, where researchers found high affinity small molecule ligands that block the binding with the histones. The inhibition of BET – histone interactions has shown to result in a disruption of transcriptional programs and so resulting in anticancer and anti-inflammatory activity, among others.

This 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 inhibitors treatment of cancer cells dependent on the oncogene c-*MYC* can result in significant anti-proliferative and cytotoxic effects.[25]

In view of the results, at least 10 BET inhibitors are in clinical trials nowadays 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 BZDs family and have also their pharmacological properties.

On November 2017, a new study was publish 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* (nº **25** in Scheme 6) 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-diiodebenzene **20** and the aniline by means of a Buchwald cross-coupling reaction. Following with introduction of alkyne under conditions of the Sonogashira coupling reaction. 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 ºC. The yield of this step was low (13%). Finally, the reduction of carbonyl group with BH_3 provided **25**.



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

They assessed this compound by 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 all the assays were done, they selected 2 of these compounds, both with excellent selectivity in BET domains, and tested them against a cancer cell panel to study their anti-leukemic effects. They showed potent antiprofiferative activity in some specific leukemia and also 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-*triazolobenzodiazepines* 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 who already exists for a determinate purpose can become the main source for study totally different and new indications.

6.4 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 alcohol withdrawal. 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 four to six 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 relieve as a result 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 recently 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 continued BZDs for over 6 months—sometimes in the absence of SSRIs—likely indicating the difficulty of discontinuing BZDs once started.[29,12]

Despite these mentioned factors, the rate of physicians prescribing this way has not stop growing in the last 25 years.[28] Because of the risks associated with BZD, this practice (simultaneous new use at antidepressant initiation) require 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, 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 proves of efficacy, there is no evidence for benefit in long-term treatment.[12]

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 of time than are recommended and before other first and second-line treatments are tried or offered.

Apart from these 4 previously mentioned, there is no other mental disorders with an evident basis for BZD treatment. As an example, this treatment in post-traumatic stress disorders (PTSD) is particularly concerning because BZDs have not proved to possess preventive 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.[12] In fact, most of CPGs strongly recommend against the use of BZDs for PTSD, such as the guideline done by the Department of Veteran 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 de recovery should be based on the improve 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 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.

Other reasons that should be considered when talking about possible addiction are, as previously mentioned, the elevated percentage of patients who continue to use BZDs for long-term or the 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.

6.5 "Z-drugs" or non-benzodiazepines

As introduced before, a new type of related drugs appeared in the 90s specifically for insomnia treatment: non-benzodiazepines receptor agonists (NBRAs) or Z-drugs. There are 3 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.[20] However, they do not have BZDs chemical structure, not even the same between them:

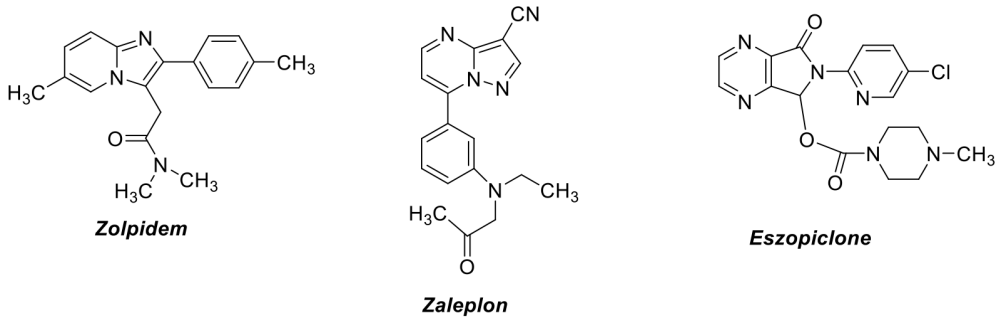
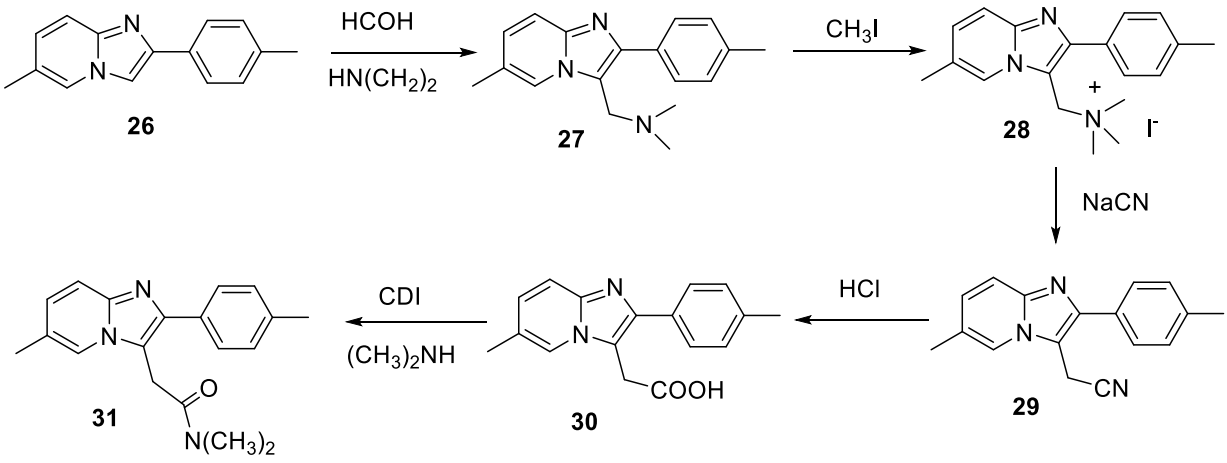


Figure 6. Chemical structure of the three-commercialized z-drugs

The synthesis of zolpidem is proposed in the Scheme 7. The amino methylation of the imidazo-pyridine 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 a dimethylamine excess to obtain the corresponding dimethylamide **31** (*Zolpidem*).



Sheme 7. Synthesis of *zolpidem* via Mannich amino-methylation[33]

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

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).

Table 3. Principal z-drugs and properties. ER= Extended Release. Due to his duration of action, *zaleplon* does not present next-day drowsiness; it can be taken within 4 o 5 hours of wake time without the risk of hangover effect.[34]

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

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 residuals effects during daytime hours, making them more clinically attractive than BZDs.[22,35]

Despite of that, there are other kind 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-drugs 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 over-expressed 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 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]

Another symptom 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 are 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.[20]

Studies have seen that Z-drugs usually present the same problems that 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.[16] 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 considerate with these drugs are their potential recreational use. As 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 safely, this overdoses often required ICU admissions, which were results of the association with other drugs and/or alcohol.[42]

6.6 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 downregulation of brain BZD receptors using a quantitative auto-radiographic 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 explanations 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 to 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 to 3 days) than with longer-acting drugs (within 5 to 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]

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 poly-drug 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 one hour.

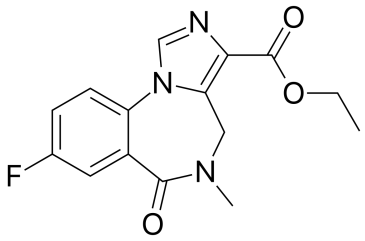


Figure 7. *Flumazenil*

It is used for:

- BZDs or Z-drugs intoxications.
- To reverse the effects of anesthesia caused by a BZD.
- To diagnose those 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.[20]

Possible treatment of dependence to avoid withdrawal symptoms

Based in 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 how it is commonly known *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 disorder, stabilization might be preferable before initiating withdrawal treatment.[7]

Various authors suggest optimal times of 6-8 weeks to several months for the duration of withdrawal, but some patients may take a year or more if they have taken BZDs prolonged use. The best results are achieved if the patient himself (not the doctor) is in control of the rate of withdrawal and proceeds at whatever rate he finds tolerable.

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 and the doctor decide 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.[48]

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*. That is due to its metabolites and long half-life that 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 to a hypnotic, different symptoms can be expected). *Diazepam* is also good to switch to, because its presentation (2mg or 10mg) makes the dose adaptation easier for every patient.

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

HALF-LIVES AND EQUIVALENT POTENCIES OF BENZODIAZEPINE ANXIOLYTICS

Benzodiazepine	Half-life (hrs) [active metabolite]	Approximate equivalent oral dosages (mg)
Alprazolam (Xanax)	6-12	0.5
Clonazepam (Klonepin)	18-50	0.5
Lorazepam (Ativan)	10-20	1
Diazepam (Valium)	20-100 [26-200]	10
Chlordiazepoxide (Librium)	5-30	25
Clorazepate (Tranxene)	[36-200]	15
Oxazepam (Serax)	4-15	20

As indicated before, there is an equivalence of doses between different compounds depending on the active metabolites and the potency (Table 4). Most-potent drugs like *alprazolam, clonazepam* or *lorazepam*, which have 10-20 times more potency that *diazepam*, are highly addictive, dependence develops rapidly, and they are particularly hard to withdraw from. In addition, their doses presentations do not allow a gradual dosage reduction when withdrawal.

3. Designing and following a withdrawal schedule

It has to be personalized based on the symptoms of each patient. It is recommended to start slowly by changing first the BZD night dose for *diazepam*. The patients that start with a high dose can reduce more mg/week than those who start with a lower dose.

The schedule should be reviewed and changed if necessary according to the progress of the patient. Stopping the last tablet is usually the most difficult part for the patients because they are afraid of how their body will react without any drug at all. However, usually the dose they are taking at that moment is already low and is having little effect. It is also important to remind the patient that if he does not succeed at the first attempt, he can always try again. The majority of patients that do not succeed, fail because they have been withdrawn too quickly or have not respected the schedule.

4. Anxiety management

It is not uncommon for many patients to be already anxious before starting withdrawal. Thus, a withdrawal plan should include some form of psychological support because an effective anxiety management can be crucial to success. It is also important to provide information about the process and inform the patient that dosage titration rarely cause intolerable distress.

Patients on very large doses of BZD (high dose abusers) either on prescription or not, probably may need to begin withdrawal in hospital. To deal with other specific symptoms there are other specifications in withdrawal guidelines:

- Insomnia: it can be helpful to take the total dose at night during the reduction period.
- Panic attack: it is important to encourage the patient to control it without any medication, using relaxation techniques, breathing exercises, cognitive therapy, etc. Knowing how to manage future attacks may also help the patient's self-confidence.
- Other symptoms such as nausea/vomiting, headaches and other pains should be treated with symptomatic and adequate drugs.

However, nowadays there is still no unification and harmonization of the withdrawal symptoms process at an international level. The results from meta-analyses of clinical trials are difficult to interpret because of the differences in methods, rates and the use of adjuvant drugs. Clinical research on optimal BZD withdrawal methods is limited. There are no studies for long-term effects of BZD such as prolonged symptoms or possibly permanent effects. The question of whether BZD can cause permanent damage to the brain or other systems remains unanswered.[49]

7. CONCLUSIONS

1) 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.

2) 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.

3) New lines of study related with BZDs, like BET inhibitor compounds, are an interesting way to change the direction of their 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.

4) It would be interesting to make a step forward towards the internationalization of the withdrawal process, allowing clinical trials to study with reliability the different reasons for failure or success, depending on the initial conditions of the patient. It would also be helpful to study the interactions and best conditions for a successful withdrawal.

5) 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 effects reports that had appeared over the recent years.

6) 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.[17]

7) The constant investigation concerning BZDs is a prove that the problems related with these drugs are an actual concern, not only as a medical issue but 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.[50]

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