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Role of the half-life in the development of substance addiction: focus on nicotine and benzodiazepine

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Summary

Introduction. The drugs of abuse circulating on the market today are an increasing number; the DSM in its latest (fifth) version eliminates the distinction between substance use, abuse and addiction and summarizes them under the generic term "substance use disorder", including tobacco, anxiolytics, opiates, stimulants, alcohol and cannabinoids. The purpose of this article is to evaluate how the half-life of the substance, related to its metabolism, modules the probability of developing addiction.

Materials and methods. A computerized search was carried out for the articles to be inserted through use of international databases such as pubmed, scopus, researchgate, google scholar, by typing in keywords such as "addiction, half-life, psychoactive substances, pharmacokinetics of nicotine, benzodiazepine", integrated with literature data. Also they are data from paper documents such as books and articles have been added. The articles related to the new therapies just approved or in the process of being approved and related studies conducted.

Discussion and conclusions. Among the pharmacokinetic properties of each xenobiotic, the half-life is a variable that depends both on intrinsic characteristics of the substance such as lipophilicity and absorption but also on the characteristics of the subject such as liver and kidney function and the presence of particular genomic polymorphisms in key genes which code for protein-enzymes of cytochrome P450 which are substrates of the xenobiotics themselves. It has been shown that substances with a short or ultra-short half-life cause addiction much more easily than those with a long half-life, giving rapid absorption peaks, resulting in rapid and intense feelings of well-being, but also short periods of permanence in the organsim with frequent and intense craving and interdose withdrawal symptoms. Much attention should be paid to the management of patients who take drugs of this type.

Key words: addiction, half-life, psychoactive, xenobiotics

Introduction

The use of psychoactive substances is a widespread practice in the general population, both as regards legal ones such as tobacco or alcohol, as well as those who are illicit. As for the former, for example, in Italy over 12 million people take nicotine daily through tobacco smoke while alcoholic drinkers are over 70 percent of the population [1]. In addition, due to the increasing prevalence of psychic pathologies linked to maladjustment such as anxiety, depression or insomnia, a significant percentage of people take psychotropic drugs, primarily benzodiazepines, with a tendency not only to an increase in "on label" prescriptions but also to you use "off label" and, unfortunately, to

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illegal ones including drug dealing [2]. Any substance taken that is foreign to the body is referred to as a "xenobiotic," including drugs, supplements, or illicit substances. Not all substances, however, have the same abusive properties, while still causing psychoactive effects in all users. In the previous version of the Diagnostic and Statistical Manual of Mental Disorders (DSM 4) there was a distinction between use, abuse and addiction, which mainly consisted of 3 characteristics [2]:

1. the presence of a psycho-physical withdrawal syndrome upon suspension due to a state of dopaminergic and noradrenergic dysregulation, typical of the state of addiction and absent or minimal in that of abuse, and absent in simple use;
2. the craving for the substance, or the strong psychic desire to take it in a compulsive and uncontrollable way by the will of the subject, despite for example the associated health complications or social, family or legal complications;
3. tolerance, or the need to take increasingly higher doses to obtain the same psychoactive effect that was previously induced by lower doses. It should be noted that tolerance is both pharmacodynamic (due to changes in the receptors of substances for down-regulation and receptor internalization with reduced sensitivity to the substance, and pharmacokinetic type due to an increase in the rate of hepatic metabolization of xenobiotics with increased clearance).

The presence of these characteristics, that is the compulsive desire and difficult to control in consumption despite the related problems, an abstinence syndrome in case of not taking the xenobiotic (even after a few hours of not taking it as in the morning upon awakening) and the induction of tolerance over time determines the status of dependence on that substance. The current DSM fifth version eliminates the distinction between abuse and addiction and speaks the generic terms of "substance use disorder", encompassing both categories within it. In the induction of addiction phenomena, various characteristics relating to both the xenobiotic and the subject come into play and, among these, one of the main ones is the half-life which, together with the potency, the degree of lipo or hydrophilicity, at the receptor interaction and absorption, lead to a greater or lesser probability of developing phenomena of tolerance and improper use [3]. From a pharmacokinetic point of view, by "half-life" of a xenobiotic we mean the rapidity with which plasma concentrations are reduced by half compared to the previous values, above all following the clearance or the volume of blood from which the xenobiotic is eliminated in the unit of weather. In general, the half-life of a compound is evaluated following the achievement of the "steady state", that is the maximum level of absorption in a given tissue or biological fluid (generally in the blood) (Fig. 1).

The half-life also determines the time needed to reach the "equilibrium state" of the xenobiotic in the plasma, that is the condition reached which, keeping the administered dose constant, the plasma level remains constant since the additional dose is exactly equivalent to that eliminated. Once this state is reached, the substance concentration of the various compartments remains the same. Generally, the time to steady-state is equivalent to 5 half-lives [4]. The elimination of a xenobiotic is the mirror image of its accumulation. In this article we want to clarify how the half-life of a psychoactive compound can influence the risk of addiction and how, on the other hand, it can also be useful for therapeutic purposes.

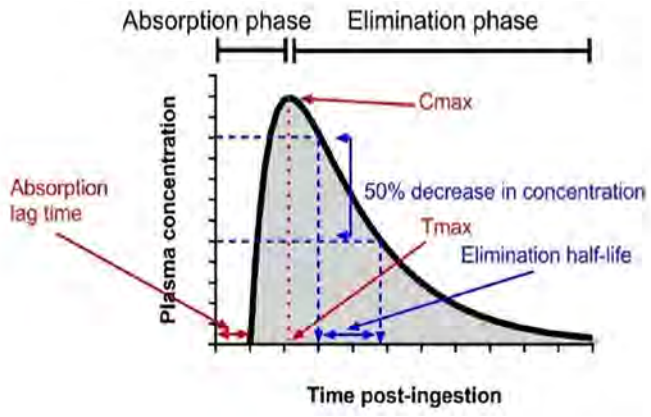

Figure 1. Concentration-time curve of a xenobiotic in plasma.

Materials and methods

A computerized search was carried out for the articles to be inserted through use of international databases such as pubmed, scopus, researchgate, google scholar, by typing in keywords such as "addiction, half-life, psychoactive substances", integrated with literature data. Also they are data from paper documents such as books and articles have been added. The articles related to the new therapies just approved or in the process of being approved and related studies conducted.

Discussion

As emerges from the literature data, most of the substances that most easily cause addiction and therefore dependence or abuse are those with a short or ultra-short half-life. This is for the following pharmacokinetic reasons:

- marked early "peak effect", i.e. the substance is capable of acutely and massively activating the mesolimbic dopaminergic circuits of the reward, causing feelings of gratification and inducing the subject to memorize the pleasant effect which, in turn, determines the thrust following the search for the same summarizing the substance;
- rapid elimination of the xenobiotic from the body, resulting in an equally rapid drop in the plasma levels of the substance, in equilibrium with the tissue ones, and therefore with interdose withdrawal symptoms.

Some specific substances will now be considered.

Nicotine

Nicotine is a natural alkaloid present in the leaves of nicotiana tabacum, belonging to the nightshade family, and is by far the most consumed psychoactive substance in the world. In Italy alone, over 23 percent of the population takes it daily through tobacco smoke, rapidly developing tolerance and addiction. It is also the substance that causes the most addiction problems given that only about 30% of smokers try to quit smoking and, of them, only about 5% every year definitively succeed [2,5]. Chemically it is composed of a pyridine molecule combined with a pyrrolidine dune, therefore with a very simple structure, but has the ability to massively activate the mesolimbic dopaminergic circuits like a few other substances. Nicotine has a short half-life of about 1.5-2 hours as it is metabolized in the liver by cytochrome P450 (CYP450) isoenzymes, which are also subject to considerable interindividual polymorphism, and is mainly converted into its metabolite cotinine, also present in blood level, which has a very long half-life of about 20 hours but is inactive (Fig. 2) [6].

The short half-life of nicotine, together with psychological aspects related to gestures and the context of intake, is the main cause of the high induction of tobacco addiction (Fig. 3).

This image shows the trend of the plasma levels of nicotinemia in the 24 hours of a standard smoker. The first cigarettes to smoke in the morning are generally in greater numbers as they are mainly used to bring back nicotinemia, which reached zero during the night, to levels deemed useful by the subject (the so-called "comfort zone", characteristic of every smoker) who experiences the gratification associated with consumption and all the other cigarettes smoked during the day have the goal of maintaining these levels constant as soon as the nicotinemia subsides due to the intense metabolism of the substance. This nicotine trend also explains any withdrawal symptoms during cessation, which appear almost immediately after the last cigarette and, despite being short-lived (a few days or weeks), are often not accepted by the smoker who returns to resume the substance. Heavy smokers often wake up at night to smoke again and bring drug levels back to or near their comfort zone, buffering any withdrawal symptoms. The reinforcing effect of nicotine, at the basis of the self-administration behavior, has also been studied in laboratory animals, in particular the self-titration characteristics of the plasma levels of the substance. Tolerance, very common and rapid, is linked both to the increase in the metabolization rate of the xenobiotic in the liver and to the phenomenon of receptor desensitization. In fact, in smokers, the cholinergic receptors, especially the alpha4beta2 subtype, undergo an up-regulation and reach 100 to 300 times greater in the brain of a smoker than that of a non-smoker and this explains the dysregulation with excessive cholinergic stimulation in case of immediate cessation without pharmacological support but also the fact that the smoker "self-medicates" with the nicotine taken with smoking to deactivate the nicotinic receptors and reduce these negative effects [7]. For this reason, during the early stages of cessation, it is useful to take replacement nicotine preparations by combining gradual release forms (transdermal patches) with instant preparations such as oral sprays or sublingual tablets, to reduce the desire to smoke overall and stop any transient craving episodes. In these cases, however, the difference does not concern so much the half-life of the substance, which is always the nicotine itself, but the pharmaceutical form and the release technology of the same.

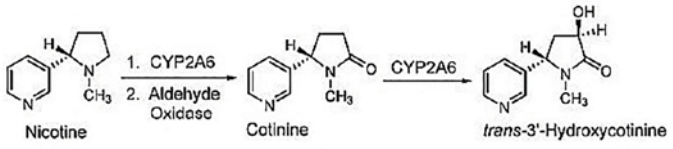

Figure 2. Metabolism of nicotine.

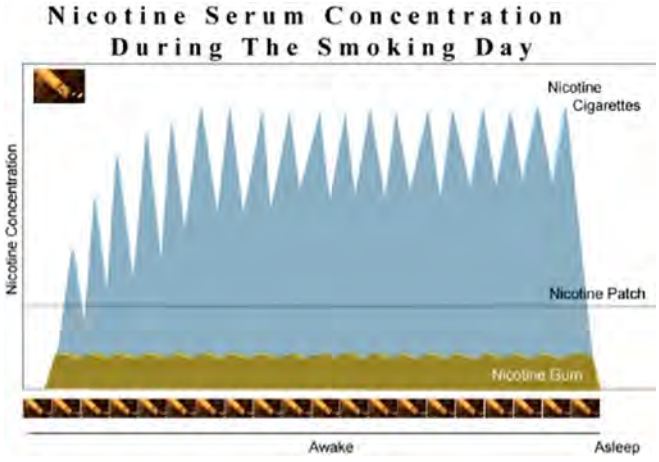

Figure 3. 24-hour plasma nicotine concentration in a traditional smoker.

Benzodiazepine

Benzodiazepines (BDZ) are a class of psychotropic drugs known mainly for their hypnotic and anxiolytic effects, but with a series of other therapeutic effects ranging from muscle relaxant to anticonvulsant to sedative and which make them not only the class of psychotropic drugs in absolute most prescribed but also, in general, one of the most commonly used types of medicines, especially among the elderly, where prescriptions have now reached levels comparable to that of antibiotics [8]. It is believed that chronic consumers of BDZ in Italy are over 3 million people, or 5% of the population. Prolonged use of these drugs causes addiction in between 40 and 80% of cases,

which can occur even after a short time, which is why in the technical data sheets of all these drugs a use that does not exceed 15 days is recommended. for insomnia and 1 to 2 months for anxiety [9]. Unfortunately, dependence on BDZ is a neglected phenomenon, even though the withdrawal crisis is potentially serious or fatal, leading to the development of seizures and important autonomic symptoms [10]. Z-drugs have no benzodiazepine structure but interact with GABAa (zopiclone-zolpidem-zaleplon). They have a particular indication for insomnia (Hypno-inducing): they preferentially interact with particular GABAa receptors with particular subunit [11,12]. The BDZ increases the probability of opening the GABA channel, therefore opening the chlorine currents, the barbiturates instead increase the opening time of the channel. The therapeutic index is, therefore, more favorable to BDZ (if used alone they do not induce death) because alone it cannot determine a hyperpolarization greater than that saturating the GABA [13]. The clinical effect of BDZ also depends on the morphofunctional heterogeneity of the gabaergic neurons: these are all preclinical evidence in the animal model, for the clinic the most important evidence is alpha1 which mediates the sedative / hypnotic effect and anticonvulsant [14]. All the other subunits help us little: we have not yet been able to find specific bdz for each subunit. The alpha12-3-5 subunit has a muscle relaxant effect.

Alpha5 present at the hippocampal level mediates amnesia and tolerance to the sedative effect.

Beta3 has been recognized as surgical tolerance as an immobilizing effect of some general anesthetics.

Alpha2 is involved in the anxiolytic effect and the architecture of sleep.

So the effects of BDZ are first of all anxiolytic (acts at the level of limbic areas and hypothalamus), muscle relaxant (on the spinal cord: sometimes it can be an effect sought in cases of spasticity or contractures, myasthenia which can depend on high sensitivity or overdose), anticonvulsant (cortical and subcortical areas [15]. Like diazepam or clonazepam used in children, they also inhibit ethanol withdrawal convulsions), sedative and hypnotic (thalamus and cortex, also recalling the anesthetic effects), anamnestic with retrograde amnesia (hippocampus and cortex: the flunitrazepam is the rape drug or it can be useful in the surgical patient so he does not remember what happens) [16]. Basically, the different effects are observed at different dosages: as the dosage increases, one passes from an anxiolytic to a muscle relaxant, anticonvulsant effect to end with the sedative/ hypnoic effect. All benzodiazepines are completely absorbed (with the exception of clorazepate), then they reach the nervous system and all other organs that receive high perfusion. The metabolic phase occurs in the liver and in many cases still active intermediates are formed which increase the duration of the drug's action. Their metabolism provide the substituent in position 1 of the ring is removed, hydroxylated in position 3 and conjugated with glucuronic acid and excretion. Their half-life varies. We have diazepam (20-50 hours) and desmetildiazepam (50-120 hours) which have long half-lives, accumulate in the adipose tissue and can lead to prolonged and lasting problems, have short-ultra-short half-lives (recommended for hypnoic effect) triazolam, estazolam and brotizolam; lorazepam and oxazepam have a short half-life (useful during the day) [17]. We also remind you that drugs such as oxazepam, lorazepam and thiolazolam do not give active metabolites that prolong the benzodiazepine effect. For those with a short half-life: boasting has little risk of accumulation and little residual effects; the disadvantage is greater risk of abstinence, risk of reduced efficacy in case of prolonged treatment. For those with a long half-life: the advantage is greater compliance and lower risk of abstinence; the disadvantage is the risk of accumulation and the risk of residual effects. This tolerance develops with the same initial dose following prolonged treatment and is due to the replacement of the alpha1 subunit with the alpha4 alpha6 subunit (there is the replacement of a histidine). Tolerance strictly influences the anticonvulsant effect (remember that diazepam is used for the treatment of epileptic seizures and not for long-term treatment of epilepsy) [18].

What are the effects of benzodiazepines on sleep?

BDZs alter both the macro and microstructure of sleep and do not induce physiological sleep: the latency, the number of awakenings, and the time of stage zero decrease (coincides with the waking stage), stage 1 (that of numbness), and stages 3 and 4 (the so-called wave sleep) decrease. slow, the latency of rem sleep increases, practically decreases the duration but increases the number of rem cycles: they produce restful sleep because they increase sleep time (stage 2) [19]. When the drug is discontinued, a rebound effect can occur with an increase in REM sleep or if it is abused, it can then lead to insomnia. Benzodiazepines also have undesirable effects: dizziness, dysarthria, ataxia (be careful because in the elderly it is easy for the elderly to fall during the night and femur breaks are elevated in conjunction with the intake of BDZ), coordination and motor deficit, and reactivity to stimuli (then the severity must be assessed); menstrual and sexual irregularities (interferes with steroidogenesis); drowsiness, numbness, asthenia; respiratory depression (but compared to barbiturates it is not as frequent unless the patient has asthma or BPCO); paradoxical effects: anxiety, irritability, aggression; depressant effects of alcohol and opioids. If associated with alcohol, it can lead to death because the alcohol in the GABA behaves like barbiturates (hence the overdose effect) [20].

Tolerance, addiction and abuse

Tolerance, especially of a pharmacodynamic type due to changes in receptor sensitivity, is more marked for the anxiolytic and hypnotic effects while it is less evident for

the muscle relaxant and anticonvulsant effects, maintained over time and the speed of it is directly proportional to the amount of stimulation of the receptor [21,22]. BDZ withdrawal syndrome is linked to a chronic neuroadaptation of GABAergic and glutamate receptors as there is down-regulation of the former and up-regulation of the latter [23]. This receptor imbalance explains on the one hand the need to continue to self-administer the substance to keep the excitatory circuits of glutamate "off" and on the other hand the fact that, following abrupt suspension or reduction of the dosage, excitatory symptoms such as tremors may occur. Ends in the hands, severe insomnia, anxiety, tachycardia, nausea, agitation which are similar to the original symptoms for which the patients took the drug, namely anxiety and insomnia. Patients therefore often confuse drug withdrawal symptoms with the exacerbation of those of origin for which it was prescribed: in general, withdrawal symptoms from BDZ have some specific characteristics [24]:

- they begin in a variable way according to the half-life, therefore being early and often severe for compounds with a short half-life such as triazolam, alprazolam. lormetazepam or zolpidem and later (5-7 days after discontinuation) and less severe for long half-life compounds;
- they are aggravated by co-abstinence from other sedatives such as opioids or alcohol;
- in a percentage of cases of 2-5% they can progress to the development of seizures of the tonic-clonic type, typically in long-term users for years and at high doses.

In 70-80% of cases, the symptoms, however, are not serious and are self-limited in 7-10 days, however in particular populations such as the elderly, psychiatric patients or in polytherapy, a lot of attention must be paid to scaling, often monitoring the patient. Because chronic intake of BDZ is associated with a risk of addiction, the international guidelines recommended the decalage of it after 4-5 weeks of use with the reduction of the daily dose by 10% per week [25]. This allows the drug to be tapered slowly but safely, having no withdrawal symptoms and progressively reducing the dose down to zero. Clearly this approach, although easy for compounds with a long half-life and therapeutic doses (eg: 20 drops of diazepam per day or 2 tablets of clonazepam), becomes difficult for compounds with a short half-life, especially if at high doses, as the patient already shows interdose withdrawal symptoms and further scaling it worsens the clinical picture, or in case of high dose intake (cases of up to 30-40 tablets per day or up to 1-2 bottles per day of these drugs have been described). Taking advantage of the property of the half-life, it is possible to opt for a replacement by passing from the administration of a compound with a short half-life several times a day with a long half-life only one to three times a day, in order to maintain adequate coverage of blood levels of the substance and to cancel or minimize withdrawal symptoms. The guidelines therefore recommend the replacement of 30-40% of the declared daily dose with an equivalent of diazepam or clonazepam, taking into account the equivalence table, gradually decreasing the dose of BDZ with a short half-life in the following days and increasing that with a long half-life up to to complete clinical stability assuming only the latter. later, after two or three weeks of maintenance, it is possible to gradually decrease the long half-life BDZ by 10% per week in a safer and less painful way for the patient [26].

The knowledge of the half-life of the substance therefore allows to set up an adequate cessation program with low risk of drop-out and high efficacy and therapeutic adherence, sometimes with the need for hospitalization for high starting doses or for poly-drug users. It is important to be able to distinguish drug withdrawal symptoms from underlying disease exacerbations and to monitor the patient over time when prescribing these potentially additive drugs.

Half-life, pharmaceutical form and addiction: the example of benzodiazepines

As previously described, various factors related to both the substance and the patient come into play in the development of addiction. The half-life of is one of the main ones but it is also related to the systemic absorption modality of the same and, therefore, to the release system from the pharmaceutical form. In the case of BDZs, for example, we have discussed how compounds with short half-lives are more additive as they give rapid absorption peaks and are metabolized just as quickly and therefore easily indicate abstinence states even interdose [27]. Let's see for example the case of alprazolam: this BDZ, marketed under various brands as well as as an equivalent, has a specific anxiolytic and in particular anti-panic activity, so much so that it is considered the reference drug to treat both acute and highly prescribed crises. also in association with antidepressants, in the first weeks as a prophylaxis of new episodes while waiting for the effect of the antidepressants themselves. Alprazolam has a short half-life and often lends itself to abuse, especially as an overdose of the prescribed daily dose and is available both as oral drops and as immediate or extended release tablets (Fig. 4).

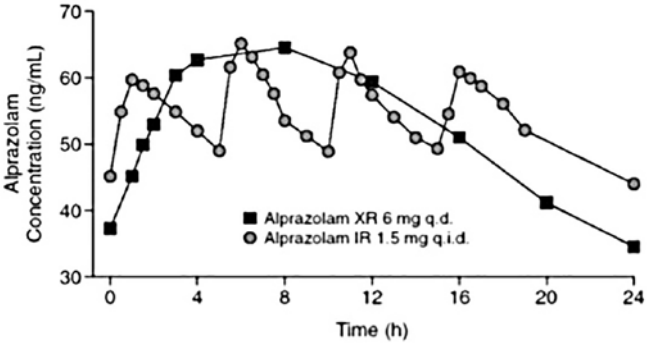

Figure 4. Immediate and prolonged-release Alprazolam plasma concentration differences.

As you can see in the image, the prolonged-release formulation allows to obtain a greater coverage of plasma levels as the active ingredient is released into the circulation more slowly, with fewer rebound symptoms and greater coverage of anxiolysis with only one or two doses per dose. day. On the contrary, the immediate release is very useful in treating the acute anxiety attack in an instant way but over time it is the one that tends to give more dependence and abuse as it determines both typical mesocortic-limbic neurobiological alterations and also psychic conditioning (the patient must always have the tablet at hand in case of attack, a reassurance system of conduct which itself becomes the cause of addiction). Furthermore, the pharmaceutical form can also influence the additive capacity of the compound: in the case of BDZ, for example, the oral drops are more manageable especially in the induction or scaling phases but, in general, if used for a long time they are more additive as they are more concentrated. Furthermore, ethanol is often used as a vehicle, with or without other alcohols, to better solubilize the active principle which is not very soluble in water. However, the same ethanol can give tolerance and abstinence, especially for patients who abuse these drugs at high doses (cases of consumption of 2 or 3 bottles a day have also been described). moreover, even flavoring can induce craving in itself, with the patient's tendency not to dilute the drug but to take it directly from the bottle. The tablets, on the other hand, allow greater accuracy of the dose, are more chemically stable and do not contain ethanol or flavoring but are less manageable in the case of scaling as patients find it difficult to divide them (even if thanks to the pill cutters this is facilitated).

Conclusions

As described extensively, the possible developmental trajectories for a person taking substances depend on various factors relating to both the person and the substance. In the latter case, the half-life is a fundamental property, also in relation to the absorption and therefore to the release modality of the substance itself. For most substances of abuse,a short half-life facilitates the induction of gratification (and therefore of behaviors of dependence) and, in the case of BDZ, for example, of the therapeutic effect, giving rapid peaks in the brain and massively activating the dopaminergic circuits of gratification (especially meso-limbic) but, on the other hand, the fast plasma clearance determines more sudden and often more intense withdrawal symptoms. On the contrary, a long half-life facilitates the induction and decalage process and allows good coverage in 24 hours of the therapeutic effect with only one or two daily administrations but can be associated with systemic accumulation phenomena with an increase in some side effects, especially for substances of a lipophilic nature such as BDZ or opioids. These properties must be carefully considered during a drug cessation therapeutic program, also in relation to the pharmaceutical form and the release mode of the active ingredient.

References

1. Amato L, Pani P. Tossicodipendenze. Una guida alle basi razionali del trattamento. Il Pensiero Scientifico 2013.
2. Lugoboni F, Zamboni M. In sostanza manuale sulle dipendenze patologiche. Edizioni CLAD 2018.
3. Roxas Amico M, Caputi PA, Del Tacca M. Compendio di farmacologia generale e speciale. Edra 2021.
4. Raja M, Raja S. Psicofarmacologia clinica. Edizioni Minerva Medica 2021.
5. Stahl S. Neuro psicofarmacologia essenziale. Basi neuroscientifiche e applicazioni pratiche. Edi-ermes 2016.
6. Schick SF, Blount BC, Jacob P, et al. Biomarkers of exposure to new and emerging tobacco delivery products. American Journal of Physiology 2017;313:L425-L452.
7. Chiamulera C. Meccanismi neurobiologici della dipendenza da nicotina. 20021. https://www.giornaledicardiologia.it/r.php?v=822&a=9169&l=12260&f=allegati/00822_2001_12/fulltext/S1-2001_06%2030-33.pdf
8. Jin Y, Yu C-X. Progress in research on techniques for prolonging half-life of protein and polypeptide drugs Chinese Journal of Schistosomiasis Control 2012;24:594-597.
9. Sleep D, Cameron J, Evans LR. Albumin as a versatile platform for drug half-life extension. Biochimica et Biophysica Acta 2013;12:5526-5534.
10. Vinkers CH, Tijdink JK, Luykx JJ. Kiezen voor de juiste benzodiazepine: werkingsmechanisme en farmacokinetiek. Nederlands Tijdschrift Voor Geneeskunde 2012;155(35).
11. Revet A, Yrondi A, Montastruc F. Règles de bon usage des benzodiazépines. Presse Medicale 2018;47:872-877.
12. Hein M, Lanquart JP, Loas G, et al. Objective sleep alterations and long-term use of short or intermediate half-life benzodiazepine receptor agonists are risk factors for high blood pressure in individuals with insomnia: a study in 1272 individuals referred for sleep examinations. Sleep Medicine 2019;53:115-123.
13. Weintraub SJ. Diazepam in the treatment of moderate to severe alcohol withdrawal. CNS Drugs 2017;31:87-95.
14. Wang PS, Bohn RL, Glynn RJ, et al. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry 2001;158:892-898.
15. Helmes E, Østbye T. Associations between benzodiazepine use and neuropsychological test scores in older adults. Can J Aging 2015;34:207-214.
16. Hallfors DD, Saxe L. The dependence potential of short half-life benzodiazepines: a meta-analysis. Am J Public Health 1993;83:1300-1304.
17. Hemmelgarn B, Suissa S, Huang A, et al. Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA 1997;278:27-31.
18. Passaro A, Volpato S, Romagnoni F, et al. Benzodiazepines with different half-life and falling in a hospitalized population: the GIFA study. Gruppo Italiano di Farmacovigilanza nell'Anziano. J Clin Epidemiol 2000;53:1222-1229.
19. Rickels K. Clinical trials of hypnotics. J Clin Psychopharmacol 1983;3:133-139.

[20] Greenblatt DJ. Pharmacology of benzodiazepine hypnotics. J Clin Psychiatry 1992;53:7-13.
[21] Schweizer E, Case WG, Rickels K. Benzodiazepine dependence and withdrawal in elderly patients. Am J Psychiatry 1989;146:529-531.
[22] Cano JP, Coassolo P. Notion de demi-vie et métabolisme des benzodiazépines. Etude critique. L'Encephale 1983;9(Suppl 2):75B-80B.
[23] Meier PJ, Ziegler WH. Benzodiazepine - Praxis und Probleme ihrer Anwendung. Schweizerische medizinische Wochenschrift 1988;118:381-392.
[24] de Vries OJ, Peeters G, Elders P, et al. The elimination half-life of benzodiazepines and fall risk: two prospective observational studies. Age Ageing 2013;42:764-770.
[25] Ochs HR. Benzodiazepine: bedeutung der Kinetik für die Therapie. Klinische Wochenschrift 1983;61:213-224.
[26] Dundee JW, Collier PS, Carlisle RJ, et al. Prolonged midazolam elimination half-life. Br J Clin Pharmacol 1986;21:425-429.
[27] Smith DA, Beaumont K, Maurer TS, et al. relevance of half-life in drug design. J Med Chem 2018;61:4273-4282.