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Role of the pharmaceutical form in the development of addiction from psychoactive substances

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Summary

Introduction. In the development of addiction and abuse of psychoactive substances, both factors related to the person, of a psychopathological and metabolic type, and factors related to the substance come into play and, in the latter case, the 3 most important are the half-life, the potency pharmacodynamics and pharmaceutical form. In this article we want to focus on the description of how this last characteristic is important in facilitating or not conducts of abuse both relating to therapeutic substances such as opioids and benzodiazepines and to illicit substances.

Materials and methods. The article was performed according to the PRISMA guidelines, where the characteristics of the studies eligible for the review included being related to the thematic of addiction, regarding mainly related to pharmacokinetics, dynamics and pharmaceutical form. ccStudies were identified by searching papers according to their relevance via PubMed/MEDLINE. Finally 38 studies and one book were suitable for the inclusion in this review.

Discussion and conclusions. In recent years, the market for psychoactive substances has undergone changes with the introduction, for the purpose of dealing, of both legitimate substances such as psychotropic drugs and new psychoactive substances, which are added to the old substances already present. The pharmaceutical form and its absorption, also linked to the route of administration, are fundamental in modulating the activity of the compounds taken and pharmaceutical forms with rapid absorption and prompt release are more often involved in drug addiction behaviors. This should be borne in mind above all in relation to the prescriptions of some classes of psychotropic drugs and especially if they are protracted for a long time in those that are more easily additive.

key words: addiction, psychotropic drugs, pharmacology, formulations, pharmaceutical chemistry

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Introduction

Substance use disorder (SUD) is a condition in which the excessive use of one or more substances leads to clinically significant impairment or distress and effects that are harmful to physical and mental health or to the welfare of other individuals [1]. The disorder is characterized by a pattern of pathological

continued use of a drug, which results in adverse social consequences related to drug use, such as failure to meet work, family or school obligations, interpersonal conflicts, or problems legal [2]. There are ongoing debates regarding the exact distinction between "substance abuse" and "substance addiction"; in DSM-5, substance use disorder replaced and unified the previous categories of DSM-IV: substance abuse and addiction. the data on the use of psychotropic substances are relevant: According to estimates, in the European Union about 83 million adults (aged between 15 and 64 years), namely the 28.9%, have taken at least one illicit substance once in a lifetime. For example, the estimate consumption, in course of life, of cocaine is about 9.6 million males and 4.3 million females, for amphetamines 5.9 million males and 2.7 million females and It is also estimated that the prevalence of opioid use ad high risk among adults (15-64 years) in 2019 represented 0.35% of the EU population, equivalent to 1 million high-risk opioid users. In 2019, there were 510,000 users on substitution treatment for addiction in the European Union from opiates, that represent 26% of requests for treatment of the drug addiction. On the other hand, opiates accounted for 76% of overdose deaths reported in the European Union in 2019. To these data is added the consumption of benzodiazepines and opioid analgesics (painkillers) out of prescription which, for example in the USA, is causing an annual number of overdoses at least 3 times higher than those for heroin and cocaine combined [3,4]. Various factors are involved in the development of addiction, relating both to the consuming subject and to the substance. Focusing on the latter, there are 3 main variables that come into play:

- the pharmacodynamic power, that is the ability of the substance to bind and activate certain receptors and to increase the mesolimbic dopaminergic transmission, ie neurons that project from the ventral tegmental area and the nucleus accumbens to the prefrontal cortex. Complete agonists are typically more additive than partial agonists while antagonists do not induce known addictive or tolerant phenomena. As for the receptor binding power, it is known that the greater the affinity and duration of it, the greater the probability of inducing addiction;
- half-life, i.e. the time the substance or its active metabolites remain in circulation, where the lower it is, the greater the chances of developing abstinence and the need for prolonged self-administration;
- the pharmaceutical form, that is the method of release of the active ingredient and of its absorption and metabolism [5].

It is precisely in relation to this last aspect that we want to deepen this article by evaluating whether different pharmaceutical forms of the same substance can induce changes such as to influence the methods of administration and the relative danger of abuse.

Materials and methods

This article was performed according to the PRISMA guidelines, thus providing a comprehensive framework which objectively assesses indications of quality of included studies. The characteristics of the studies eligible for the review included being related to the thematic of addiction, regarding mainly related to pharmacokinetics, dynamics and pharmaceutical form. We used studies published between 1980 and 2022 [6]. The studies were excluded if they did not relate to any of the specific subjects of addiction considered in the review (neurobiology, risk factors, consequences and relationship to free will/ self-determination). Studies were identified by searching papers according to their relevance via PubMed/ MEDLINE (http://www.ncbi. nlm.nih.gov/pubmed). After performing the initial literature search, the first 400 study titles and abstracts (seriated according to ''best match'') were screened for eligibility by the first author. Full texts of all potentially relevant studies were subsequently retrieved and further examined for eligibility: 38 studies were suitable for the inclusion in this review. Besides the mentioned studies, one textbook of psychiatry was also included in the review. The PRISMA flow diagram (Fig. 1) provides more detailed information regarding the selection process of the bibliography. Results In addition to the use of an Addiction textbook, the search in Pubmed/MEDLINE database resulted in 38 scientific articles meeting the inclusion criteria.

Discussion

The pharmaceutical form identifies the physical formulation in which each type of product, medicinal or otherwise, is presented. In fact, it contains the active principle responsible for the therapeutic or toxicological effect in addition to other substances present as excipients, which favor the maintenance of the pharmaceutical form itself and its stability / conservation and on the other hand intervene in the release of the active principle itself. It should be noted here that the excipients are not always chemically inert; for example, many liquid formulations of benzodiazepines contain 16% of ethanol together with flavoring, which often intervenes in the development of addiction (many patients, for example, for lormetazepam report direct intake from the bottle without diluting it precisely for the search for the taste of substance) [7]. The same goes for street illicit drugs which are always adulterated; in the case of opioids the purity never exceeds 40-70% while for cocaine and stimulants in general it is greater. Regarding the pharmaceutical forms in the development of addiction, some considerations must be made. In the case of purely recreational abusers, the effect of the substance is sought in a short time and therefore formulations that release the substance rapidly will be preferred [8]. This involves the choice, for example, of oral liquid formulations (drops) or solid forms (orosoluble tablets) as the release of the

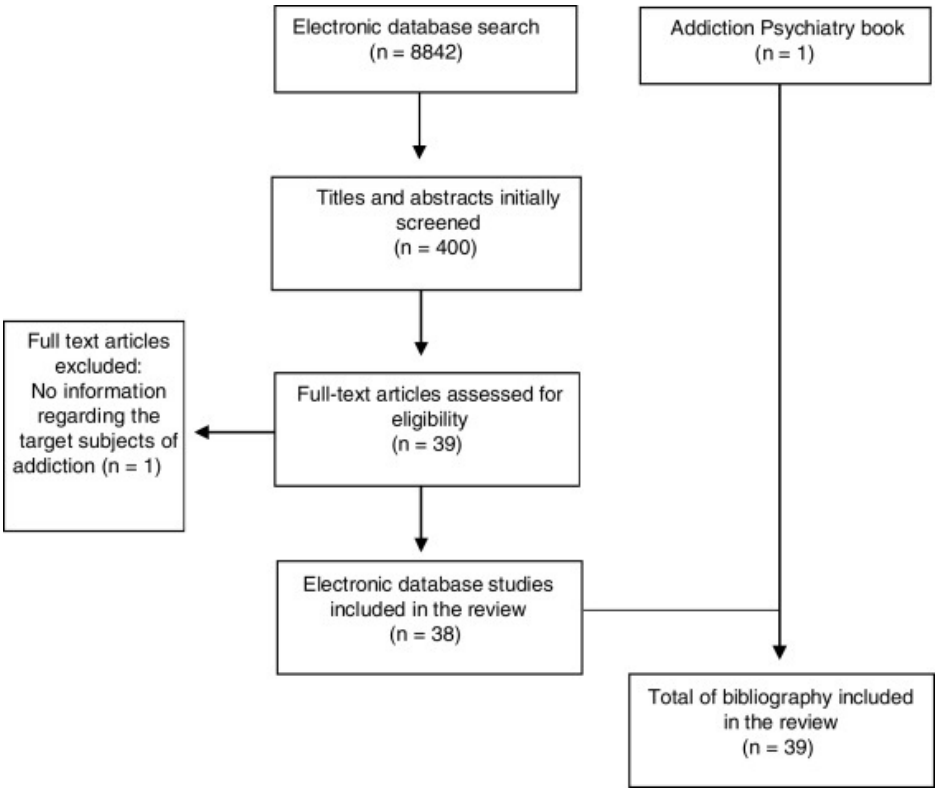

Figure 1.
PRISMA flow diagram for the article.

active ingredient from the pharmaceutical form occurs in a few minutes or even instantaneously [9]. The same applies in the case of patients with iatrogenic dependence on benzodiazepines and opioids: the data show that, in addition to preferring compounds with a short half-life such as lorazepam, alprazolam or morphine, oxycodone, etc., these subjects develop abusive behaviors especially in the case of immediate release formulations or make a misuse of prolonged release formulations by crushing them (either by chewing or pulverizing them before ingestion), thus eliminating their main pharmaceutical properties and making them immediately absorbable [10].

Biopharmaceutical of oral formulations

The pharmaceutical form used to deliver the active ingredient influences its bioavailability. The oral formulations can be divided into solid, semi-solid and liquid [10]. The solid forms, in turn, can be classified on the basis of the release of the active ingredient (immediate, prolonged, delayed or repeated) and the design (tablets, hard or soft capsules, pods, etc.). It should be borne in mind that, for an active ingredient to be absorbed enterally, it must always be in solution in gastric and enteric fluids. This implies that the greater the steps that it must carry out to "free itself" from the original shape, the greater the absorption time and therefore the delay in the onset of the effect. In the case of liquid solutions, the active principle is already immediately available for mucosal absorption and no release must take place; in the case of suspensions, on the other hand, the speed of dissolution is the major variable that influences the speed of absorption (the size of the fine or micronized particles accelerates this passage). In the case of tablets, the first step is the disintegration of the pharmaceutical powder particles into smaller aggregate particles, followed, after wetting in the digestive fluids, by their dissolution (Fig. 2) [11,12,13].

In the case of the coated forms, the presence of an external gastro-resistant polymeric film creates a physical barrier between the tablet and the aforementioned fluids, adding a further dissolution step and this allows to control the site or the speed of release. In the case of tablets, two clarifications must be made:

- the most rapidly absorbed forms are the sublingual (bypassing the first hepatic passage and the gastrointestinal transit, being immediately released into the circulation with a rapid effect) and orodispersible/orosoluble (dissolved in the mouth and then ingested: they follow the normal enteral path of a tablet but have the advantage of reaching the stomach already in solution and therefore are absorbed quickly) [14];
- the modified release formulations are coated with a specific film-forming layer which, if altered for example by trituration, causes the very rapid release of large

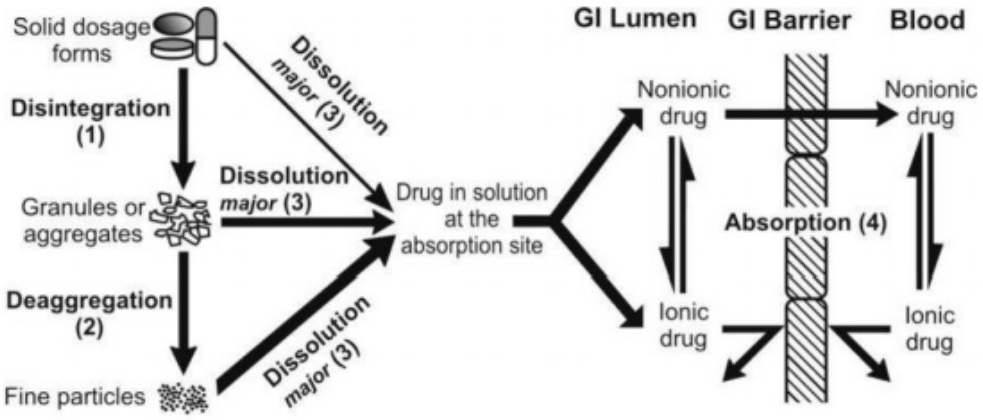

Figure 2.
Drug release from solid pharmaceutical forms.

doses of active principle which will be more rapidly absorbed [15].

Finally, a clarification must be made on syrups, given that methadone is in this form: they are liquid solutions containing high concentrations (over 45%) of sugars and polyalcohols (e.g. glycerol) which, in addition to masking the unpleasant taste of some active ingredients, they prevent crystallization and microbial contamination, favoring their conservation [16].

Some specific cases concerning illicit substances or drugs subject to misuse will now be considered.

- *Opioids drugs:* the phenomenon of the abuse of this substances, includes painkillers, in the USA is epidemic in the last years and the overdoses of these compounds have exceeded by at least 3 times those of heroin. The phenomena which we witness most are attributable to 2 types. One is the misuse/diversion of opioids used in the replacement therapy of subjects with previous heroin addiction, such as methadone or buprenorphine/suboxone tablets, which are sometimes taken in different ways from those prescribed [17,18]. It should be remembered that by misuse we mean the use of a drug in a different way from the prescription, modifying the modalities of assumption or the dosages while by diversion we mean the unauthorized way in which subjects obtain the drug [19]. In particular the major problems are firstly the intravenous misuse of methadone, with the high risk of blood hyperviscosity and possible ischemia or phlebitis, sometimes with local gangrene at the injection site and secondary hyperglycemia given the high sugar concentration, and also of buprenorphine after pulverized adverse reactions, with the risk of embolisms and acute intoxication reactions (the intravenous route determines a 100% availability of the substance as opposed to the enteric one). It must be said that in the literature there is a greater risk of misuse with buprenorphine than methadone, however also the suboxone formulation was found to be not free from misuse phenomena, even if in smaller proportions [20]. Surely buprenorphine alone is subject to injective use. generally in small doses at a time, using fragments of tablets to avoid saturating the receptors and maintain the gratifying effect by minimizing the unwelcome ones (in some countries, not in Italy, suboxone is also available in soluble leaflets to be adhered to the oral mucosa and difficult to detach precisely to prevent diversion and misuse after controlled recruitment, however the very thin thickness makes it easy to introduce them illegally, for example in prison). Six-monthly subcutaneous opioid implants are being studied to maintain abstinence [21]. The second problem is the use of painkillers outside of medical prescriptions for recreational purposes or in patients with chronic pain and the development of tolerance and addiction [22]. The commercial introduction of prolonged-release formulations of potent drugs such as oxycodone or hydromorphone has sometimes led to their administration after pulverization or by chewing, causing rapid highs and absorption. The same goes for the sublingual tablets and fentanyl lollipops, over 70 times more potent than morphine, which has made these compounds popular in the new psychoactive substances. It must be said that the risk of addiction is much greater for these formulations than, for example, transdermal patches due to the different kinetics of drug release, slower and more constant for the patches and faster and shorter for the sublingual forms or nasal sprays (Fig. 3) [23].
- *Benzodiazepine:* BDZ are marketed in injectable vials, tablets / capsules or oral drops and, with some exceptions, such as all active ingredients (about 30 in Italy) have more than one pharmaceutical form available. We will not go into the pharmacological details of BDZ here but remember that, aside from the ampoules which are used only in healthcare settings and rarely at home, the solid and liquid oral formulations

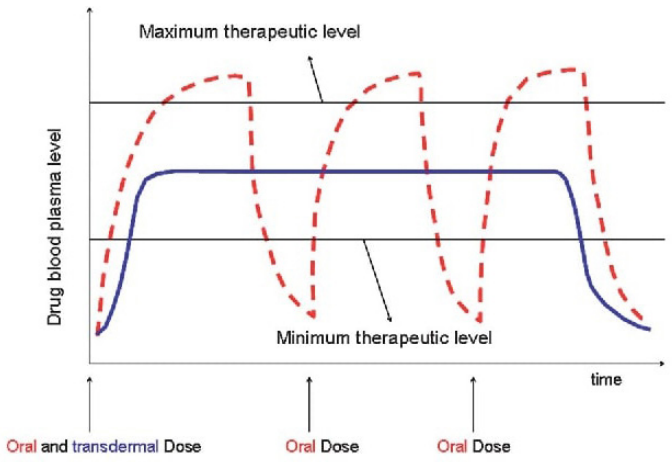

Figure 3.
Oral vs transdermal drugs release.

do not present the same risk of abuse. In particular, the tablets/capsules allow a more precise dosage and also sometimes the possibility of being divided and therefore the scaling of the dose [24]. Furthermore, there are modified release formulations that induce slow absorption and delayed plasma peak: these formulations have proved to be less additive probably as they induce less release of dopamine in the meso-limbic circuits and less "high effect" [24]. The drops, on the other hand, are more concentrated and often, being the BDZs not very soluble in water, they contain ethanol as a solubilizer up to 16% (itself responsible for any additivity, especially if they are taken undiluted but directly from the bottle) [25]. They also contain flavoring to increase the palatability. These factors put together, in addition to the greater speed of absorption since they are aqueous solutions, make it easier to abuse. Also the slowness of dripping and the presence of alcohol have been offered/suggested as possible causes for the increased risk of developing dependence to the oral formulation of lormetazepam rather than to other anxiolytic and hypnotic drugs. Costa et al. in a study have assessed the time of dripping of the most used benzodiazepines and z-drugs oral solution products under experimental conditions and the different employed excipients through a comparative analysis of the Summaries of Product Characteristics. A wide range of the median overall dispensing time was found across the eight products included in the analysis. The data suggest that the pace of dripping and the presence of alcohol can be considered themselves causes that triggered the drugs abuse. More precisely, the quantity of alcohol per bottle has been found negligible at therapeutic doses; however, when these are exceeded, they may have clinical implications for patients [26].

- *Other drugs:* even if less commonly than the previous ones, in recent years other psychotropic drugs have been reported, mostly by case reports, as a cause of mainly physical addiction and for which the pharmaceutical form has proved to be involved [27,28]. We report, for example, the case of quetiapine, a second generation antipsychotic dopaminergic antagonist D1 and 2 and serotonergic 5HT1A and 2, as well as alpha-adrenergic and histaminergic. In Italy it is available in fast and modified release presses [29,30]. The first evidence of quetiapine abuse appears in September 2004 in the American Journal of Psychiatry. In the letter to the editor, more than 30% of patients held in a Los Angeles County prison were used by mouth or by inhalation of the pulverized tablets. The effects sought were associated with the anxiolytic and sedative properties of the substance, i.e. as an aid to sleep or to calm the effects of other substances of abuse, rather than for antipsychotic properties [31,32,33]. The inmates simulating psychotic problems, had easy access to the prescription of the substance making it attractive even on the illegal market between inmates and ex-inmates once out of prison. A potential use of quetiapine for the treatment of opioid and cocaine addiction is currently being investigated in the clinical setting [34,35]. A 2005 study, published in the Journal of Clinical Psychiatry, reports positive results in the use of the drug for the treatment of opiate addiction, but some scholars are perplexed about the drug's possible addictive properties [36]. The trituration of the prolonged-release tablets and their rapid absorption favors the rapid onset of anxiolytic and calming effects but also that of withdrawal symptoms such as headache, nausea, vomiting, nervousness, tachycardia. The rapid response to drug rechallenge is typically typical [37].

Conclusions

In recent years, the attention in research on substance addictions has focused a lot on their pharmacological properties and on what factors could influence their dynamic and kinetic behavior once taken. In addition to the half-life, which however remains fundamental, the pharmaceutical formulation and the methods of recruitment are also the masters allowing to modify the metabolic behavior, the onset of psychic or physical effects and their intensity and above all the additivity [38,39]. With the exception of the injectable formulations, which remain the most problematic, and the transdermal ones, which are not very additive due to the slow absorption kinetics and the long constancy of effects, the oral formulations in drops or buccal formulations are the most additive together with the pulverization of the release ones prolonged, because they all determine the rapid release and absorption of high doses of the active ingredient and the onset of high. Conversely, those with prolonged release and/or long half-life and transdermal ones can be useful in the cessation of addiction by stabilizing the patient more from withdrawal symptoms for greater receptor occupation.

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