Open Peer Review on Qeios

Addiction to Psychoactive Prescription Drugs: Can the Excipients of the Formulations Play a Role?

Amelia Morgillo[1], Edoardo Marovino[2]

1 University of Siena
2 University of Pavia

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

In the development of drugs misuse and addiction, references are often made to the study of the API (active principle ingredient) as the main cause, which is certainly true, but there is a tendency to overlook the possible role of certain excipients which may be involved in the preferential development of certain formulations, especially in the case of benzodiazepines and opioids and other psychoactive legal drugs. In this article, we will try to describe the reasons why some excipients can be involved in this phenomenon, briefly describing their main characteristics and evaluating both how they can affect the biopharmaceuticals of the active ingredient and how they can specifically be involved in the development of addiction.

Amelia Morgillo[1,*] and **Edoardo Marovino**[2]

[1] *Department of Medicine and Surgery – University of Siena*

[2] *Postgraduate school of pharmacology and clinical toxicology - Dept. of Medical Biotechnology and Translational Medicine, University of Milan*

[*]Corresponding Author: Amelia Morgillo, University of Siena, Via Innico Caracciolo 14, Airola(Bn) 82011.

Introduction

Prescription drug abuse is a widespread phenomenon around the world, especially when it comes to psychoactive drugs. In fact, by definition, abuse/dependence develops in the context of the use of drugs that have euphoric, anxiolytic pharmacological properties, and which mediate a positive reinforcement-gratification, activating, more or less directly, the mesolimbic dopaminergic reward circuits.[1] Consequently, drugs such as opioids, benzodiazepines but also, in general, substances with an exciting action (amphetamines, stimulants) or depressants (antidepressants, antiepileptics, GABA-pentinoids, muscle relaxants, antihistamines, some antipsychotics such as quetiapine in the fast formulation) have been associated with diversion , misuse and abuse and, in some subjects, the development of craving, tolerance and

addiction.[2]

Important definitions

- **diversion:** illicit transfer of a drug, sold with medical prescription, by the patient who received the prescription and who had the drug dispensed to another person illicitly and for non-medical purposes
- **misuse:** generic term that indicates "misuse" of the drug, outside of medical indications (e.g. for doses, dosage, method of administration, duration, etc...)
- **abuse:** use of the drug in excessive doses and/or for an excessive duration compared to what is prescribed. The concept of abuse does not necessarily imply that of dependence, where instead it indicates a form of serious abuse associated with an excessive and continuous desire to take the drug, possible symptoms of intoxication and withdrawal on discontinuation.

Various classes of drugs are subject to misuse, including thyroid preparations, doping drugs like anabolic steroids, diuretics, erythropoietin, beta 2 agonists... but the mainly drugs involved to abuse behaviors are those that specifically can induce psychological addiction and physical dependence and tolerance, like some classes of psychoactive drugs. Undoubtedly the nature of the API (active pharmaceutical ingredient), with its pharmacodynamic/kinetic characteristics, is the main cause of the possible development of this phenomenon.[3] However, the possible role of some particular pharmaceutical formulation and excipients is often overlooked. In fact it should be remembered that an active ingredient is never administered and formulated as such but always in association with excipients to make a specific pharmaceutical form, which are by no means biologically inert as was believed in the past but can influence:

- the method of pharmaceutical production and storage for the shelf life of the drug
- the characteristics of release of the active ingredient (API) and its bioavailability, as well as the route of administration and parameters such as peak effect time and solubility
- aesthetic presentation and palatability, especially for liquid and/or pediatric formulations

In relation to these characteristics it is therefore important to evaluate, in the case of drugs of abuse, also how these factors can influence the probability of developing greater illicit use and how, for example, to intervene in the drug prescription for the cessation of abusers, as many products are available on the market in different pharmaceutical forms.[4]

Excipients: Main Types and Characteristics

The excipients of the pharmaceutical formulations have an important role as the API, generally cannot be administered as such; the formulation allows the patient to receive it in the most appropriate and effective way possible (note that excipients do not cure the disease, but the pharmaceutical preparation cannot do without them!). A general overview is described in Figure 1; they can be classified based on the role:

- **constitutive**, such as diluents (they give mass to the solid formulation, such as lactose, microcrystalline cellulose, mannitol, starch, sorbitol...) and moisture absorbents (vegetable carbon, starch, glycerin,...)[5]

- role in **production** such as lubricants (stearic acid), binders (gums, starch, gelatin, hypromellose...), non-stick agents (talc), glidants (flow agents for powder mixtures such as silica derivatives), surfactants (stabilizers for liquid preparations such as tweens, spans, sodium lauryl sulfate...), viscosifiers for suspensions and emulsions...
- role in the **release of APIs** such as disintegrants for tablets and capsules (starch, alginates...), film-forming release coating polymers (cellulosic derivatives such as acetophthalate, HPMC...) and wetting agents
- role in **preservation** (benzalkonium, parabens, chlorhexidine, alcohols, etc.), **flavoring and sweetening agents** (sucrose, saccharin, aspartame, menthol...)[6]

In Figure 2 we see the basic steps of the biopharmaceutical of solid oral drug pharmaceuticals (SODP) and liquid formulations (LODP).

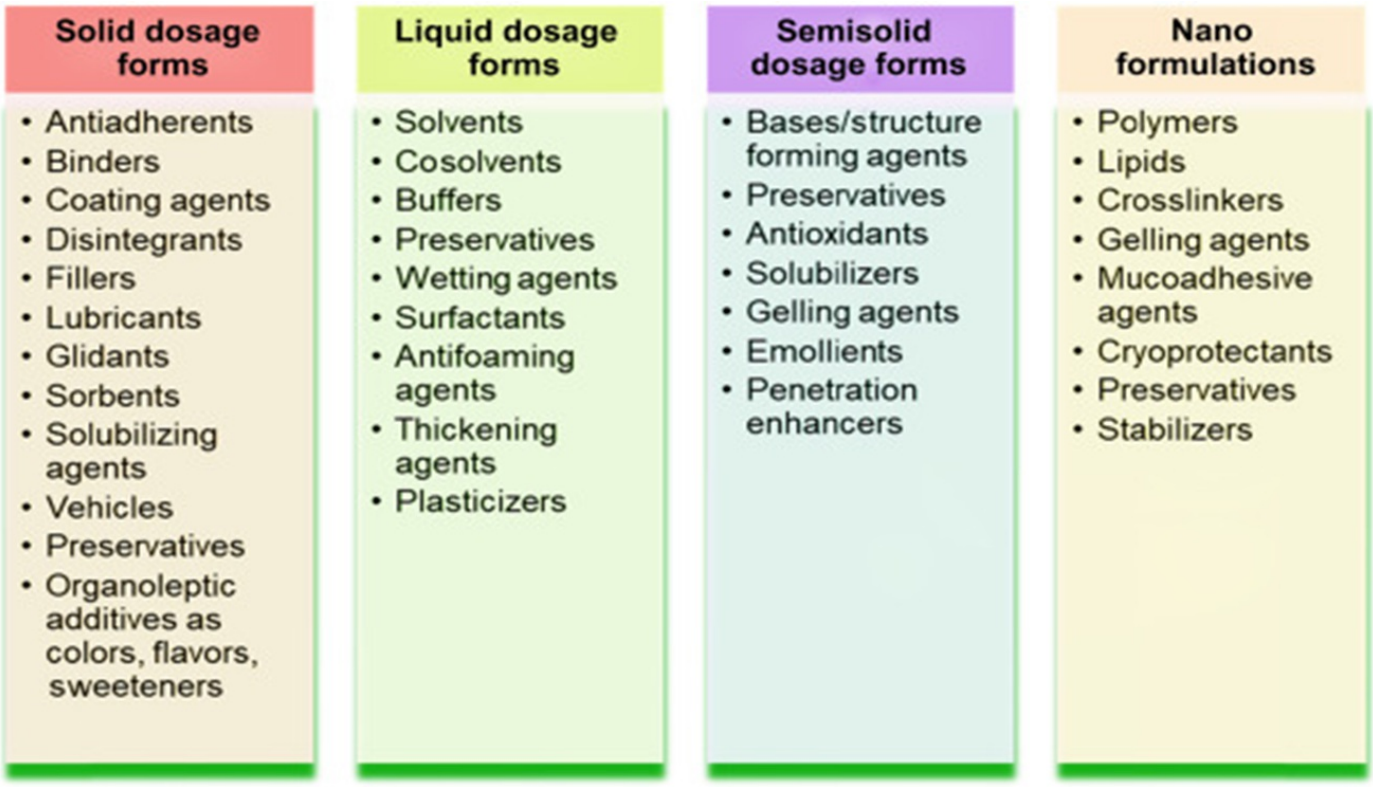

Figure 1. *General overview of pharmaceutical excipients*

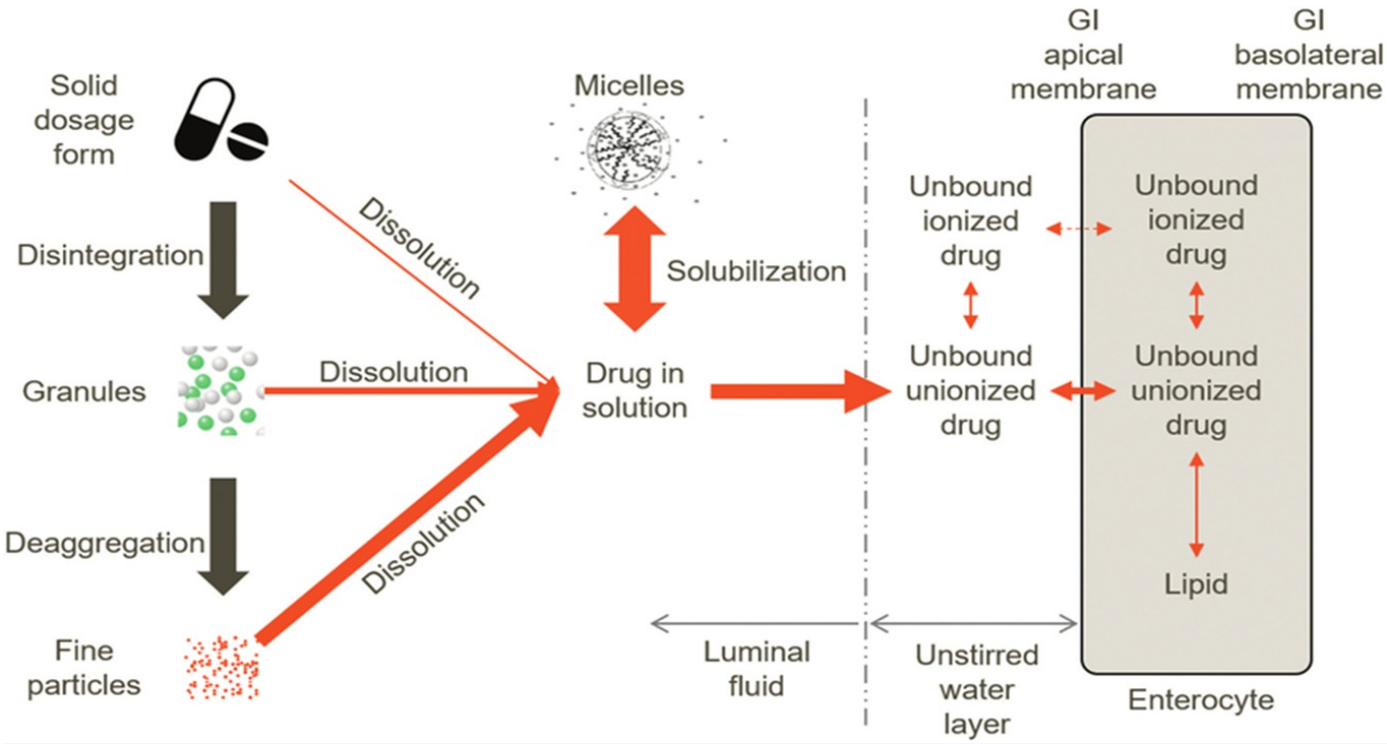

Figure 2. *Biopharmaceutical characteristics of oral drugs formulations*

To guarantee the relative steps that allow to obtain a solution from a solid formulation or, if it already was, to keep the drug in liquid form, the excipients become fundamental. Furthermore, they also have the task of not interacting negatively or, if possible, of keeping the chemical identity of the API intact. Many psychoactive drugs are marketed in different formulations, liquid and solid, each of which has advantages and disadvantages over the other. In general we can say that (Figures 3 and 4):

- short acting formulations such as liquid and rapidly absorbed solid formulations (sublingual, oromucosal, buccal, etc.) have a higher potential of abuse[7]
- long acting oral modified formulations, such as film-coated ones, giving levels that are more stable over time and less high, have in themselves less potential for abuse but, if chewed/crushed, they lose this property, releasing a bolus of drug at a very high dose, becoming not only euphoric but potentially toxic

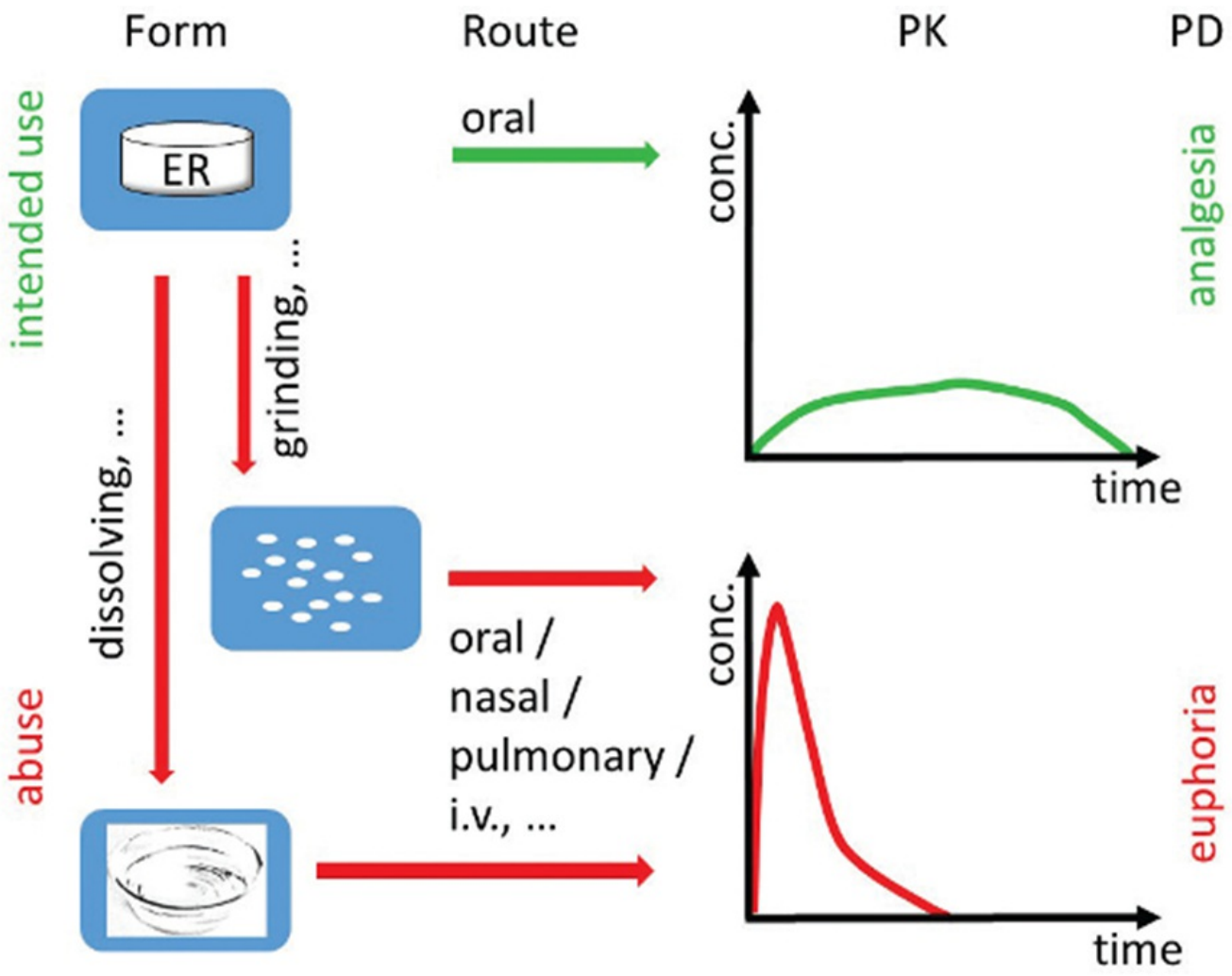

Figure 3. *Effect of dosage form manipulation on the PK and PD of the SODP*

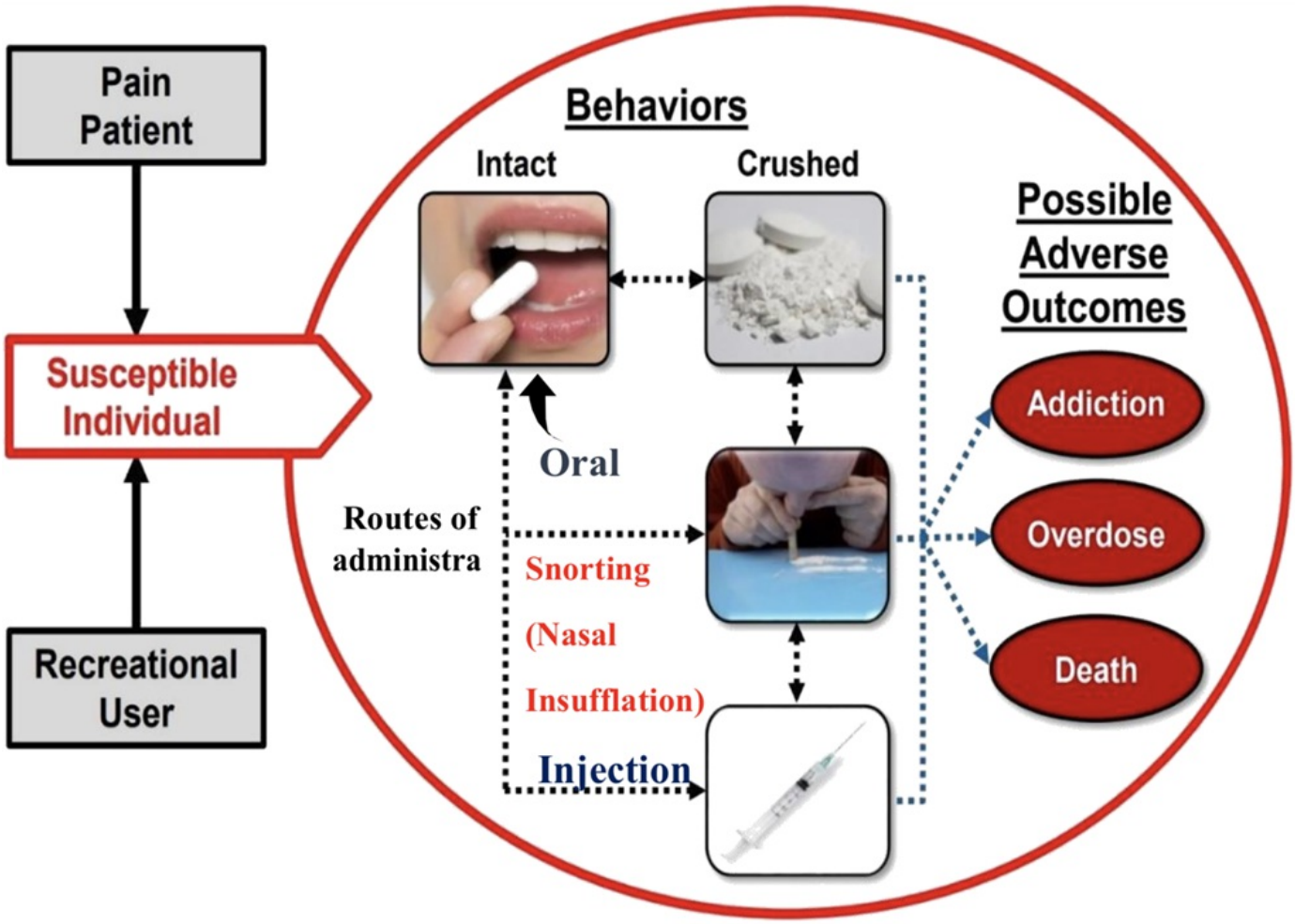

Figure 4. *Possible patterns of abuse of psychotropic drugs*

What Role Can Excipients Have In the Risk of Abuse and Diversion of Formulations?

In evaluating the role of excipients, it is useful to distinguish between solid and liquid oral pharmaceutical forms.[8] In the latter case, the most common methods of misuse are 1) direct intake of the drug from the primary container without dilution in water and/or without the use of the tools contained to dose it correctly such as droppers or syringes or dosed glasses ;[9] 2) parenteral injection, often intravenous, of a concentrated liquid formulation after withdrawal with a syringe and needle and direct injection (very dangerous due to the risk of overdose and chemical phlebitis at the injection site; 3) mixing the liquid contents of the drug with solvents non-aqueous, often with psychoactive (e.g. alcohol) or flavoring properties or which improve their solubility and therefore absorption. In these cases, the excipients that most influence the effects are the flavoring agents, which improve the palatability of the active ingredient, and which can encourage its use especially by children or predisposed subjects. They can be of natural origin such as sucrose, sorbitol, mannitol, xylitol or synthetic.[10] Also some cosolvents, added to the formulation to increase the solubility of poorly hydrophilic APIs, which do not contain ionizable groups and which can have psychoactive effects. We recall the example of alcohols (ethanol, glycerol) and propylene glycol in oral liquid formulations of benzodiazepines.[11] However, in the case of solid formulations, such as tablets, capsules and oral granules, the methods of misuse can be: 1) frequent direct intake of high

doses with normal administration methods; 2) the trituration/pulverization of the formulations and subsequent intake intranasally or, after dissolving in water, intravenously.[12] In the first case, rapidly absorbed formulations such as oro-soluble, sublingual or effervescent ones are more implicated, as the absorption of the API is very rapid.[13] In the second case, however, the subject alters the release kinetics of the API by removing the original protective film of the pharmaceutical powder and inducing its rapid absorption.[14] This results in the intake of a large bolus of API designed to be released in 12 to 24 hours and, consequently, high risk of poisoning by overdose, especially among the naïve.

Conclusions

The problem of the misuse and diversion of psychoactive and non-psychoactive medicines remains epidemiologically relevant, especially among primarily drug-addicted subjects but also in patients with an initial lawful prescription followed by pathologic behavior relating to the secondary drug addiction, especially in the case of opioids and benzodiazepines.[15] The possible role of the excipients of the formulations as a contributory cause of the problem has to date been little studied in the literature, especially due to the difficulty in obtaining scientifically objective data.[16] We can certainly state that, for liquid formulations, flavorings contribute to the pleasure of drug administration and, in predisposed subjects, they can be the first factor that favors direct intake from primary packaging without dilution; alcohols and glycols as preservatives can directly induce addiction, especially if taken in high doses.[17][18] For both liquid and solid formulations, the disintegrants, solubilizers and excipients that accelerate the dissolution of the API, favoring its absorption, can favor its abuse while the excipients to delay its release are generally more protective, if they are not crushed or chewed. It will be interesting in the future to develop excipients that prevent the incorrect handling of solid formulations, discouraging the misuse of these drugs.[19]

References

1. ^*Sharif S, Guirguis A, Fergus S, Schifano F. The Use and Impact of Cognitive Enhancers among University Students: A Systematic Review. Brain Sci. 2021 Mar 10;11(3):355. doi: 10.3390/brainsci11030355. PMID: 33802176; PMCID: PMC8000838.*
2. ^*Schifano F, Chiappini S, Corkery JM, Guirguis A. Abuse of Prescription Drugs in the Context of Novel Psychoactive Substances (NPS): A Systematic Review. Brain Sci. 2018 Apr 22;8(4):73. doi: 10.3390/brainsci8040073. PMID: 29690558; PMCID: PMC5924409.*
3. ^*Haukka J, Kriikku P, Mariottini C, Partonen T, Ojanperä I. Non-medical use of psychoactive prescription drugs is associated with fatal poisoning. Addiction. 2018 Mar;113(3):464-472. doi: 10.1111/add.14014. Epub 2017 Sep 28. Erratum in: Addiction. 2018 Jul;113(7):1366. PMID: 28841781.*
4. ^*Karjalainen K, Haukka J, Lintonen T, Joukamaa M, Lillsunde P. The use of psychoactive prescription drugs among DUI suspects. Drug Alcohol Depend. 2015 Oct 1;155:215-21. doi: 10.1016/j.drugalcdep.2015.07.1195. Epub 2015 Aug 8. PMID: 26282109.*
5. ^*Frauger E, Nordmann S, Orleans V, Pradel V, Pauly V, Thirion X, Micallef J; réseau des CEIPs. Which psychoactive*

prescription drugs are illegally obtained and through which ways of acquisition? About OPPIDUM survey. Fundam Clin Pharmacol. 2012 Aug;26(4):549-56. doi: 10.1111/j.1472-8206.2011.00950.x. Epub 2011 May 12. PMID: 21564282.

6. ^*Gonçalves DP, Silva IV, Rangel LB, Rezende LC. Prescription of psychoactive drugs in patients attended by the SUS at Manhuaçu - MG (Brazil). Pharm Pract (Granada). 2011 Oct;9(4):200-6. doi: 10.4321/s1886-36552011000400004. Epub 2011 Dec 12. PMID: 24198857; PMCID: PMC3818735.*
7. ^*Torp HA, Skurtveit S, Skaga NO, Gustavsen I, Gran JM, Rosseland LA. Pre-injury dispensing of psychoactive prescription drugs in a ten years trauma population: a retrospective registry analysis. Scand J Trauma Resusc Emerg Med. 2021 Aug 28;29(1):125. doi: 10.1186/s13049-021-00939-6. PMID: 34454541; PMCID: PMC8399706.*
8. ^*Chan WL, Dargan PI, Haynes CM, Green JL, Black JC, Dart RC, Wood DM. Misuse of prescription medicines is as prevalent as the use of recreational drugs and novel psychoactive substances in Singapore: an unrecognised public health issue? Singapore Med J. 2022 Oct;63(10):572-576. doi: 10.11622/smedj.2020024. Epub 2020 Mar 17. PMID: 32179926; PMCID: PMC9728315.*
9. ^*Tjäderborn M, Jönsson AK, Sandström TZ, Ahlner J, Hägg S. Non-prescribed use of psychoactive prescription drugs among drug-impaired drivers in Sweden. Drug Alcohol Depend. 2016 Apr 1;161:77-85. doi: 10.1016/j.drugalcdep.2016.01.031. Epub 2016 Feb 6. PMID: 26875672.*
10. ^*Prisco L, Sarwal A, Ganau M, Rubulotta F. Toxicology of Psychoactive Substances. Crit Care Clin. 2021 Jul;37(3):517-541. doi: 10.1016/j.ccc.2021.03.013. PMID: 34053704.*
11. ^*Wille SMR, Richeval C, Nachon-Phanithavong M, Gaulier JM, Di Fazio V, Humbert L, Samyn N, Allorge D. Prevalence of new psychoactive substances and prescription drugs in the Belgian driving under the influence of drugs population. Drug Test Anal. 2018 Mar;10(3):539-547. doi: 10.1002/dta.2232. Epub 2017 Jul 27. PMID: 28640970.*
12. ^*Soremekun RO, Omole OE, Adeyemi OC, Oshatimi AM. Assessment of use of psychoactive and other non-prescription drugs among students of selected tertiary institutions in Ekiti State South West Nigeria - A baseline study. Heliyon. 2021 Feb 26;7(2):e06232. doi: 10.1016/j.heliyon.2021.e06232. PMID: 33681493; PMCID: PMC7930107.*
13. ^*Zancanaro I, Limberger RP, Bohel PO, dos Santos MK, De Boni RB, Pechansky F, Caldas ED. Prescription and illicit psychoactive drugs in oral fluid--LC-MS/MS method development and analysis of samples from Brazilian drivers. Forensic Sci Int. 2012 Nov 30;223(1-3):208-16. doi: 10.1016/j.forsciint.2012.08.048. Epub 2012 Sep 20. PMID: 23000138.*
14. ^*Bachtarzi R, Boureau AS, Mascart C, Batard E, Montassier E, Bémer P, Bourigault C, Berrut G, de Decker L, Chapelet G. Psychoactive drug prescription and urine colonization with extended-spectrum β-lactamase-producing Enterobacteriaceae. Infect Drug Resist. 2019 Jun 28;12:1763-1770. doi: 10.2147/IDR.S200029. PMID: 31303771; PMCID: PMC6612047. 15.*
15. ^*Iglseder B. Doping für das Gehirn [Doping for the brain]. Z Gerontol Geriatr. 2018 Feb;51(2):143-148. German. doi: 10.1007/s00391-017-1351-y. Epub 2017 Dec 5. PMID: 29209802.*
16. ^*Chiappini S, Schifano F. What about "Pharming"? Issues Regarding the Misuse of Prescription and Over-the-Counter Drugs. Brain Sci. 2020 Oct 14;10(10):736. doi: 10.3390/brainsci10100736. PMID: 33066476; PMCID: PMC7602178.*
17. ^*Batisse A, Eiden C, Peyriere H, Djezzar S; French Addictovigilance Network. Use of new psychoactive substances to mimic prescription drugs: The trend in France. Neurotoxicology. 2020 Jul;79:20-24. doi: 10.1016/j.neuro.2020.03.015.*

Epub 2020 Mar 30. PMID: 32240674.

18. ^*Orsolini L, Francesconi G, Papanti D, Giorgetti A, Schifano F. Profiling online recreational/prescription drugs' customers and overview of drug vending virtual marketplaces. Hum Psychopharmacol. 2015 Jul;30(4):302-18. doi: 10.1002/hup.2466. PMID: 26216567.*
19. ^*Falci DM, Mambrini JVM, Castro-Costa É, Firmo JOA, Lima-Costa MF, Loyola Filho AI. Use of psychoactive drugs predicts functional disability among older adults. Rev Saude Publica. 2019 Jan 31;53:21. doi: 10.11606/S1518-8787.2019053000675. PMID: 30726502; PMCID: PMC6390663.*