

Damage reduction as endpoint in the management of substance addiction

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SUMMARY

Objectives

The treatment of addiction is very complex and results from the integration of pharmacological and psychological techniques whose end-point is generally to obtain and maintain total abstinence from substances of abuse for the individual patient; however, this goal in clinical practice is often very difficult to achieve given the high psycho-behavioral dependence on many substances, the frequent psychiatric and poly-abuse comorbidity and the low motivation of many patients, at least at the beginning, to stop completely and definitively with one or more substances that often accompany them for many years or decades. Thus in recent times it has appeared as an idea the implementation, generally more realistic, of methods that imply the reduction and change of consumption, and consequently also of the physical damage, associated with psychoactive substances. In this article we will deal with the methods that lead to this result, with practical examples where this is already applied and with possible ideas for the future management of some situations of frequent clinical confirmation.

Materials and methods

The work was carried out by searching on sites of scientific articles such as PubMed, Researchgate and Google Scholar, by typing in keywords such as “addiction”, “harm reduction”, “addiction drug therapy”, as well as in paper manuals of psychiatry and psychopharmacology.

Results and conclusions

We have found many articles, both recent and past years, of studies and data that testify that harm reduction is, for many subjects, a more realistic and easily achievable endpoint, both as an intermediate step towards complete abstinence and as an objective primary, especially in the case of significant psychiatric comorbidity, poly-abuse or unfavorable socio-economic conditions and in some cases, such as for tobacco smoking or intravenous drug use, it also allows to reduce physical complications and public health expenditure, going for the benefit not only of practitioners working in mental health centers but of all branches of medicine, including general medical care.

Key words: damage reduction, psychoactive substances, addiction, psychopharmacology

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Introduction

The consumption of psychotropic substances has played an integrated role in human history for millennia, but with notable differences both like the substances used and in the reasons for their use. The meaning of the assumption can be various, religious, ritualistic, self-medicating (to “chemically” affect a negative mood or psychic tension as in the case of alcohol) or for the pursuit of pleasure, as well as to improve their performance (this is the case, for example, of stimulants, cocaine in the first place, without excluding nicotine and caffeine). Just think, for example, that all over the world 48% of the total adult population consumes alcohol at least occasionally, 33% smokes tobacco and at least 5% consumes illicit substances¹. In Italy the situation in recent years is not very different; according to data from the anti-drug police department², in 2019 almost 55 drug emissions and 223,541 cannabis plants were seized (with

a decrease of 55.7 and 57.4% from 2018), in addition to 59,457 doses/narcotic substances tablets (+ 74.4%). 82% of the substances seized are cannabis products: the quantities of hashish and marijuana respectively, a difference from previous years, are substantially equivalent. In Italy, there are about 550 seats and in 2019 they assisted over 136,000 drug addicts, of which over 65% with heroin-related problems and over 30% from cocaine. Alcoholic services take care of over 90,000 patients, which however are about 10% of the total real number of alcoholics in Italy (which amounts to over 800,000 patients potentially deserving of treatment) and over 5 million people are considered “drinkers at risk”, ie non-alcohol dependent but abusers and potentially susceptible to the development of alcohol-related physical diseases over time ³. The total abstinence does not always constitute a feasible or acceptable goal given that a strong ambivalence often prevails between the awareness of having to stop consuming a substance that compromises the state of health and the constant desire to seek pleasure and its gratifying effects so that the individual is free to make a personal choice about his or her modality of use of the substances themselves. It is therefore essential in the beginning to understand what the patient wants to achieve first, as well as his level of motivation and self-efficacy ⁴. It should be kept in mind that in this class of patients (not sufficiently motivated for total and immediate cessation and often with little family and social support) the short-term relapse rates (within 6 months) are very high; this is why in recent years the idea of a new possible management model has been born that does not imply an immediate detachment from the substance but remodeling and review of the relationship between the employer and the substance itself. This is how the idea of the approach based on “harm reduction” was born, a model already in use for some substances and which seems to give more feasible and consolidable results in the long term than complete abstinence, which can in any case then be obtained at a later time. The management approach based on harm reduction implies a paradigm shift that sees in the first place, not the rapid and complete withdrawal from the abused substance but a reduction in its frequency of use or a different way of taking it that results in both the overall improvement of the psychophysical health of the patient and an incentive for a subsequent possible complete abstinence. In detail, an approach of this kind involves various aspects ^{5,6}:

- the reduction of consumption induces an improvement in the physical health of the subject, with a minor cumulative dose and this allows to delay, slow down or avoid the damage, depending on the type of substance, the time of therapy in the history of the disease and patient-related factors such as age and comorbidities;

- improves mental health by reducing both the psychic effects of chronic intoxication (eg pro-depressive effect of alcohol and opioids or stimulating effects such as insomnia, anxiety, and mania from cocaine or amphetamines) and episodes of acute intoxication and binge, with positive effects also on the possible psychiatric comorbidity;
- furthermore, for some substances, the passage from injection to enteral administration or through special instruments (we will see later) significantly reduces the risk of transmission of serious and chronic infections such as HIV and HCV, improving expectancy and quality of life. How damage reduction can be implemented are 3: reduction of the frequency of consumption, of the dose taken in a single time and, in the case of venous users, change of administration by non-injection route or by using sterile disposable material, properly disposed of later. We will now see in detail the application models currently already in use.

Materials and methods

The work was carried out by searching on some sites of scientific articles (PubMed, Researchgate and Google Scholar) by typing in keywords such as “addiction”, “harm reduction”, “addiction drug therapy”. Moreover, up-to-date paper books relating to addiction psychiatry and psychopharmacology were used. In drafting the work we focused on selecting only recent articles or texts where harm reduction was explicitly mentioned as a primary or secondary endpoint, without neglecting however the relationship of this approach with the traditional one of maintenance with agonists and comparing them for specific groups of substances, evaluating both the potentially beneficial effects on mental health and physical comorbidities.

Discussion

Tobacco

Tobacco smoking remains a truly global epidemic. Widespread after the discovery of America and now cultivated in various parts of the world, the tobacco plant (*Nicotiana tabacum*) is part of the Solanaceae family and is by far the most abused substance also given its high ability to induce psycho-addiction. To date, more than 13 million people smoke in Italy (ISTAT 2020 data) and where every year between 70 and 80 thousand die from smoking-related diseases, mainly tumors, cardiovascular and respiratory diseases, and where, of the more than 40 thousand new diagnoses at the year of lung cancer, 85% is directly attributable to smoking. On the other hand, psychiatric patients tend to smoke 2-3 times more than the general population and, while representing a minority of it, consume alone up

to 44% of total cigarettes, paradoxically receiving less assistance and advice to quit ⁷. In recent years, much has been done to discourage consumption, from the increase in cigarette prices to anti-smoking advertising campaigns to the creation of real anti-smoking centers, currently over 300 throughout the country. Unfortunately, all this seems not to be enough and most smokers remain relatively insensitive to the motivational drive to change and the data show it: only 30% try to quit smoking every year, and of these only 5% become abstinent long term ⁸. What reasons? The most important is that tobacco use is both physical and behavioral addiction to nicotine even though it is commonly accepted as a simple habit or bad habit and there is still a great deal of neglect among doctors and healthcare professionals who only rarely offer true and their paths to their clients. There is no acceptable threshold dose for smoking: total and permanent abstinence alone is the central goal in the management of the smoking patient, but this goal is poorly accepted especially by heavy smokers (up to 60 cigarettes a day). So the health authorities have tried to find a “middle way” to obtain the initial therapeutic engagement for these subjects and today there are two important approaches to harm reduction in this population ^{9,10}:

- the exclusive switch to electronic cigarettes (e-cigs, now on the market for over fifteen years) or to heated tobacco products (IQOS, more recently introduced): toxicological studies have shown the reduction of exposure by over 90% of the polluting particulate in subjects “vapors” compared to traditional smokers and as regards IQOS the reduction is between 30 and 70% depending on the chemical species involved ¹¹⁻¹³. The e-cigs were the first devices initially developed to promote the complete cessation of tobacco but the current guidelines are more in favor of harm reduction as it has not been demonstrated uniformly in studies that subjects who switch to ‘exclusive use of the e-cig always manage to stop permanently, even if this determines the absorption of nicotine always by inhalation and therefore much more similar to the traditional cigarette. The IQOS, which arrived on the market in 2015, is a hybrid between the two as they contain tobacco which, however, is not burned but only heated up to about 350 degrees to vaporize the nicotine ¹⁴. According to some studies, the transition to the use of these new devices would make it possible to significantly reduce the incidence and mortality rate from cancer but to date in Italy no health policies are promoted in this sense, preferring the perspective of prohibition which is certainly effective. but unfortunately poorly accessible for many at-risk groups of the population (including adolescents, highly addictive smokers, psychiatric patients);
- the use of traditional anti-smoking drug therapies not to achieve total cessation but to allow a reduction in

consumption without causing the patient to suffer excessive nicotine withdrawal symptoms between one cigarette and the next (this is because, given the short half-life of the nicotine, heavy smokers tend to light the next cigarette every time the nicotine is reduced to zero, especially in rapid metabolizers and in subjects who have developed high tolerance). Various studies have, for example, showing that the use of nicotine transdermal patches stabilizes the patient by reducing the desire to smoke overall, especially during nocturnal awakenings, in the morning, and in times of stress, improving compliance ^{15,16}. This method allows the strong smoker to perceive being able to control consumption, managing to stay a few more hours without the need to smoke and therefore allowing, at least in some, to increase their self-efficacy and fully bring out the will for complete cessation. The same goes for the other nicotine releasing pharmaceutical forms and also for varenicline, taking into account that the best results are obtained by combining two pharmaceutical forms for NRTs (transdermal patch and quick release preparations as needed) and also psychological support is always important because it maintains and improves motivation and strengthens the therapeutic alliance ¹⁷.

Among the new treatment strategies is the use of two partial agonists, varenicline and cytisine, which since the early 2000s has shown great promise in making patients quit smoking or at least in reducing the number of cigarettes. Varenicline, an $\alpha 4 \beta 2$ nicotinic cholinergic partial agonist, on the market since 2006, it has revolutionized the management strategy of heavy smokers in anti-smoking centers because it is not only capable of acting on withdrawal symptoms, reducing or canceling them, but above all capable of reducing the craving for tobacco, stabilizing mood and levels of anxiety typically increased during smoking withdrawal ⁷. Agonist nicotine therapies, which replace the substance as it is taken with smoking, release nicotine with a different kinetics than smoked one, which after an average of 8 seconds immediately reaches the CNS, instead with transdermal patches it is released slowly during 24 hours, giving constant nicotine but without the positive reinforcement linked to rapid peaks and also rapid formulations such as oral sprays or sublingual tablets, while waiting for the withdrawal symptoms, do not completely cancel them and do not improve the craving (but they can still be valid if the person is highly motivated and does not have a high addiction).

Alcohol

The use of alcohol is attested in all cultures since ancient times and occurs along a continuum ranging from episodic and very moderate use to heavy, sporadic, or daily consumption, which can give rise to serious forms of ad-

diction and associated somatic pictures¹⁸. Consumption patterns vary considerably from individual to individual but overall in recent years we have witnessed a change in them in Western society, passing from the more classic, “Mediterranean” one, ie mainly low or medium alcoholic beverages and during meals or in any case in convivial situations, to the “Nordic” one, with the prevalent use of medium-high alcohol drinks, often between meals and with the specific aim of researching psychoactive effects rather than the pleasure of associated taste; among young people, it is now fashionable to consume with binge modality, ie six or more alcoholic units in a short period for the pure search for a “high”, especially by associating other psychoactive substances such as caffeine in energy drinks and psychostimulants¹⁹. The DSM-V reformulated the diagnostic criteria for alcoholism by linking both actual addiction and abuse under the term “alcohol use disorder” (AUD). Alcohol can cause damage to various organs and systems and 70% of patients with alcohol-related diseases are social drinkers and not alcoholics, which represents only about 5% of the population. 35-40% have a risky consumption and it is precisely among these that most of the subjects who will develop related physical problems, on average after a latency of 10-30 years from the first contact with the substance, must be sought. Even in the case of AUD, the treatment aims to obtain abstinence from consumption but we know it to be very difficult: it is, in its natural history, a rather resistant disorder to treatment, generally with many relapses with a strong psycho stimulus, physical to the resumption of consumption due to the mesencephalic neurobiological changes, patients have an intense reactivity to environmental stimuli and emotions. Episodic consumption typically begins in adolescence and is a common habit and generally decreases from around the age of 30. Of consumers at risk, about a third continue towards addiction while the majority maintain or reduce their income^{20,21}. Of the alcoholics, without treatment, most have a strong tendency to progress and, after the rare periods of abstinence, most, due to sensitization, return to their original consumption in a short time. Of the subjects attending a comprehensive treatment program, 45% achieve long-term abstinence, 35% have a remitting-relapsing path, and 20% show a progression of damage. The highest risk is recorded during the first 3 months of the program (70-80%). With a view to harm reduction, as previously explained for tobacco, starting from 2013 the authorities approved the marketing of a new drug, nalmefene, a class C drug obtainable with a standard repeatable prescription and marketed in 17-milligram tablets. This drug has some peculiarities compared to the others in use: it was in fact designed to be prescribed for the reduction of consumption in adult patients with alcohol dependence who have a high-risk intake but with-

out physical symptoms of suspension and who do not require immediate interventions. detoxification, together with ongoing psychosocial support, aimed at adherence to treatment and reduction of alcohol consumption, only in patients who continue to have a high-risk drinking level two weeks after the initial assessment⁷. This is a very different goal from the classic one which instead provides for the rapid achievement of complete abstinence from alcohol consumption and was designed for abusive patients, especially in binge mode, not immediately willing to stop drinking completely but who need (and who are willing) to reduce consumption. The dosage is also particular: in fact, nalmefene is taken as needed: the patient must take a tablet, preferably 1-2 hours before the scheduled time for alcohol consumption, every day when he perceives the risk of consuming alcohol. If the patient has started drinking alcohol without taking the drug, he should take one tablet as soon as possible. The maximum daily dose is one tablet (higher dosages have not shown additional benefits in preclinical studies). The use of drugs that modulate the opioid system in the treatment of alcoholism is not a new concept: naltrexone (NTX), an antagonist on endogenous opioid receptors, has already been approved for some time (1994) to manage alcohol dependence. as it reduces the pleasure associated with the consumption of drinks and the craving associated with abstinence^{22,23}. However, while the NTX also indicates the maintenance of opioid abstinence, nalmefene is specific for alcoholism as it reduces the reinforcing effects of alcohol and has a particular action profile. Although it is a selective ligand of opioid receptors, it is not a pure antagonist like naltrexone but rather a modulator, with different factions in the various receptor subtypes (it is the antagonist on mu and delta receptors and partial agonist on kappa receptors)⁸. It also has a long half-life and the data from preclinical and clinical studies and the literature do not suggest any form of addiction or abuse potential. The patient who takes nalmefene reports a reduced need for alcohol and above all a clear reduction of binge episodes and an easier non-problematic abstinence. However, these are patients who do not need immediate detoxification, for whom traditional drugs and protocols remain valid, but who still deserve a reduction in intake that is not easily obtainable without other pharmacological support. Nalmefene is contraindicated in patients who are taking opioids or who have recently used them or with current or recent addiction as it can trigger a withdrawal crisis in these subjects. However, it can also be used in patients with non-advanced liver disease.

Illicit substances

The use of illicit substances has seen, since the 1980s, an epidemiological change, with a reduction in the consumption of opioids (primarily heroin) and a progressive increase in the use of natural and synthetic

stimulants. This phenomenon is attributable to social and cultural factors but also related to the availability of the substances themselves and their characteristics: heroin depresses nervous functions, inducing sedation, drowsiness, lethargy, and severe physical and mental dependence, as well as various typical somatic complications opioids; stimulants, on the other hand, activate mental functions resulting in euphoria, disinhibition, greater fatigue resistance and increased performance and for these reasons they are often used by adolescents and by a segment of the population that is also well integrated socially and in contexts of polyabuse, especially together with alcohol ^{9,10}. But one of the most characteristic factors is that heroin gives the typical feelings of gratification especially if administered by injection and most heroin addicts self-administer the substance intravenously several times a day given its short half-life. However, this entails various physical consequences, first of all, the high risk of transmission of blood infections such as HIV, HCV, and HBV due to the exchange of syringes between potentially infected people, as well as that of undergoing vascular complications such as phlebitis and embolic diseases caused by contaminants present in the substance. However, it must be said that this practice is not exclusive to heroin: stimulant substances such as cocaine, amphetamines, ketamine can also be injected (remember the classic combination of heroin and cocaine, known as “speedball”). The use of non-sterile injecting practices was the main determinant in the 80s and 90s which contributed to the spread of the infections mentioned above in this population and still today, albeit to a much lesser extent, remains a significant social scourge ²⁴. For all these substances there is no acceptable threshold dose and the final goal remains complete and definitive detoxification but, in a significant percentage of cases, due to the lifestyle, the addictive environment, and the associated complications, it is not possible to achieve sufficient adherence to treatment and patients relapse after a short time or will never go to a SerT. Thus, since the late 1980s, an attempt has been made to answer a question: can drug addicts learn how to use drugs responsibly, if not by stopping their consumption, at least by adapting it to avoid the most dramatic consequences? The strategic solution would therefore not be to use all the energy in an attempt to fully recover drug addicts but to learn to live with the phenomenon and promote, as much as possible, strategies to reduce the harm related to consumption ^{9,25}. Thus, especially abroad, operating models have been applied aimed at least reducing the damage related to the methods of recruitment, moving to legal administration under medical supervision. In particular, three interventions already in use should be remembered ²⁶:

- the distribution of sterile syringes via mobile units;
- the opening of centers for controlled consumption and information on the responsible use of drugs;
- the controlled distribution of heroin.

Such programs have already spread in Europe (in the Netherlands, for example, since 1984, in Denmark and Great Britain since 1986, and Switzerland since 1998). These policies do not in themselves imply the principle of legalization, although many promoters of these models are also in favor of it for some substances as it would lead to an increase in the quality of the drug with a decrease in the impurities contained and a reduction in the price of substances and related phenomena such as crime and prostitution. Since the discovery of HIV and HCV viruses, both in the 1980s and of their mode of transmission, the distribution of free sterile material (syringes, tampons, water) to drug addicts has begun in the first place, encouraging their return from these, used syringes for their correct disposal. Even today there are “low-threshold services”, organized mainly in mobile street units and first reception centers and represented by volunteers who implement this distribution of sterile material in the places preferentially frequented by these people also through regional projects ^{27,28}. The effects of these measures were immediately positive: in Italy, the prevalence of HIV infection among drug addicts fell from 60% in 1986 to values of about 3% in recent years (up to the 1990s, with the availability of HAART, caused rapid spread and death within 1-3 years from the infection). The same applies to HCV, albeit with less dramatic results: the seroprevalence of the infection among drug addicts up to the 1990s was very high, close to 100%, being much more contagious per syringe than HIV ⁷ and it can also be transmitted simply by sharing other used instruments other than syringes such as filters. Today, also thanks to the new direct-acting antivirals, mortality has decreased sharply and new infections are reducing over time ⁷. Concerning the controlled distribution of substances in Switzerland on 13 May 1992, the Federal Council ruled in favor of the controlled experimental distribution of heroin to seriously addicted drug users. Today, this therapeutic approach is part of everyday life in Switzerland. In total there are 21 centers distributed throughout the territory; the DiaMo Narcotis laboratory in Thun produces every year, under strict supervision, between 200 and 300 kilos of diamorphine, the pharmaceutical form of heroin. According to various sources, crime related to drug dealing has reduced as drug addicts are no longer forced to commit crimes to obtain the doses, each of them is considered a patient and covered by the health insurance fund, subjected to medical treatment and psychological assistance. In Italy to date, low-threshold units have been a reality for many years but, as regards the controlled distribution of

substances for serious and recurrent cases, there are neither interventions already approved of this type nor short-term legislative proposals that provide for such methods of management, even if the heroin problem is far from solved. Finally, it should be remembered that also the use of a partial agonist drug, varenicline, which has contributed a lot to increase the percentage of subjects who are able to obtain abstinence or a reduction in the consumption of illicit opioids thanks to some of its particular characteristics. An example of the utility of buprenorphine in the management of heroin withdrawal, which has accompanied methadone in an almost similar way in terms of efficacy, even if still fairly little prescribed. A disadvantage concerns its formulation in sublingual tablets as some heroin addicts have started over the years, after having solubilized the tablets in water, to inject them into a vein. For this reason, today there is a tablet formulation that combines buprenorphine and naloxone: this opioid antagonist is not active orally as it is not absorbed but, if injected into a vein, it reaches the brain where it rapidly antagonizes the effects of opioids and also, in subjects addicted, often triggers withdrawal symptoms¹¹. This aspect is not possible instead with methadone, a complete agonist, often used directly in the vein with the risk of both overdose and venous or arterial puncture injuries such as phlebitis and moreover it is a syrup in a sugar solution, associated with an increased risk of diabetes and metabolic problems.

Benzodiazepines

Benzodiazepine abuse (BDZ) is a major problem in all care settings, both inpatient and outpatient, and all of these compounds have abusive properties, albeit with differences in half-life and hypnotic and anxiolytic potency. It is estimated that in Italy the users of these compounds are about one in 10 adults and that over 3 million people are "long term users", therefore off-label. Unfortunately 40 to 80% of these subjects have a dependence on these drugs^{29,30}. Abusers are usually offered as a strategy or with a slow dosage or, in the case of short half-life drugs such as triazolam, alprazolam, or lorazepam, switching to long half-life compounds, complete agonists such as diazepam or lorazepam. clonazepam, with the same logic of switching from heroin to methadone, stabilizing plasma concentrations and reducing interdose withdrawal symptoms and allowing for easier downsizing. In recent years, however, a new technique has taken hold for high dose abusers (over 50 milligrams of diazepam-equivalent per day for at least 6 months) based on the use of flumazenil as a slow subcutaneous infusion for one week of hospitalization, associated with prophylaxis. antiepileptic³¹. Flumazenil, BDZ receptor antagonist, if administered not as a rapid bolus but as a slow infusion acts as a partial agonist allowing the restoration of the dysregulated GABA-A

receptors in chronic BDZ abuse, restoring their normal function and restoring the original sensitivity that such patients they had lost over time^{7,12}. Currently in Italy this treatment is carried out only by the addiction medicine department of the Verona Polyclinic¹³.

Conclusions

The problem of managing addictions remains a huge but poorly represented public health issue to date in Italy, despite the data indicating an increase in consumption, especially among the under-30s. Various strategies have been adopted to cope with this problem and among these a leading role sees those that imply the reduction of harm for those subjects with important addictive behaviors and not immediately willing or able to stop their consumption especially for psycho-concurrent social events¹⁴. The goal of harm reduction services is not the abstention from substance use, as that of traditional care services (although abstention is obviously a desirable but not immediately necessary development). The operators who deal with this meet people in the places of consumption and The relationship between operators and consumers is informal, with a non-judgmental approach because the primary objective is to prevent people from dying, avoid the transmission of diseases and prevent social damage. They also play a control role that benefits everyone and contain the health costs of any hospitalization and treatment for diseases such as hepatitis C or HIV and are a tool to hook the undeclared, which would not turn to the Sert. Various have been described, both for legal and illegal substances (the latter above all for their mode of intake) but to date, unlike the scenario of other European countries, Italy does not have health policies aimed in this direction, involving on the one hand the presence of centers that work very well and take care of over 136 thousand patients followed over time but a large number of potential patients continue to escape health control, endangering their health and that of others due to the spread of infections serious¹⁵.

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Conflict of interest statement

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Authors' contributions

We worked in an integrated way on the development of the article, both contributing to the drafting of all the paragraphs and to the complete bibliography and web-

site research. AM and EM had the idea of writing the article. AM initiated and contributed to implement the research of the sources and developed the theory and EM performed the calculations. Together, AM and EM verified the methods, investigating the specific aspect and AM has supervised the results of this work. All Authors discussed the results and contributed to the final manuscript.

Ethical consideration

The articles that contributed to this review were reviewed by considering international ethical standards.

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