New therapeutic approaches in alcohol dependence: reduction of consumption as a step in the therapeutic goal

Nuovi approcci terapeutici nei disturbi correlati all'uso di alcol: la riduzione del consumo come step terapeutico

G. Fertonani Affini, E. Savi, P. Garofani, S. Zaltieri, V. Nucera, L. Giustina, M.C. Antonioni

Dipartimento Assistenziale Integrato Salute Mentale e Dipendenze Patologiche – DAISM-DP – Ser.T. PR – Funzione Alcologica – Az. USL Parma

Summary

Objectives

Disorders related to the abuse of alcohol should be considered as a social and health emergency. The alcohol dependent patient runs the risk of developing physical, psychological, social, economic and legal problems. Thus, there is a need to find new therapeutic strategies for the treatment of alcohol dependence. Abstinence has always represented the elective therapeutic approach in alcohol dependence; nevertheless, considering abstinence as the only successful result in clinical treatment does not allow capturing significant aspects in consumption patterns of patients. From the literature, significant results have emerged regarding reduction of alcohol consumption in terms of frequency and quantity, which can become a marker of clinical progression towards abstinence.

Methods

The present is an in-depth analysis of the existing literature (from 1962 to 2012) on possible therapeutic interventions in the treatment of alcohol dependence. The literature focuses on the relationship between "reduction of consumption versus abstinence", with both representing possible treatments in alcohol dependence.

Results

The results of a large body of research seem to agree in emphasizing a linear correlation between systemic exposure to alcohol and morbidity and mortality. On the other hand, the scientific evidence does not indicate precise and identifiable thresholds for the damage incurred from ethanol. In the light of the available data, the concept of reduction of alcohol consumption versus abstinence has become useful from clinical, social and economic aspects. The opportunity to reduce risk and organ damage, to involve the patient in a therapeutic program towards abstinence, to prevent the development of alcoholism into more severe forms and to reduce the social and economic impact are important indicators that can be achieved considering the therapeutic strategies examined.

Conclusion

From analysis of the literature, it is possible to understand that reduction of alcohol consumption can be an intermediate valid goal both therapeutically and socially, and acceptable for those patients unable or unmotivated to achieve abstinence, in order to reduce the clinical risks associated with heavy drinking. During treatment there is an important and active dual role of both the doctor and patient who should share common goals resulting from accurate analysis of the motivation and personological characteristics of the patient. New pharmacological strategies can be useful to reach this therapeutic goal. Nalmefene, a modulator of the opioid system with antagonist activity on opioid mu and delta receptors and partial agonist activity on kappa opioid receptors, appears to be especially effective in reducing ethanol consumption.

Key words

Abstinence • Alcohol Dependence • Heavy drinking • Reduction of alcohol consumption • Morbidity • Mortality • Nalmefene

Introduction

Even if the scientific community retains that achieving abstinence is still the primary objective for patients affected with alcohol abuse disorders, there is growing knowledge about the therapeutic limits of this concept. Considering abstinence as the only possibility of clinical-therapeutic success does not take into account significant aspects of alcohol consumption models. Increasing awareness of the patient means creating a cognitive path of change where reduction in consumption, in terms of frequency and quantity, can become an indicator of clinical progression towards abstinence. Individual (biological, personal, cognitive, relational) and cultural characteristics of the patient, and the course of the pathology related to alcohol dependence, allow the identification of therapeutic steps in reducing consumption that progressively lead to a condition of awareness of abstinence.

Correspondence
Giuseppe Fertonani Affini, via dei Mercati 15/B. Dipartimento Assistenziale Integrato Salute Mentale e Dipendenze Patologiche - Ser.T. Parma – Funzione Alcologica, 43100 Parma, Italia • E-mail: gfertonani@ausl.pr.it

The concept of reduction of alcohol consumption in rehabilitative paths

The social and economic costs of alcohol-related pathologies are extremely high in terms of morbidity and mortality. In the US, 4% of the adult population, over a one year period, suffers from alcohol dependence [1 2]. Alcoholism seems to be one of the most important public health problems, and worldwide is the fourth cause of disability [3]. The alcohol dependent patient can develop physical, emotional, social, financial and legal problems. In Italy, the mean annual consumption per person is 8.02 litres, which is lower than mean consumption in other European countries (Spain 10.03 litres, Greece 13.24 litres, France 13.24 litres; data from 2011). In Italy, in total, there are 36.4 million occasional and daily drinkers, and among these there are 8.18 million drinkers at risk considering non-moderate drinking and binge-drinking. It is estimated that there are about 1 million alcohol dependent individuals in Italy [4]. Of these, only 58,122 are seen by Health Services for Dependent Pathologies [5] (Fig. 1).
Considering this, there is considerable need to find new therapeutic strategies for this pathology. In this regard, an elective course for cure has always been considered the road to abstinence. However, for several years, multiple authors, analyzing the results of many studies, have taken into consideration other therapeutic alternatives [6]. One such alternative is reduction of alcohol consumption to return to 'moderate', 'controlled' or asymptomatic' use [7]. Reducing consumption is an approach to public health that is part of a larger intervention in reducing damage with the aim of limiting the negative consequences of alcohol abuse, for both the drinker and the community, by encouraging and reinforcing alternative behaviours [8]. An approach involving reduction is accepted by and encouraged in the UK [9], in Europe, and in part by Australia Canada [10-12]. In the US, however, abstinence is the preferred course for alcohol dependent individuals. Lately, there has been some discussion regarding treatment of alcohol dependence, considering a continuum of abstinence, reduced consumption and abuse (Fig. 2).
In the past, from a scientific point of view, there has been ample discussion on this subject [14]. For some authors, when dependence appears, the subject no longer has control over alcohol consumption, and thus the only possible way to halt the disease is through abstinence. Others however, have taken into consideration the possibility of adopting a strategy towards reduction in consumption. This type of strategy takes into account the different types of alcoholism and, consequently, favours a personalized approach to treatment [15]. Connors [16] noted that, even in the 1940s, following the course of patients under cure for alcoholism, a subgroup of individuals could be identified that were able to resume alcohol use after a period of abstinence, without any apparent difficulty [17-19]. In this regard, the study of Davies should also be mentioned [18], who observed that of 93 alcohol dependent subjects, 7 drank in a reduced manner after a follow-up of 7-11 years. Of these 7, only one maintained the ability to drink moderately during later follow-up. Even the results of the Rend Report [17], a longitudinal study on treated alcoholics, showed that after 18 months some patients had began controlled consumption of alcohol. Another study carried out on 70 individuals subjected to abstinence or reduction therapy showed that in both treatment groups the consumption of alcohol decreased (4 drinks/day *vs*. 10, 3 drinks/day *vs*. 5, respectively), and was maintained at two years of follow-up [20].

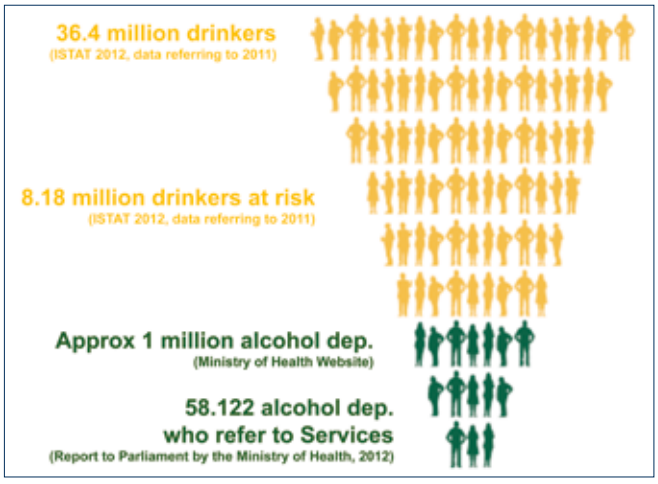

FIGURE 1.
Drinkers and alcohol dependent individuals in Italy [4]. *Bevitori e alcolisti in Italia* [4].

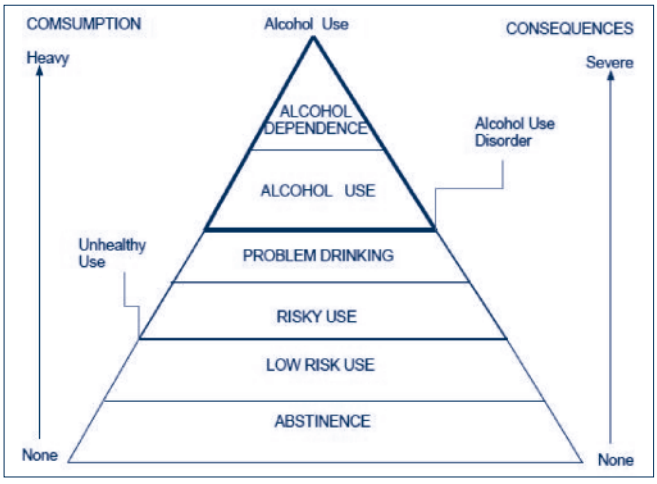

FIGURE 2.
Alcohol consumption spectrum (from Saitz, 2005, p. 598) [13]. *Lo spettro del consumo di alcol (da Saitz, 2005, p. 598)* [13].

One study considered 4 groups of subjects (N = 99) that were followed-up at 3, 5, 7 and 8 years [21]. Of these, 14 subjects presented asymptomatic drinking behaviour, and did not show signs of dependence or negative consequences. Of these 14 individuals, 10 had received a diagnosis of alcohol dependence. Considering this study, it is possible to think that some patients may be able to maintain controlled consumption of alcohol without returning to excess [7]. This may be possible based on individual characteristics such as: young age, sex (women appear more able to reduce consumption), social and psychological stability, less severe dependence [22-26], are employed and have confidence in one's ability to moderate consumption. On the other hand, abstinence is considered elective treatment for patients who are less motivated to resume non-abstinence, in the presence of medical or psychological conditions caused by continuous use of alcohol, for patients under pharmacological therapy that is dangerous in combination with alcohol, for subjects that present with severe alcohol dependence and a history of previously failed attempts at controlling substance abuse behaviour [27]. Reduction in consumption is also contraindicated in women who are pregnant or breastfeeding [27].

Considering that with alcohol dependent patients it is not simple to construct a therapeutic alliance due to the severity of the problem or the tendency to deny/minimize the problem, intuition and experience of the physician are important as he/she must be able to understand the personological functioning of the subject, and propose ad hoc treatment considering both the limits and resources available. During treatment, in addition to the physician, even the patient must have an active role. In this regard, a therapeutic alliance between the patient and physician can have significant advantages in terms of establishing treatment objectives, understanding the motivation of patients and reducing drop-outs. The formulation of a functional therapeutic course should be preceded by thorough analysis of the questions that allow negotiation of a treatment plan that considers the expectations of both the individual and the physician. In this regard, some studies have shown that patients who are presented more than one treatment alternative are more likely to become involved in therapy.

This was demonstrated by a longitudinal study [28] on 106 alcohol dependent individuals who were given the opportunity to choose between abstinence and moderate consumption. Initially, 46% of subjects (N = 49) chose abstinence while 44% (N = 47) initiated a course towards controlled consumption. After 4 weeks of treatment, 89% (N = 42) of subjects who chose abstinence reached their goal compared to 51% (N = 24) of those who chose moderate consumption (three subjects were lost to follow-up). The authors also showed that after the first 4 weeks of treatment, 49% (N = 23) of subjects that chose moderate consumption were willing to choose abstinence. On the other hand, those who initially chose abstinence could consider reduction in consumption, if this was tolerated. Even a controlled study in New Zealand [29], in which dependent subjects were allowed to choose what they felt was the most appropriate treatment, revealed a greater predisposition to abstinence. This suggests that reciprocal agreement between the patient and caregiver facilitates a realistic treatment goal.

In conclusion, according to these studies, it can be deduced that the choice of controlled consumption is a therapeutic strategy that can increase the proportion of individuals willing to accept treatment. This is significant considering the fact that less than 10% of individuals with alcohol abuse and dependency problems undertake cure [23]. Therefore, greater flexibility may help to create a therapeutic alliance and achieve a positive result. Establishing a contract with the patient, especially with those who manifest doubt and resistance, can thus be beneficial. For example, subjects can be supported by a physician to remain abstinent for 3 months with the subsequent possibility to resume moderate consumption. Another approach foresees that the patient reduces consumption with the possibility to initiate abstinence at any time, whenever it is deemed necessary [30].

Offering the possibility of choice and renegotiation appears to provide additional functionality to the patient with alcohol dependence [31]. Such a choice allows attributing an active role in the healing process, without losing sight of the objectives and motivation as related to the characteristics of the individual. In terms of treatment, recognition of the patient's choice by the physician seems vital. If the physician retains that reduction of consumption is an alternative, then even the patient will consider this as a possibility. With the aim of reducing prejudices, which even physicians have when considering reduction, it would be a significant advance to develop guidelines that include non-ambiguous parameters to define reduction. This would comprise, for example, consensus concerning what is considered a standard drink keeping in mind the quantity and frequency of consumption [32], and a shared and contingent plan for intervention and strategies for negotiation with the patient [7]. There is still a lack of agreement on these issues.

According to the US Department of Agriculture [33] and US Department of Health and Human Services [34], moderate drinking is defined as 1 drink/day for women, 2 for men and 1 per day for men and women over the age of 65 years. For others, moderate consumption is defined as 3 drinks/day and < 12 drinks/week for women, 4 drinks/day and < 16 drinks/week for men; 1 drink/day and < 8 drinks/week for individuals over the age of 65 years [35]. The existing literate has defined parameters that

allow considering one a heavy drinker on the basis of the amount of alcohol consumed, and is ≥5 drinks/day for men, and ≥4 drinks/day for women [36-40]. The consumption of more than one drink per hour and to drink according to predefined habits (in the same place with the same people at the same time) should also be considered significant. Individuals need guidance so that consumption of alcohol does not become a coping strategy, to not drink and drive, and to not drink during pregnancy or while breastfeeding. By educating individuals to not consume alcoholic beverages in a continuous manner, keeping a diary of what, how much and where alcohol is consumed, can be useful to monitor the subject's relationship with alcohol.

The studies examined allow greater critical reflection on possible therapeutic alternatives for alcohol dependence. From the available data, it is possible to think about the fact that treatment aimed at reduction in consumption can be part of the cure of alcoholism. Reduction and abstinence should not be viewed as irreconcilable strategies for intervention, but can be seen as parts of a continuum, as options of choice that are both aimed at cure, keeping in mind the personological functioning of the patient. A dependent individual, in order to initiate treatment with motivation, needs to confront the physician considering present needs in relation to the severity of the disease and individual as well as other resources available. For the subject to be able to choose the course of treatment is a predictive factor for better adherence. Moreover, the possibility to negotiate the treatment course and modify it according to individual needs, difficulties and improvements during treatment seems to facilitate a good outcome. One strong point that emerges from the above-cited literature concerns the ability of the physician to individuate the motivations of the patient and engage him/her in the therapeutic plan. Understanding the severity of the dependence and asking for help allows the physician to choose the most effective treatment. In addition, a good therapeutic alliance should be considered as essential to all types of treatment.

Relationship between excessive drinking and morbidity and mortality: reduction in consumption *versus* abstinence

Many epidemiological studies have demonstrated a close relation between excess consumption of alcohol (heavy drinking) and damage to health, automobile accidents and organ damage [41]. High levels of alcohol consumption (men: > 60 gm/day; women: > 40 gm/day) are associated with a high clinical risk for health complications [42]. Monitoring the quantity and frequency of consumption has provided accurate scientific evidence on the relationship between morbidity and mortality in the spectrum of alcohol use [43]. In a meta-analysis of 156 studies involving 116,702 subjects, it was shown than increasing the daily dose of alcohol increased the risk of organ damage, and in particular for 15 pathologies [44]. Other studies have documented a linear relationship between breast cancer and excess consumption of alcohol, and the risk progressively increased by 9% for every 10 gm of alcohol over 60 gm/day in women [45]. Concerning the female population, it would appear that gender is a positive predictive factor for the possibility to reduce consumption. In one study, 52 males and 38 females with problems of alcohol dependence were enrolled. Three months after treatment the percentage of subjects with moderate consumption was significantly higher in females than in males (75% *vs*. 35%, respectively). At one year, women had achieved more success than men in going from excessive to controlled consumption [46].

Excessive consumption is an individual phenomenon, but is often interpreted as a condition that is influenced by cultural aspects on a community level. Extensive research has shown that where there are conditions that permit excessive consumption of alcohol, there is a linear correlation with traffic accidents, violent acts and hospitalization [47].

Other studies have evaluated the therapeutic opportunity of reduction versus abstinence [18 17], and many investigations have compared abstinent and non-abstinent patients. Subjects had to control and monitor a variety of clinical conditions including: instructions for self-monitoring of blood alcohol concentration (BAC), counselling, education about alcohol-related problems, adverse conditions such as electric shock to the fingers and watching video registrations of oneself. The results of these studies have allowed for the consideration that reducing consumption of alcohol is a valid therapeutic option. Other meta-analyses have identified the clinical characteristics of patients eligible for treatment aimed at reducing alcohol consumption. These include female gender, age between 20-30 years, good psychopathological condition, social and job stability, and good cognitive preservation [7 25].

Many investigators have identified and monitored several indicators such as the period of time in going from moderate to excessive drinking, and the number of daily episodes of excessive drinking [48]. Other studies have added new variables, such as the number of days of consumption and the percentage of days of excessive consumption to achieving complete abstinence. For example, the MATCH project [49] used the combination of the percentage of abstinent days and excessive consumption compared to moderate consumption. The COMBINE [50] study utilized the combination of the percentage of abstinent days and the time between the first episode of excessive consumption of alcohol.

Such a heterogeneity of outcome measures represents the diverse forms of alcoholism and allows for reflection on the limitations of categorical approaches based only on the achievement of abstinence. A reduction in the consumption of alcohol produces new neuroadaptations in gratification circuits that maintain dependence. Phenomena of synaptic plasticity and improvement in the connectivity between neurons in the prefrontal cortex, nucleus accumbens, hippocampus and amygdala favour neurocognitive recovery of executive control. These phenomena have an impact on overall mental functioning with reordering of behaviour, attenuation of psychopathological elements induced by alcohol and greater adherence to therapy. Controlled/moderate drinking can be viewed as a final therapeutic objective, but also as a therapeutic passage towards complete abstinence.

Therapeutic prospects

With reduction of consumption versus abstinence in mind, it is worthwhile considering the available pharmacological and psychotherapeutic therapies. The former target modulation of the 'craving' dimension and reduction of the awaited gratification (positive reinforcement). Craving is a psychopathological condition characterized by irresistible desire to assume a substance. An unsatisfied desire can lead to physical and psychological suffering. Craving is defined as a status of the nervous system consequent to an adaptation to alcohol which alters the normal will of the individual that forces consumption of alcohol in spite of the knowledge of the damage it is causing [51]. From a neurobiological point of view, the craving dimension is sustained by alteration in the GABAergic/glutamatergic, dopaminergic, serotoninergic and opioidergic systems. The psychobiological model developed by Verheul [52] has three main types of craving that have different diagnostic and therapeutic approaches. The typology of the characteristics related to craving for alcohol allows individuation of the different subtypes of alcoholics. Craving reveals the neurobiological adaptation of the gratification circuits induced by alcohol. Several authors have suggested specific pharmacological therapy for the three subtypes of craving defined by the psychobiological model. In particular, they suggested naltrexone and sodium oxybate for reward craving; acamprosate, baclofen and sodium oxybate for relief craving; and an SSRI, baclofen, topiramate and ondansetron for obsessive craving [53].

Modulation of craving is needed to attenuate the abstinent symptomology induced by a reduction in consumption, to stabilize a new, more functional neurobiological structure towards controlled use of a substance and favour adherence. During the course of reduction of consumption, modulation of craving is a fundamental strategy. The pharmacological aspect is important, but correct information on how to recognize, confront and deal with craving is also needed.

Another means to favour reduction in alcohol consumption is to reduce the awaited gratification (positive reinforcement). The acute use of alcohol stimulates the release of beta-endorphins, encephalin and dynorphin [54]. The beta-endorphins and encephalin bind to endogenous opioid receptors mu (MOR) and delta (DOR) which mediate, respectively, the euphoric effects and positive reinforcement of alcohol [55]. Dynorphin, on the other hand, binds to opioid receptor kappa (KOR) and mediates the aversive effects related to the consumption of alcohol [56]. The KOR/dynorphin system is diffusely distributed throughout the central nervous system, and is implicated in several physiological and pathophysiological conditions related to behaviour and motivation [57]. This condition identifies the KOR/dynorphin system as a therapeutic target for neuropsychiatric disturbances [58]. In alcohol dependence, the KOR/dynorphin system is hyperactivated, and is responsible for the dysphoric/anhedonic symptomology. This phenomena contributes to the effects of negative reinforcement induced by alcohol [59]. In fact, in chronic alcohol dependence the response of opioid receptor mu is attenuated, while the response of the kappa receptors is increased [60]. This neuroplasticity induced by alcohol on the KOR/dynorphin system and how this neuroadaptivity can contribute to the pathophysiology of alcohol dependence is significant, and represents a potential therapeutic target for the cure of alcoholism.

A neuromodulator of the opioid system, namely nalmefene, has been investigated in a multicentre, randomized, placebo-controlled study, using nalmefene-as-needed [61]. Nalmefene is a modulator of the opioid system with antagonist activity on opioid receptors mu and delta, and partial agonist activity on opioid receptor kappa [62]. The mechanism of action proposed for nalmefene is to reduce the reinforcing affects of alcohol, and it can be used in patients who have decided to reduce the consumption of alcohol. The study showed a clinical benefit for nalmefene-as-needed in patients with alcohol dependence. Nalmefene was superior to placebo in reducing excessive consumption of alcohol (measured with heavy drinking/days) and total alcohol consumption at month 6. A significant reduction of the number of heavy drinking/days and total consumption of alcohol was observed from the first month, which was maintained throughout the duration of the study. Overall, the total consumption of alcohol at month 6 in the nalmefene group was reduced by 60% compared to 47% in the placebo group. The difference between nalmefene and placebo of about two heavy drinking days/month and 11 gm alcohol/day was clinically significant. Moreover, the benefits of reduction in alcohol consumption during treatment with

nalmefene were also seen in improvement in the CGI score (Clinical Global Impression), and a significant difference in indices of hepatic function (GGT and ALAT) compared to placebo. The use of nalmefene-as-needed constitutes a new pharmacological treatment both in terms of efficacy and personalization of therapy. It can be considered acceptable for patients that desire to reduce excessive consumption, but not complete abstinence.

Concerning psychotherapeutic treatment, it should be noted that monitoring the consumption of alcoholic beverages during prevention of recurrences allows the patient to use strategies and resources to affront the condition. The individual must be accompanied by comprehension of the mechanisms that lead to recurrence, and in particular to the recognition of high-risk situations [63].

A craving diary can be very useful, in which the patient is asked to note the level of desire for alcohol keeping in mind several factors: the moment in which the experience presents itself, when it goes away and the strategies used to deal with it.

The patient can be helped to confront craving using strategies that allow them to think of something else, in such a way that time passes, and the craving thereby decreases. Moreover, it is fundamental that the experience is shared with another person, accepting it and reflecting on the fact that it will have a resolution. For the patient, it is important to focus on the corporeality and describe the parts of the body in which the tension is felt. Several recent studies have shown the efficacy of meditation (mindfulness) as an anti-craving strategy and to prevent recurrence [63].

A third-generation cognitive-behavioural approach is the metacognitive therapy proposed by Wells [64]. The metacognitive model of pathological dependence (theory of intrusion elaborated by desire) [65] explains the maintenance of the disturbance on the basis of the following process: exposition to conditioned subthreshold stimuli associated with alcohol fuels the presence of intrusive thoughts and memories associated with alcohol abuse. These latter can be elaborated voluntarily. Such a voluntary process is oriented to prefigure images, information and memories relative to the experience of alcohol consumption is defined as a wishful thought. In the short term, the wishful thought helps to manage negative mental states, shifting attention and thoughts far away from this, and focusing on positive emotions and sensations connected with alcohol consumption. In the medium to long term, the wishful thought produces an escalation of craving if the desired object continues to be imagined but not obtained, and increases the possibility of increasing consumption.

Research [66] has shown that the wishful thought seems to have a role in the transition from excessive consumption to abuse, and may also be related to maintenance of the degree of severity of alcoholism. According to the metacognitive model, patients can benefit from learning how to recognize the activation of wishful thinking, how to control it and shift one's attention elsewhere. However, this approach appears to be indicated only for problematic drinkers, or for those with moderate alcohol abuse.

Conclusions

Disturbances correlated with the use of alcohol should be considered as a social and health emergency. Nonetheless, the available scientific evidence does not provide precise and identifiable limits over which ethanol-related damage occurs, although it is clear that there is a linear correlation between systematic exposition to alcohol and morbidity and mortality. In this regard, campaigns aimed at primary prevention should avoid using the term 'moderate alcohol consumption'. The concept of reduction versus abstinence has become useful in terms of clinical, social and economic considerations. The possibility of reducing risk and limit organ damage, the opportunity to involve the patient in a therapeutic course of modular treatment aimed at abstinence, the possibility of prevention to avoid evolution into more severe forms of alcoholism and the need to reduce the social and economic impact of alcohol are important goals that can be reached in view of all the therapeutic strategies taken into consideration. Reduction in alcohol consumption can be a valid intermediate objective from social and therapeutic standpoints, and is even acceptable for patients who are not able or who are poorly motivated towards abstinence in order to reduce the clinical risks related to consumption of high levels of alcohol. New pharmacological strategies can be helpful in achieving such a therapeutic objective. In particular, nalmefene, a modulator of the opioid system with antagonist activity on opioid mu and delta receptors and partial agonist activity on opioid kappa receptors, appears to be efficacious in reducing alcohol consumption.

Conflict of interest

Dr. Giuseppe Fertonani Affini received a "grant" to search for the article published. The amount received will be allocated for a scholarship aimed at research into alcohol-related problems.

Bibliografia

1 Grant BF, Harford TC, Dawson DA, et al. *Prevalence of DSM-IV alcohol abuse an dependence: United States, 1992*. Alcohol Health Res World 1994;18:243-8.

2 Grant BF, Dawson DA, Stinson FS, et al. *The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002*. Drug Alcohol Depend 2004;74:223-34.

3 Murray CJL, Lopez AD. *The global burden of disease*. World Health Organization. Cambridge, MA: Harvard University Press 1996.

4 Ministero della Salute. http://www.salute.gov.it/dettaglio/pdPrimoPiano.jsp?id=227&sub=2&lang=it

5 Ministero della Salute. *Relazione del Ministro della Salute al parlamento sugli interventi realizzati ai sensi della legge 30.03.2001 n° 125: "Legge quadro in materia di alcol e problemi alcol-correlati"*. Sanità Pubblica e Innovazioni Direzione Generale della Prevenzione. Ufficio VII, Roma 2012.

6 Cahalan D, Cisin IH. *American drinking practices: summary of findings from a national probability sample: II. Measurement of massed versus spaced drinking*. Q J Stud Alcohol 1968;29:642-56.

7 Ambrogne JA. *Reduced-risk drinking as a treatment goal: what clinicians need to know*. J Subst Abuse Treat 2002;22:45-53.

8 Tucker JA. *Changing addictive behavior: historical and contemporary perspectives*. In: Tucker JA, Donovan DM, Marlatt GA, editors. *Changing addictive behavior: bridging clinical and public health strategies*. New York: Guilford 1999, pp. 3-44.

9 El-Guebaly N. *Are attempts at moderate drinking by patient with alcohol dependency a form of russian roulette?* Can J Psychiatry 2005;50:266-68.

10 Brochu S. *Abstinence versus non-abstinence: the objectives of alcoholism rehabilitation programs in Quebec*. J Psychoactive Drugs 1990;22:15-21.

11 Dawe S, Richmond R. *Controlled drinking as a treatment goal in Australian alcohol treatment agencies*. J Subst Abuse Treat 1997;14:81-6.

12 Rosenberg H, Devine EG, Rothrock N. *Acceptance of moderate drinking by alcoholism treatment services in Canada*. J Stud Alcohol 1996;57:559-62.

13 Saitz R. *Unhealthy alcohol use*. N Engl J Med 2005;352:596-607.

14 Sobell MB, Sobell LC. *Controlled drinking after 25 years: how important was the debate?* Addiction 1995;90:49-52.

15 Hodgins D. *Can patient with alcohol use disorders return to social drinking? Yes, so what should we do about it?* Can J Psychiatry 2005;50:264-5.

16 Connors GJ. *Drinking moderation training as a contemporary therapeutic approach*. Drugs and Society 1993;8:117-34.

17 Armor DJ, Polich JM, Stambul HB. *Alcholism and treatment*. Prepared for the United States National Institute on Alcohol Abuse and Alcoholism. Santa Monica, CA: Rand 1976.

18 Davies DL. *Normal drinking in recovered alcoholics*. Q J Stud Alcohol 1962;23:94-104.

19 Miller WR. *Controlled drinking: a history and critical review*. J Stud Alcohol 1983;44:68-81.

20 Sanchez-Craig M, Annis HM, Bornet AR, et al. *Random assignment to abstinence and controlled drinking evaluation of a cognitive-behavioral program for problem drinkers*. J Consult Clin Psychol 1984;52:390-403.

21 Miller WR, Zweben A, DiClemente CC, et al. *Motivational enhancement therapy manual: A clinical research guide for therapists treating individuals with alcohol abuse and dependence*. Project MATCH monograph series, vol. 2. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism 1994.

22 Humphreys K, Tucker JA. *Toward a more responsive and effective intervention systems for alcohol-related problems*. Addiction 2002;97:126-32.

23 Humphreys K. *A research-based analysis of the Moderation Management controversy*. Psychiatr Serv 2003;54:621-2.

24 Rosemberg H, Davis LA. *Acceptance of moderate drinking by alcohol treatment services in the United States*. J Stud Alcohol 1994;55:167-72.

25 Rosenberg H. *Prediction of controlled drinking by alcoholics and problem drinkers*. Psychol Bull 1993;113:129-39.

26 Miller WR, Leckman L, Delaney HD, et al. *Longterm follow-up of behavioral self-control training*. J Stud Alcohol 1992;53:249-61.

27 Miller WR, Caddy GR. *Abstinence and controlled drinking in the treatment of problem drinkers*. J Stud Alcohol 1977;38:986–1003.

28 Hodgins DC, Leigh G, Milne R, et al. *Drinking goal selection in behavioral self-management treatment of chronic alcoholics*. Addict Behav 1997;22:247-55.

29 Adamson SJ, Sellman JD. *Drinking goal selection and treatment outcome in out-patients with mild-moderate alcohol dependence*. Drug Alcohol Rev 2001;20:351-9.

30 Miller WR, Page AC. *Warm turkey: other routes to abstinence*. J Subst Abuse Treat 1991;8:227-32.

31 Adamson SJ. *Initial preference for drinking goal in the treatment of alcohol problems: II. Treatment outcomes*. Alcohol Alcohol 2010;45:136-42.

32 Heather N, Tebbutt J. *Definitions of non-abstinent and abstinent categories in alcoholism treatment outcome classifications. A review and proposal*. Drug Alcohol Depend 1989;24:83-93.

33 U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Nutrition and your health: guidelines for Americans. (Home and Garden Bulletin No. 232)*. Washington, DC, 1990.

34 U.S. Department of Health and Human Services. *Tenth special report to the U.S. Congress on alcohol and health, June 2000 (DHHS Publication No. 00–1583)*. Rockville, MD, 2000.

35 Sanchez-Craig M, Wilkinson A, Davilla R. *Empirically based guidelines for moderate drinking: 1-year results from three studies*. Am J Public Health 1995;85:823-8.

36 Anton RF, Moak DH, Waid LR, et al. *Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: result of a placebo-controlled trial*. Am J Psychiatry 1999;156:1758-64.

37 Kranzler HR, Modesto-Lowe V, Van KJ. *Naltrexone versus nefazodone for treatment of alcohol dependence: a placedo-controlled trial*. Neuropsychopharmacology 2000;22:493-503.

38 National Institute on Alcohol Abuse and Alcoholism. *The physician's guide to helping patients with alcohol problems*. Publication No. 95-3769. Rockville, MD: National Institutes of Health 1995.

39 O'Malley SS, Jaffe AJ, Chang G, et al. *Naltrexone and coping skills therapy for alcohol dependence: a controlled study*. Arch Gen Psychiatry 1992;49:881-7.

40 Volpicelli JR, Alterman AI, Hayashida M, et al. *Naltrexone in the treatment of alcohol dependance*. Arch Gen Psychiatry 1992;49:876-80.

41 Cherpitel CJ, Tam T, Midanik L, et al. *Alcohol and nonfatal injury in the U.S. general population: a risk function analysis*. Accid Anal Prev 1995;27:651-61.

42 Midanik LT, Tam T, Greenfield TK, et al. *Risk functions for alcohol-related problems in a 1988 U.S. National sample*. Addiction 1996;81:1427-37.

43 Greenfield TK, Kerr WC. *Tracking alcohol consumption over time*. Alcohol Res Health 2003;27:30-8.

44 Corrao G, Bagnardi V, Zambon A, et al. *A meta-analysis of alcohol consumption and the risk of 15 diseases*. Prev Med 2004;38:613-9.

45 Smith-Warner SA, Spiegelman D, Yaun S, et al. *Alcohol and breast cancer in women. A pooled analysis of cohort studies*. JAMA 1998;279:535-40.

46 Sanchez-Craig M, Leigh G, Spivak K, et al. *Superior outcome of females over males after brief treatment for the reduction of heavy drinking*. J Stud Alcohol 1994;55:167-72.

47 Hingson R, Winter M. *Epidemiology and consequences of drinking and driving*. Alcohol Res Health 2003;27:63-78.

48 Finney JW, Moyer A, Swearingen CE. *Outcome variables and their assessment in alcohol treatment studies: 1968-1998*. Alcohol Clin Exp Res 2003;27:1671-79.

49 Project MATCH Research Group. *Matching alcoholism treatments to patient heterogeneity: project MATCH post-treatment drinking outcomes*. J Stud Alcohol 1997;58:7-29.

50 COMBINE Study Research Group. *Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: rationale and methods*. Alcohol Clin Exp Res 2003;27:1107-22.

51 Anton RF. *Pharmacological approaches to the management of alcoholism*. J Clin Psychiatry 2001;62(Suppl 20):11-7.

52 Verheul R, Van der Brink W, Geerlings P. *A three-pathway psychobiological model of craving for alcohol*. Alcohol 1999;34:197-222.

53 Addolorato G, Abenavoli L, Leggio L, et al. *How many cravings? Pharmacological aspects of craving treatment in alcohol addiction: a review*. Neuropsychobiology 2005;51:59-66.

54 Gianoulakis C, Krishnan B, Thavundayil J. *Enhanced sensitivity of pituitary beta-endorphin to ethanol in subjects at high risk of alcoholism*. Arch Gen Psychiatry 1996;53:250-7.

55 Stromberg MF, Casale M, Volpicelli L, et al. *A comparison of the effects of the opioid antagonists naltrexone, naltrindole and betafunaltrexamine on ethanol consumption in the rat*. Alcohol 1998;15:281-9.

55 Lindholm S, Weme M, Brene S, et al. *The selective kappa-opioid receptor agonist U50, 488H attenuates voluntary ethanol intake in the rat*. Behav Brain Res 2001;120:137-46.

56 Tejeda HA, Shippenberg TS, Hentiksson R. *The dynorphin/kappa-opioid receptor system and its role in psychiatric disorders*. Cell Mol Life Sci 2012;69:857-96.

57 Walker BM, Koob GF. *Pharmacological evidence for a motivational role of kappa-opioid system in ethanol dependence*. Neuropsychopharmacology 2008;33:643-52.

58 Walker BM, Zorilla EP, Koob GF. *Systemic kappa-opioid receptor antagonism by nor-binaltorphimine reduces dependence-induced excessive alcohol self-administration in rats*. Addic Biol 2011;16:116-9.

59 Walker BM, Valdez GR, McLaughlin JP, et al. *Targeting dynorphin/kappa opioid receptor system to treat alcohol abuse and dependence*. Alcohol 2012;46:359-70.

60 Mann K, Bladstrom A, Torup L, et al. *Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene*. Biol Psychiatry 2013;73:706-13.

61 Bart G, Schluger JH, Borg L, et al. *Nalmefene induced elevation in serum prolactin in normal human volunteers: partial kappa opioid agonist activity?* Neuropsychopharmacology 2005;30:2254-62.

62 Cibin M, Hinnenthal I. *Trattamento integrato dell'alcolismo: gli strumenti e i luoghi dell'intervento*. Nòoc 2012;3:189-211.

63 Tomas M. *La mindfulness e la prevenzione della ricaduta nel trattamento dei disturbi da uso di sostanze*. In: Hinnentahal I, Cibin M, editors. *Il trattamento residenziale breve delle dipendenze da alcol e cocaina: il modello Soranzo*. Torino: SEED 2011.

64 Wells A. *Metacognitive therapy for anxiety and depression*. New York: Guilford Press 2009.

65 Kavanagh DJ, May J, Andrade J. *Tests of the elaborated intrusion theory of craving and desire: features of alcohol craving during treatment for an alcohol disorder*. Br J Clin Psychology 2009;48:241-54.

66 Nigro N, Caselli G, Spada MM. *Pensiero desiderante e dipendenze patologiche*. XVI Congresso Società Italiana Terapia Comportamentale e Cognitiva, Roma 2012.