

Meeting report

Complementary therapies for treating alcoholism
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The Congress was opened with the Session presented by G. Bardazzi and L. Abenavoli.

Alcohol abuse and dependence hold an important role in the public health due to both the medical consequences and economical costs. In Italy, it is estimated that there are approximately one million of alcohol-dependent subjects and that in the year 2000 almost one hundred thousand patients were discharged from the hospital with a clinical diagnosis completely attributable to alcohol [1]. These data correspond to an overall rate of 172.2/100,000 persons [2]. Alcohol abuse and the related consequences alcohol-attributable mortality, productivity loss, absenteeism, hospitalization have important implications in the social costs. Alcohol abuse is estimated to be responsible of around 5–6% of the Italian Gross Domestic Product (GDP) [2]. The pharmacological treatment of patients with alcohol dependence play a key role to achieve alcohol abstinence and prevent relapse, especially if it is conceived together with the psychosocial interventions already used for many years. Within pharmacological approaches, some recent small preliminary data suggest the possible utility of the Complementary Medicines (CMs) in the treatment of alcohol dependence. CM is defined as “*diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine*” [3].

In spite of the utility of the CM it is described in different diseases, the data concerning its possible use in alcohol-dependent patients are controversial [4–7] and do not permit to draft a final conclusion.

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Acupuncture represents the most common investigated CM [8]. Phytotherapeutic compounds have been investigated mostly in pre-clinical studies [9,10]. On the contrary, few data are available on the possible role of the homoeopathy in alcohol dependence [11].

For example, a recent study [12] highlighted that only 16.50% of Italian Alcohol and Drug Addiction Services use CMs for alcohol dependence treatment and that acupuncture is the most common among CMs. Moreover, CMs are conceived as an instrument included into more standardized treatments for alcohol dependence (drug treatment, psychotherapies, self-help groups) and not as an alternative approach.

This possible approach in the use of the CMs in alcohol dependence seems of interest. In fact, growing evidence suggests that it is not conceivable as a standardized therapy for every patient but different subtypes of alcohol-dependent patients could benefit from different specific treatments [13,14]. Accordingly, CM could represent a possible further instrument in order to try to better personalise the treatment of alcohol dependence.

In the first session of the Congress the phytotherapy in alcohol dependence was presented by L. Abenavoli, L. Leggio and G. Addolorato. For several centuries medical plants have been used for the treatment of alcohol dependence, particularly in China. Recent lines of experimental evidence suggest that novel pharmacological approaches for treatment of alcohol dependence could stem from some natural substances [15,16].

The antidepressant properties of the St. John's wort — *Hypericum perforatum* L. (Hypericaceae) are well-known since Hippocrates' time. Recent pre-clinical and clinical studies [15,16] have demonstrated that *H. perforatum* is effective in the treatment of mild to moderately severe depressive disorders. *H. perforatum* contains several biologically active compounds, including naphthodianthrone (hypericin and pseudohypericin), fluoroglucynol derivatives (hyperforin, adhyperforin), several flavonol glycosides, biflavones, phenylpropanes, proanthocyanidins, tannins, xanthenes and some amino acids as the gamma-aminobutyric acid (GABA) [17,18]. Hypericin and hyperforin have been proposed to mediate several of the *H. perforatum* effects. It has been suggested that the antidepressant effects of *H. perforatum* might be mediated by the increase of serotonin, dopamine, norepinephrine or by stimulation of sigma and opioid receptors in the central nervous system [19].

According to the high comorbidity between depressive states and alcohol dependence [14], some studies have investigated *H. perforatum* efficacy in the alcohol-seeking behavior. In particular, recent studies showed the ability of St. John's wort extracts to halve voluntary alcohol intake in different lines of selectively alcohol-preferring rats [15,16,20]. This effect could be due to the block of the reuptake of serotonin and dopamine with the consequent increase of these neurotransmitters in the synaptic cleft. Moreover, it has also been showed that hyperforin inhibits GABA uptake [21] and *H. perforatum* blocks the GABA reuptake [19].

Opioid receptor antagonists, such as naloxone and naltrexone, have shown their efficacy to reduce alcohol intake in both rats and humans [22]. A pre-clinical study evaluated the effect on alcohol intake by the combined administration of *H. perforatum* and opioid receptor antagonists. When naloxone (1 mg/kg) or naltrexone (0.5 mg/kg) were given before different intragastric doses of *H. perforatum*, the attenuation of alcohol intake was more pronounced than that one observed after *H. perforatum* alone [23]. These results suggest a synergistic action of opioid receptor antagonists and *H. perforatum* in reducing alcohol intake in animals. Since the crude extracts have been given only by the intragastric or intraperitoneal route, the best site of action remains to be detected. In summary, it has been hypothesized that *H. perforatum* alone or in association with others drugs might reduce voluntary alcohol intake in alcohol-preferring rats.

The antidrunkenness properties of the extracts of *Pueraria lobata*, also known as kudzu, have been known since the traditional Chinese medicine. An experimental study demonstrated that the daily intraperitoneal administration of a crude extract of *P. lobata*, roots halved alcohol intake in alcohol-preferring Syrian Golden hamsters when a choice between alcohol solution and water was given [24]. In this study, two putative active principles have been identified. Indeed, the administration of the two major isoflavones present in *P. lobata* extracts, daidzin and daidzein, reduced ethanol intake in Syrian Golden hamsters with an efficacy similar to the one observed using the *P. lobata* extract. The ability of *P. lobata* to reduce alcohol consumption in animals has been also showed testing a herbal mixture comprising PL [25]. Interestingly, this mixture is commonly used in China to prepare the so-called 'tea of sobriety'. Finally puerarin represents the most concentrated isoflavonoid in kudzu although it is not as potent as daidzin. The beneficial effects of puerarin on alcohol intake in alcohol-preferring rats and monkeys reported in literature also suggest the potential utility of puerarin as an anticraving agent [15,16].

According to the animal data, a preliminary clinical study explored the effect of kudzu root extract on thirty-eight patients affected by alcohol dependence and randomly assigned to receive either kudzu root extract (1.2 g twice daily)

or placebo [26]. Sobriety level and a visual analogic scale to assess alcohol craving were assessed. Kudzu root appeared to be no better than placebo in reducing alcohol craving and/or promoting sobriety. Unfortunately the authors did not report the concentrations of the active isoflavones in their kudzu extract. More recently Lukas et al. [27] performed a study to test the efficacy of a kudzu extract in a group of “heavy” alcohol drinkers treated with either placebo or a kudzu extract for 7 days. After the 7-day period, subjects had the opportunity to drink their preferred brand of beer in a naturalistic laboratory setting. Kudzu treatment resulted in significant reduction in the number of beers consumed, an increase in the number of sips and the time to consume each beer and a decrease in the volume of each sip. These changes occurred in the absence of a significant effect on the urge to drink alcohol. The authors concluded that kudzu may be a useful adjunct in reducing alcohol intake although the exact mechanism by which kudzu suppresses ethanol intake remains to be clarified.

The dried roots of *S. miltiorrhiza* are used in traditional Chinese medicine for the treatment of several pathologies e.g.: insomnia. Pre-clinical data suggest that extracts from the *S. miltiorrhiza* (tanshinone IIA, cryptotanshinone and miltirone) are effective in reducing voluntary alcohol intake in animal models of excessive alcohol drinking [20]. Specifically, SM extracts have been found to suppress acquisition [28] and maintenance [29, 30] of alcohol drinking behavior in selectively bred Sardinian alcohol-preferring rats given a choice between and alcohol solution and water. Recently Colombo et al. [31] have found that miltirone is the possible active chemical component responsible for the reducing effect of *S. miltiorrhiza* extracts on alcohol intake in Sardinian alcohol-preferring rats. The ability of miltirone to reduce alcohol intake in rats could be explained by the previously reported anxiolytic effect of miltirone [32].

Ibogaine is a major indole alkaloid contained in the *Tabernanthe iboga* root bark a plant of West Central Africa. The stimulating effects of *T. iboga* are well-known for centuries. Ibogaine has been claimed to be effective in treating multiple forms of drug abuse, including morphine, cocaine, heroin and nicotine [15,16]. Moreover, it has been proposed that ibogaine exerts its anticraving effects by stimulating dopaminergic and serotonergic systems [33]. Accordingly, *T. iboga* seems to be able to markedly reduce voluntary alcohol intake in alcohol-preferring rats [20]. This effect was not related to a possible interaction between *T. iboga* and alcohol, as showed by the virtually equal blood alcohol levels in both ibogaine- and placebo-treated rats. It is also of interest that the reducing effect on alcohol intake has been observed only when ibogaine was injected intraperitoneally or intragastrically but not when it was injected subcutaneously. This feature suggests that the active principle of ibogaine could be a metabolite produced by the liver [34]. Accordingly, it has been hypothesized that both ibogaine and its analog may reduce alcohol intake by modulating dopaminergic and serotonergic systems [15,16,20].

Panax ginseng has been used in the traditional Korean medicine for several therapeutic applications, including also alcohol intoxication. Initially, it was proposed that ginseng accelerated alcohol metabolism and lowered blood alcohol levels by increasing ADH activity and plasma clearance [35]. However, a more recent animal study has demonstrated that the administration of red ginseng extract is able to alter alcohol absorption from the gastrointestinal tract [36].

In summary, several plant-derived compounds have been shown to significantly reduce alcohol intake mostly in animal studies [15,16,20]. Although several neurotransmitter systems seem to be involved in their effects on alcohol-seeking behavior, the exact mechanisms of action of these compounds remain to be clarified. Until extensive clinical studies are carried out, it will be difficult to extrapolate the findings on animal models of alcohol dependence to a human cohort. The role of these compounds in the treatment of alcoholism will ultimately depend on the outcome of carefully conducted clinical trials. Nevertheless, the extensive positive findings in animal models suggest that the outcome of clinical trials is likely to be positive as well especially when pharmacological treatment is combined with psychological support counselling.

In the second session of the Congress the acupuncture in alcohol dependence was presented by F. Cracolici, C. Quaranta and L. Polero. Acupuncture has been used in some countries and especially in China for centuries with the aim to treat several diseases. In the last decades, the possible utility of acupuncture in the field of drug addiction has been also investigated [37,38]. Acupuncture is divided in somatic acupuncture and auricular acupuncture. Starting from China, auriculo-therapy was the first most widespread method. Successively, in the Western countries two leading new-born schools focused their attention for the somatic acupuncture in France and for the auriculo-therapy in the United States.

When, a neurosurgeon from Hong Kong, used electro-acupuncture bilaterally upon the auricular region of lungs together with methadone. This protocol was initially used to treat opiate addiction and successively also in the treatment of alcohol, tobacco and benzodiazepine withdrawal symptoms [39,40]. In 1974 the complete point set was established, including also points of the classical acupuncture (HT5, HT7, BL10, GV13, TE14, SI12) [41].

Successively, Michael Smith formulated an auriculo-therapy protocol for the treatment of addiction called Acupuncture Detoxification (Acudetox) and consisting in the bilateral stimulation of five auricular points [42,43]. This protocol constitutes the basis of the research programme referring to the National Acupuncture Detoxification Association (NADA) founded by Smith himself in 1985. Auriculotherapy played the essential role to bring the traditional Chinese medicine closer to the treatment of addictions. Indeed, its simplicity and the absence of side effects suggest its possible utility in alcohol addiction.

With regards to somatic acupuncture, the French school of acupuncture has given the most important contribution. Another important experience has been developed by Roustan in a clinic for alcohol detoxification. He described the energy evaluation observing the typical symptoms and signs of withdrawal and introduced the use of two Shaigu GB-8 and Yuji Lu LU-10 points (according to the sources of Soulié de Morant) as the basis of its treatment [44].

In Italy the most common acupuncture seems to be the auriculo-therapy, a feature related to the activity of the NADA association and the diffusion of the Acudetox protocol in our Country. However, a study carried out on alcoholic patients not responding to traditional therapies (pharmacological therapy, support groups, etc.) proved that somatic acupuncture, associated with conventional treatment, can bring about an improvement in the clinical management and in the patients' quality of life with respect to a group treated only by conventional treatments [45]. The acupuncture treatment pattern included the following points: Qiha CV-6, Tanzhong CV-17, Yuji Lu LU-10, Shaigu GB-8, Xuanzhong GB-39, Qimen LR-14. Sixteen sessions were set, the first 8 every two weeks and the following ones once a week [45].

Experimental data lead to hypothesize that acupuncture could be helpful in acting on several neurotransmitter systems (dopamine, endorphins, serotonin). In particular, manual acupuncture and electro stimulation (both somatic and auricular) could induce a functional increase in the monoaminergic systems and modulate the endogenous release of endorphins and serotonin.

Accordingly, Bullock et al. conducted a study on the effectiveness of acupuncture in alcohol detoxification [46]. This study showed a reduction of craving and alcohol intake in patients who were submitted to acupuncture in the "right" points, in comparison with those who were treated in "false" points [46]. Other following studies have reported contradictory results [47–54]. The different results could be explained by several factors, including the different setting and the low number of patients treated. Moreover, it is debatable which methodology of acupuncture should be used (somatic, auricular or both), the most effective mode of stimulation (manual or electric) and the combination of points to be used.

The main subjective effects reported by patients and that could be attributed to the acupuncture therapy (both somatic and auricular) are reported here in a decreasing order of frequency: relaxation, reduction in stress and anxiety levels, reduction in craving of the substance of abuse, sensation of mind "relieving" and improvement in intentions, excellent control on the changes in mood tone, improvement in sleep quality) and greater energy and wellness.

In conclusion, alcohol dependence represents a complex disease for which acupuncture integrated with conventional therapies could represent a valid support, at least in some patients.

In the third session of the Congress the homeopathy in alcohol dependence was presented by G. Santini and Stefania Graziosi.

Homeopathy is a clinical–therapeutic methodology with possible applications in several acute and chronic pathologies. It is based upon the use of medicines diluted up to the complete disappearance of the substance used (beyond the Avogadro constant) [55]. The latter based his long and careful studies upon the so-called "Law of Similitude or Similarities" [56], according to the Hippocratic aphorism of *similia similibus curantur* ("similar things take care of similar things") and to the "Law of Individualization" [57]. Homeopathy is conceivable for patients as dynamic and functional psychophysical units. The main aim of the homeopathy is to optimize the psychophysical reactive capacities of the patients and to modulate their immune system [58,59]. As regards to alcoholic patients, it could be hypothesized that the use of medications is able to perform a deeper and slower action, to reduce the damage due to the absorbed alcohol and to improve alcohol detoxification. Among the different homeopathic approaches potentially useful in alcoholic patients, the following compounds could be useful in alcoholism: *Nux vomica*, *Lachesis*, *Arsenicum album*, *Sulphuricum acidum*, *Ranunculus bulbosus* (i.e. *Bulbous Buttercup*), *Quercus glandium spiritus* [60,61].

However, at present, no data are available on the possible utility of these compounds in alcohol dependence. Consequently, both animal studies using Preferring model animal and clinical data on alcoholic patients are needed to draft the preliminary conclusions.

Conclusions of the meeting

Growing evidence suggest that different subtypes of alcohol-dependent patients could benefit from different specific treatments [13,14]. Accordingly, Complementary Medicine (CM) could represent an approach able to better personalise the treatment of alcoholic patients. The use of some CMs together with other more standardized therapies could be of interest. In fact the possible improvement of the quality of life already suggested [4] and the possible presence of few side effects could ameliorate the treatment compliance. The low costs and the empathy between the patient and the therapist could represent further interesting features. However many aspects have to be clarified. The lack of definitive randomized and controlled studies demonstrating CMs effectiveness and safety represents the most important limit. In summary they represent a promising approach in the treatment of alcohol dependence. However, a more number of well-designed studies are needed before introducing the CMs in the treatment of alcohol dependence.

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