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Behavioral dysregulations by chronic alcohol abuse. Motivational enhancement therapy and cognitive behavioral therapy outcomes

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Summary. Patients with alcohol use disorder (AUD) do not manifest homogeneous clinical symptoms. Various studies described both cognitive impairments and psychiatric disorders among people with AUD. This disorder is one of the most frequent mental disorders in developed countries, due to excessive alcohol consumption. Alcohol is toxic as it increases the production of reactive oxygen species (ROS) and can cause dependence. This causes negative effects on brain development and cognitive functions that affect the individual's work, health, and social life. Current pharmacology treatment for alcohol addiction is based on direct action against the neurotransmitters involved in alcohol dependence. AUD patients without comorbid psychiatric disorders or severe cognitive deficits are defined as "pure alcoholics". To date, poor is known about effective treatments for this typology of AUD patients. Psychotherapy is largely used in resolving many psychiatric disorders, including substance use disorders. Motivational enhancement therapy (MET) and cognitive-behavioral therapy (CBT) are two psychotherapies used to achieve and maintain abstinence in patients affected by substance use disorders. This short review aims to describe two CBT and MET and to present the advantages and disadvantages of these two psychotherapies in the treatment of AUD.

Key words. Alcohol use disorders, cognitive-behavioral therapy, motivational enhancement therapy, reactive oxygen species.

Disregolazioni comportamentali da abuso cronico di alcol. Terapia di potenziamento motivazionale e risultati della terapia cognitivo comportamentale.

Riassunto. I pazienti con disturbo da uso di alcol (AUD) non manifestano sintomi clinici omogenei. Vari studi hanno descritto sia i disturbi cognitivi che i disturbi psichiatrici tra le persone con AUD. Questo è uno dei disturbi mentali più frequenti nei paesi sviluppati, a causa del consumo eccessivo di alcol. L'alcol è tossico in quanto aumenta la produzione di specie reattive dell'ossigeno (ROS) e può causare dipendenza. Ciò provoca effetti negativi sullo sviluppo del cervello e sulle funzioni cognitive che influenzano il lavoro, la salute e la vita sociale dell'individuo. L'attuale trattamento farmacologico per la dipendenza da alcol si basa sull'azione diretta contro neurotrasmettitori coinvolti nella dipendenza da alcol. I pazienti AUD senza disturbi psichiatrici in comorbilità o deficit cognitivi gravi sono definiti "alcolisti puri". A oggi, si conosce poco sui trattamenti efficaci per questa tipologia di pazienti con AUD. La psicoterapia è ampiamente utilizzata per risolvere molti disturbi psichiatrici, compresi i disturbi da uso di sostanze. La terapia di potenziamento motivazionale (MET) e la terapia cognitivo-comportamentale (CBT) sono due psicoterapie utilizzate per raggiungere e mantenere l'astinenza nei pazienti affetti da disturbi da uso di sostanze. Questa breve rassegna si propone di descrivere due CBT e MET e di presentare i vantaggi e gli svantaggi di queste due psicoterapie nel trattamento dell'AUD.

Parole chiave. Disturbi da uso di alcol, specie reattive dell'ossigeno, terapia cognitivo-comportamentale, terapia di potenziamento motivazionale.

Alcohol use disorders

Alcohol use disorder (AUD) is the most common and untreated mental disorder worldwide, especially in more developed countries. Approximately 2 billion people consume alcohol in the world with 76.3 million who met the criteria for the AUD diagnosis[1]. According to the National Institute on Alcohol Abuse and Alcoholism, AUD is defined as a medical condition characterized by an impaired ability to stop or control alcohol abuse despite its negative effects[2-5]. AUD is a heterogeneous disorder for its medical, behavioral, cognitive, and social implications[6,7]. Chronic alcohol consumption is correlated with different diseases, although positive effects are gained when a moderate quantity of alcohol is used. Moderate alcohol consumption may increase the cardioprotective effect by upregulating the capacity of remo-

ving cholesterol, esterification of cholesterol, and the transfer of cholesteryl ester from high-density lipoprotein to the liver[8-11]. On the contrary, binge and chronic alcohol consumption cause injury, cirrhosis, stroke, cancer, and gastrointestinal diseases[12-15].

Stressors and psychiatric illnesses, such as depression, anxiety, and bipolar disorder, can contribute to the development of AUD, as people believe they can solve their problems by drinking alcohol[16-19]. Indeed, different types of stressful factors like exposure to early life stress, acute stress, chronic stress, and posttraumatic stress disorders are responsible for the development of alcohol dependence[20]. In addition to psychological factors, alcohol addiction is caused by environmental factors, social factors, and biological factors, such as genetic predisposition[21]. Indeed, different studies have identified the presence of genetic variants involved in alcohol metabolism, and the pathogenesis and treatment of AUD[22].

According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), the diagnosis of AUD is done by using interview tests and psychometric tools for collecting signs and symptoms. One of the most used tests in the world is the AUD Identification Test. This test was developed by the World Health Organization as a ten-item questionnaire to identify risky and harmful alcohol consumption, and it helps and helps drinkers to reduce or quit alcohol consumption[23]. Measuring alcohol consumption through laboratory tests is also crucial for monitoring and managing dependence in abusers. Biomarkers of alcohol consumption are divided into direct biomarkers of ethanol metabolism, or indirect biomarkers, i.e., markers of cell and tissue damage induced by ethanol[24]. Among direct biomarkers, we find ethyl glucuronide (EtG): a metabolite of ethanol detectable in blood, urine, and hair[25]. In the urine, EtG is used as a marker of acute intoxication as it remains detectable in the urine for 2/3 days. Instead, in the hair, EtG is used as a marker of chronic consumption as it remains detectable for months[26]. Amongst indirect biomarkers, we find the carbohydrate-deficient transferrin (CDT): a robust marker of chronic alcohol consumption in men and non-pregnant women[24]. Unfortunately, it is not appropriate for pregnant women for the possible false positives due to the week of pregnancy.

Oxidative stress

Oxidative stress is the result of an imbalance between the production of reactive oxygen species and the ability to promptly eliminate reactive species and repair the resulting damage[27]. The loss of these defense mechanisms increases the production of reactive oxygen species (ROS) which damage cellular structures, such as proteins, lipids, and DNA[28]. Oxidative stress can cause severe DNA mutations up to the rupture of both strands[29]. Oxidative stress is involved in various acute and chronic disruptions, such as cardiovascular diseases, acute and chronic kidney diseases, neurodegenerative diseases, biliary diseases, liver diseases, and cancer[30,31].

Alcohol is toxic as ethanol metabolism is directly involved in the production of ROS[32]. ROS are highly reactive oxygen-containing molecules that can react and damage complex cellular molecules. Furthermore, alcohol can alter the levels of some metals in the body, thus inducing the production of ROS. Finally, alcohol lowers the levels of antioxidants such as superoxide dismutase which can eliminate ROS[33]. In recent years it has been shown that resveratrol, a non-flavonoid phenol, and hydroxytyrosol may reduce the formation of oxygen radical species in the serum caused by chronic alcohol consumption[34-39].

Effect alcohol on the human organism

The effects of alcohol on the human organism are heterogeneous, varying with the type of beverage, dose, sex, and age[40]. Women are found to be more susceptible to the effects of alcohol than men when considering the same amount ingested. Genetics also plays a crucial role as ethanol metabolism, reward neurological circuits, and therapeutic outcomes depend on specific inherited genetic variations[41]. Alcohol abuse is associated with numerous diseases. In particular, alcohol intoxication is correlated with cardiovascular diseases, liver diseases, cancer, and neurodegenerative diseases[14,15].

In the last decades, numerous studies highlighted a strong relationship between alcohol abuse and cardiovascular diseases such as coronary heart diseases, stroke, hypertension, and peripheral arterial diseases. Acute alcohol intoxication and chronic consumption increases both systolic blood pressure and diastolic blood pressure and is associated with a higher risk of developing hypertension. In the study by Zhang and colleagues, results show how alcohol consumption from 0 to 20 g/day was associated with a reduced risk of stroke. Instead, alcohol consumption greater than 30 g/day was associated with a higher risk of stroke. Regarding coronary heart disease, a strong association was found between alcohol consumption and reduced risk of developing coronary heart disease in various countries of the world except in South Asian ethnicity. In 2016, the World Health Organization (WHO) found that 19% of all alcohol-attributable deaths in 2016 were from cardiovascular diseases[42].

Excessive use of alcohol also promotes neurodegenerative diseases. Peng et al. highlighted a correlation between excessive alcohol consumption and the development of Alzheimer's disease and Parkinson's

disease, but this link has not been confirmed in the onset of amyotrophic lateral sclerosis[43]. Furthermore, in Alzheimer's disease patients a reduced cognitive decline was observed when the patient stopped drinking alcohol[44].

Alcohol is the second main cause of chronic liver diseases and is one of the main triggers for the development and progression of liver cirrhosis. Chronic alcohol exposure induces a low expression of the cytokine interferon-γ which is an inhibitor of hepatic fibrosis[45]. Moreover, ROS can trigger the production of profibrotic cytokines and collagen in liver cells[33]. In a study conducted in the north of Italy, 13.5% of the sample developed alcoholic liver diseases after the exposition to high alcohol intake[46]. In addition, alcohol plays a synergy role with other risk factors of liver damage like hepatitis virus B or C, human immunodeficiency, and nonalcoholic fatty liver diseases[47].

Cancer represents one of the leading causes of mortality in the world. In 2020, nearly 4% of cancers worldwide are caused by alcohol abuse[48]. Chronic alcohol abuse increases the risk of several types of cancer, including upper aerodigestive tract cancers, liver, colorectal, and breast. The mechanism that associates alcohol consumption with carcinogenesis is due to the production of acetaldehyde, a carcinogenic molecule, increased ROS production, increased inflammation, and reduced immune function[45].

Drinking alcohol during pregnancy can also alter fetal development causing negative fetal events known as Fetal Alcohol Spectrum Disorders (FASD)[49-52]. FASD collects different conditions appearing in children, including microcephaly, dimorphism, psychomotor retardation, behavioral disorders, attention and concentration problems as shown in human and animal models[6,53,54]. Actually, due to the nonexistence of a safe threshold of alcohol consumption, the only possible solution recommended by medical authorities is to avoid any form of alcohol drinking during pregnancy and lactation[55-57].

Cognitive damage induced by alcohol abuse

Alcohol abuse has negative psychiatric and psychological consequences also throughout the disruptions of neurotrophins, polypeptides known to regulate the growth, survival and development of nerve cells[58-62]. Prolonged and excessive use of alcohol is a risk factor for the development of schizophrenia, dementia, bipolar disorder, depression, insomnia, and other disorders[63]. Bolton et al. found in their study that 24.1% of people with mood disorders used alcohol and drugs[64]. Stressful events during childhood and other chronic stressors have a great effect on health leading to the development of mental disorders (figure 1). Alcohol consumption reduces stress, but at the same time its prolonged use alters the activity of the hypothalamus-pituitary-adrenal cortex causing neuroadaptive changes[20,65]. Sometimes even abstinence can lead to anxiety and dysphoria which stimulate a high use of substances[19].

Schizophrenia is a cognitive disorder whose symptoms are hallucinations, disorganized speech, trouble with thinking, and lack of motivation[66]. The correlation between AUD and schizophrenia appears to be established[67]. In one study it was found that 18.9% of those with a diagnosis of substance-induced psychosis had alcohol as their most-used substance[68].

Dementia is a neurodegenerative disease characterized by a progressive deterioration of cognitive abilities over time[63]. Chronic alcohol abuse has been shown to cause dementia and cognitive decline. This disorder is defined as alcohol-related dementia[69]. It was highlighted that people defined as heavy drinkers have a higher risk of developing dementia than abstains and light-moderate drinkers[70]. On the contrary, Solfrizzi et al. we're not able to show a relationship between the quantity of alcohol consumed and the incidence of cognitive impairment[71].

Bipolar disorder is a mental illness that causes an uncommon shift in mood, activity levels, energy, and concentration[72]. Previous works have shown a correlation between bipolar disorder and substance use disorders, particularly for AUD[73]. The bipolar condition is often worsened by the use of substances such as alcohol and drugs[74].

Insomnia is related to alcohol dependence as the percentage of insomniacs who also use alcohol increases with increasing exposure to alcohol[75]. Previous studies have shown that patients who suffered from insomnia, intermittent sleep, and difficulty falling asleep, are exposed to a higher risk of developing alcohol dependence[76].

Many studies have also shown that people with anxiety disorders are more predisposed to abuse alcohol[77]. It has also been seen that withdrawal is associated with various anxiety symptoms including panic attacks[78].

Treatment of alcoholism

Alcohol addiction involves several neurotransmitters and their respective receptors in the brain, including dopamine, serotonin, opioid peptides, glutamate, and GABA[79]. Current drug treatment for alcohol addiction targets mainly the neurotransmitter systems[80]. One of the most common methods is based on the administration of benzodiazepine or diazepam[81]. In addition, disulfiram, acamprosate, and naltrexone, all approved by the FDA, can also be used to prevent further alcohol consumption[82]. These drugs are administered either during hospitalization in a health care

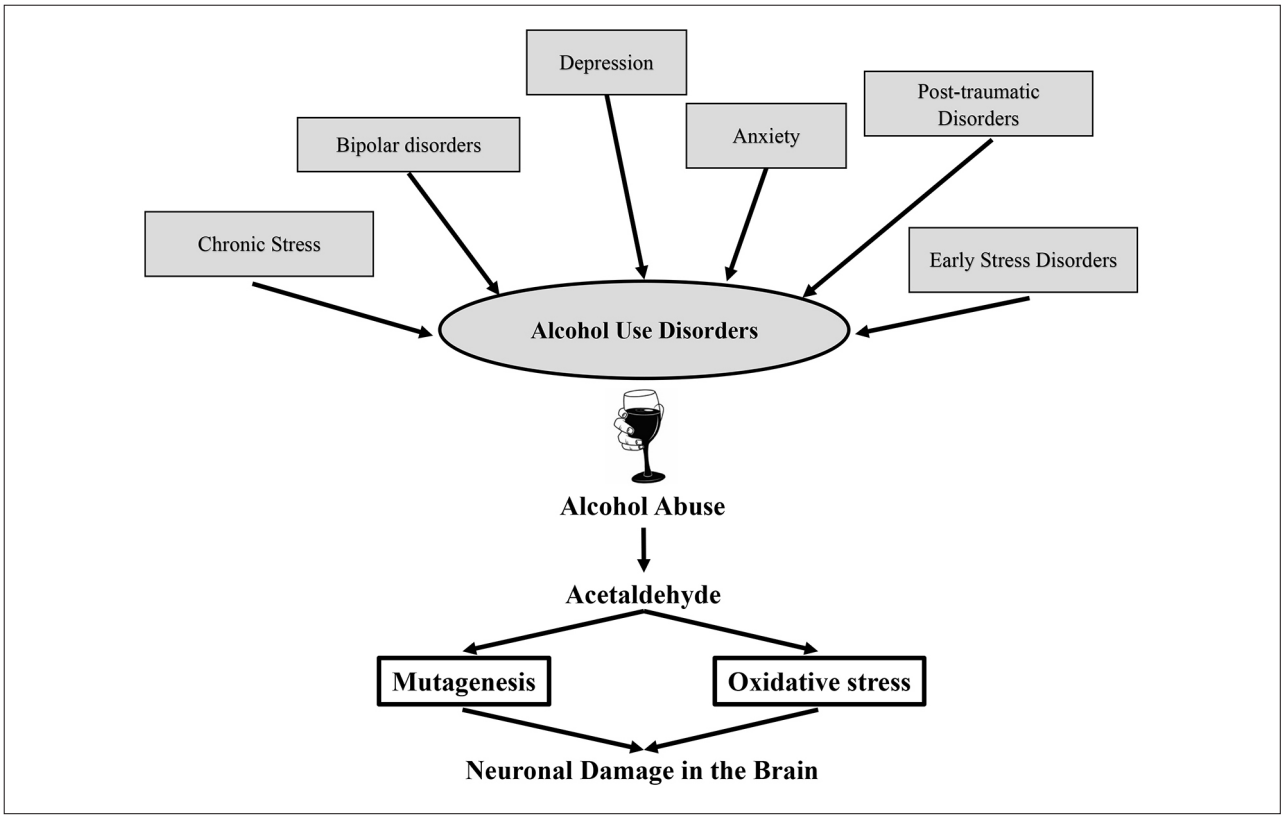

Figure 1. Stressful stimuli and mental disorders can increase alcohol consumption. A close correlation exists between alcohol abuse and mental disorders such as bipolar disorders, depression, post-traumatic disorders, and anxiety. Furthermore, early and chronic stressful stimuli can cause the onset and chronicity of alcohol consumption. This is due to the positive and relaxing but short-lived effects of alcohol consumption. When alcohol consumption becomes uncontrolled and its negative and toxic effects prevail, a pathological condition called alcohol use disorder may develop. This is a medical and heterogeneous disorder characterized for its pathological, behavioral, cognitive, and social implications. Alcohol is toxic as its metabolic products cause cell damage. Their main harmful metabolites are Acetaldehyde and Reactive oxygen species (ROS). Acetaldehyde is carcinogenic in humans and can directly damage DNA. ROS are highly reactive molecules that can react and damage complex cellular molecules. Together, acetaldehyde and ROS cause damage and neuronal death leading to cognitive impairment.

institution or sometimes to people who remain in the community under close observation. Disulfiram is an aldehyde dehydrogenase inhibitor. It causes an increase in the acetaldehyde in the circulation and causes hangover symptoms. When patients taking disulfiram start drinking, they will experience unpleasant hangover symptoms. Acamprosate acts on GABA and the glutamate system by reducing the intensity of alcohol withdrawal, thus reducing the risk of relapse[83]. Naltrexone is an opioid antagonist, used for the treatment of alcohol and opioid dependence. The μ opioid receptor and endorphin induce a feeling of euphoria among individuals with AUD and different studies support that blocking the sensation of euphoria may reduce the risk of relapse and excessive alcohol consumption[83].

Psychotherapy in the treatment of alcoholism

Psychotherapy was defined by Brent et al. as «a modality of treatment in which the therapist and patient(s) work together to ameliorate psychopathologic conditions and functional impairment through a focus on the therapeutic relationship, the patient's attitudes, thoughts, affect, and behavior; and social context and development»[84]. In recent years, many studies have shown that this psychological approach to therapy was highly effective in resolving many psychiatric conditions, including substance use disorders[85,86]. The implementation of psychotherapy must follow international guidelines and its aim is always to reduce symptoms, prevent relapses, improve cognitive, social, and emotional functioning, improve the quality of life and self-awareness[87].

AUD is mainly dealt with through psychological interventions. In a study, the importance of psychotherapy is emphasized for adolescents suffering from alcohol abuse disorders[88]. According to some testimonies from members of anonymous alcoholics, the Hamburg review states that the purpose of psychotherapy must be lifelong abstinence to avoid loss of control caused by small doses of alcohol. It was seen that twelve-step

facilitation therapy (TSF), motivational enhancement therapy (MET), and cognitive-behavioral therapy (CBT) are the psychotherapies most used to achieve and maintain abstinence[89]. TSF is based on a program that facilitates the active involvement of alcoholics and emphasizes in patients twelve spiritual principles. Among them, the first five are based on acceptance, surrender, and moral inventories[90].

MET is a therapy that leads the patient through a motivational interview, of a directive and non-authoritarian nature, to behavioral change[91]. CBT aims to identify, in about 12 sessions, those situations of "high risk" for patients, that is, those conditions that increase the use of alcohol, making the subjects more responsible and with greater self-control. Despite the efficacy demonstrated in recent years of these treatments, there is great individual variability in the response. For example, a motivational interview is appropriate for a moderate AUD, while more protracted intervention will be required for an individual with a more severe disorder. For this reason, the "personalized medicine" approach is becoming increasingly popular in the resolution of this disorder[92]. The effectiveness of the therapy also depends on the fidelity of the treatment[93]. The Institute of Medicine in the United States, analyzing the literature, stated that there is no one best approach for all individuals, that patients may respond differently to different therapeutic approaches, and that treatment programs should be built with the various approaches that have proven effective. This problem of patient heterogeneity and its effects on therapy can be limited through the subdivision of patients into subgroups[92]. National Institute on Alcohol Abuse and Alcoholism funded The Project MATCH, which consisted of dividing more than 1,700 patients into the three main types of psychotherapy CBT, MET, and TSF. It was shown a significant improvement in most patients[94]. The United Kingdom Alcoholism Treatment Trial UKATT research team compared in terms of costs, health outcomes, and consequences for public sector resource the social network behavior therapy, a more intensive, socially based treatment, and MET, a more intensive, socially based treatment[95].

Motivational Enhancement Therapy (MET)

MET is based on Motivational Interviewing (MI) and is typically very short as it needs 3-sessions of client-centered intervention[96]. It centers on improving patient motivation for variation in addictive behavior and solving ambivalence by growing intrinsic motivation[97]. In particular, MET aims to help these people to reach a reason for the change. It can be called a "motivational conversation"[98]. The therapist must bring about a behavioral change in the patient and strengthen the commitment to maintain this change. It examines the pros and cons of change by focusing on motivational factors[99]. It can be added to other therapies or used on its own. In the first case, MET has been found to reduce the abandonment of other treatments[100]. The COMBINE study investigated an intervention for alcoholics that combined MI-based therapy with alcohol medications[101]. The MI technique is having a wide diffusion in recent years with 212 ongoing projects that are analyzing effectiveness[102]. Despite this, negative results were shown in some clinical studies[103]. Amrhein et al. focused attention on the patient's language during his therapy, creating a scale of the different preparatory language that goes from positive affirmations, of subjects in favor of a change, to negative affirmations of less favorable subjects. Those patients with favorable preparatory language had the best results[99]. The importance of patient commitment and determination was confirmed a few years later by Hodgins and his collaborators[104].

Cognitive-behavioral therapy (CBT)

CBT is certainly the most used treatment for alcohol and other substance use disorders. Its purpose is to identify potential situations in which patients are at risk of relapse and to teach them methods to overcome them, both behaviorally and cognitively[105]. CBT is based on Marlatt and Gordon's model of relapse prevention providing training to the patient that allows him to face moments at risk of relapse. It has been standardized in the MATCH project as approximately 12 sessions of 7-8 hours, which are videotaped. The breath test in which sobriety is measured precedes them. Therapy must be completed in 90 days. The meetings can be individual or group[106].

The purpose of the sessions is to lead patients to master the skill of maintaining alcohol or drug abstinence. The points on which CBT is based are: (1) identification of the intrapersonal and interpersonal triggers that can cause a relapse, (2) training on reaction skills, (3) training on substance rejection skills, (4) analyzing functionally the use of those substances and (5) stimulation of activities not related to use. It includes self-control, identifying situations of alcohol use, setting goals, learning and practicing skills, and the rewards for achieving goals[107]. This technique requires active participation on the part of the patient[108]. Over the years it was shown to improve effectiveness on the heterogeneous population of alcohol users. The same positive result was obtained from the use of CBT for substance use disorders[109]. Behavioral Self-Control Training is a variant of CBT developed by Miller[110]. This variant aims at self-monitoring, therefore the management of alcohol consumption by the patient[111].

CBT is used for many mental disorders, not just those due to alcohol, but also anxiety, schizophrenia,

chronic migraine, obesity, bipolar disorder, depression, personality disorder, or other substance use disorders[109]. Carroll in his work underlines the importance of defining CBT as a dynamic model that evolves to improve his technique and have greater success in addictions[112]. Cognitive-behavioral therapy is also chosen because it has a longer duration of effects than other techniques and is very effective when used in combination with pharmacotherapy[113]. In the field of alcoholism, the combination of pharmacological and psychosocial treatments has aroused more interest but the effectiveness of the combination in preventing relapses must be further ascertained[114]. CBT has also been combined with other valid treatments such as Motivational Interviewing and this combination brought more valid results than the results obtained from the techniques used individually. The Cannabis Youth Treatment is a manualized treatment that uses a combination of both techniques[115]. Gonzalez and Dulin conducted a 6-week study of 52 people with alcohol disorders, the treatments were provided by a MET/CBT smartphone app and at the end of the six months, there was a strong reduction in alcohol consumption[116]. The combined use of CBT and MI requires particular attention to the conflicts that exist between the two techniques. CBT aims at absolute abstinence while Motivational Interviewing supports the autonomy of the client who can independently choose the goal to be achieved[117]. To date, CBT has been shown to give positive results compared to a lack of treatment, but studying the duration of effect and effectiveness compared to other treatments has led to conflicting and non-homogeneous results[109]. Butler et al. analyzed a meta-analysis on CBT and some psychiatric disorders concluding that a specific meta-analysis is needed for CBT used for substance use disorders[118]. Therefore, CBT is an effective therapy for alcohol or other substance disorders but is most effective when used in combination with drug therapy and psychosocial treatment.

MET versus CBT: efficacy of the treatment on abstinence

It is essential to validate and standardize approaches for the psychological treatment of AUD that increase the probability of success and are increasingly affordable. Many psychosocial treatments, including MI, have been shown to achieve good results at low cost. The United Kingdom Alcohol Treatment Trial in their study chose to use MET therapy being as effective as CBT and TSF but less expensive[119].

The comparison between CBT and MET is based on some considerations: i) CBT and MET are validated AUD treatments; ii) that MET is more expensive than CBT; iii) CBT exists in a short form. CBT treatment appears to have stronger power to keep patients on treatment especially during the first three months and in these initial months, dropout occurs more often. Coriale et al. investigated and compared the efficacy of short form of CBT and MET in a cohort of men and women with AUD without comorbid or severe psychiatric disorders or cognitive impairment («pure alcoholics»)[120]. It was found that after one year of treatment of pure alcoholics with CBT and MET, in patients following MET there was a higher percentage of people who did not complete therapy. This abandonment was linked to the relapse especially during the first three months. What did not vary between the two therapies was the consumption of alcohol per day and the percentage of days of abstinence. In the same year, in a study conducted on college students who consumed alcohol, it was shown that MI administered in a short group is as effective as CBT[121]. In a previous study conducted with AUD patients admitted to Sapienza University of Rome, it was found that after one year of treatment with CBT, 47% of patients persisted in attending. In contrast, with MET-based treatment, only 17% had standard care. Khan et al. found that combining CBT and MET for two years resulted in a significant increase in abstinence[122].

Conclusions

The studies cited in this review lead to the conclusion that cognitive and motivational therapies are important for improving AUD symptoms. Being a heterogeneous disorder, AUD needs further studies to be able to say with certainty which among MET or CBT are the best therapy. According to previous studies, we do hypothesize that these two therapies if added to drug treatment may provide better results. Finally, from the data we have to date, it emerges that the less expensive and intensive MET treatment gives significantly the same results of CBT.

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