ALCOHOL CRAVING AND ANTICRAVING STRATERGIES

Dr Priyanka Shukla, Assistant professor, Dept. of lifelong learning and extension, CSJM University, Kanpur.
Dr Debasish Padhi, Assistant professor, Dept of Psychiatry, Rama medical college, Kanpur.

ABSTRACT

Alcohol abuse is a worldwide problem causing serious physical, psychological, social and economic consequences. Craving is a subjective experience of desiring, needing or longing for the euphoric or sedative properties of a drug. Alcohol craving presents as an irresistible urge to drink or as intense thoughts about alcohol (ICD-10, 1992). Relapse is defined as the time that elapses between a point in time (e.g., baseline, end of treatment) and the occurrence of a relapse episode. Various drugs have been used in the recent years which have been able to reduce craving in alcoholism by targeting specific neurochemical substrates of brain. Similarly various psychosocial approaches have been found to be effective in reducing craving and relapse in alcohol dependence. Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity) was designed to compare the effectiveness of 3 common modes of psychosocial interventions in alcoholism i.e. CBT (Cognitive behavior therapy), MET (Motivational enhancement therapy) and TSF **(**Twelve-step Facilitation Therapy).

Key words- Alcohol Abuse, Craving, Relapse, CBT, MET, TSF

Alcohol abuse is a worldwide problem causing serious physical, psychological, social and economic consequences. The majority of epidemiological studies, including the Epidemiological Catchment Area Study (Messer *et al*, 2004) and the National Comorbidity Study (Kessler *et al*, 1994) indicate lifetime prevalence rates of approximately 13.8-20.1% for alcohol abuse related disorders. The lifetime risk for alcohol dependence is approximately 10-15 % for men and 3-5% for women. The age of onset of alcohol problems severe enough to lead to a diagnosis of alcohol dependence ranges from middle twenties to approximately forty years of age (Schuckit, 2005). Alcohol dependence is particularly characterized by variety of comorbidities ranging from medical conditions associated with alcohol consumption such as liver cirrhosis or esophagus varices to psychiatric disorders such as depression, anxiety, psychosis and personality disorders (Hillemacher & Bleich, 2008).

CRAVING IN ALCOHOLISM:

Craving is a subjective experience of desiring, needing or longing for the euphoric or sedative properties of a drug. Alcohol craving presents as an irresistible urge to drink or as intense thoughts about alcohol (ICD-10, 1992). This construct also subsumes the intent to use alcohol, anticipation of positive outcome, anticipation of relief from withdrawal symptoms & negative affect, lack of control over use and cue-induced autonomic responses (Singleton et al, 2003). The development of craving plays an important role in the development of alcohol dependence, maintenance of the alcohol taking behavior and has been implicated in relapse (Drummond, 2001). Hence, it is necessary to have a proper understanding of the nature of craving and its underlying mechanisms, which can have a pivotal role in the management of alcoholism.

A three-pathway psychobiological model of alcohol craving has been proposed by Verheul et al (1999) types are reward craving in which describes as desire for rewarding resulting usually from either dopaminergic/opioidergic system dysregulations. The personality style of the individual is characterized by reward or novelty seeking. Relief craving another form that results from the desire for reduction of tension or arousal. The dysregulations of the GABAergic /glutaminergic system has been implicated. Obsessive craving has been defined as lack of control over intrusive thoughts about drinking. This type of craving results from a relative serotonin deficiency state. The three-pathway model describes the etiological and phenomenological differences of craving, which can have significant bearing on choosing the treatment strategies.

- ***Reward Craving:*** It describes the desire for the rewarding, stimulating and /or enhancing effects of alcohol, It correlates with *anticipation of positive outcome from drinking*.
- ***Relief craving:*** It results from the desire for reduction of tension or arousal. The dysregulations of the GABAergic /glutaminergic system has been implicated. It

correlates with the *anticipation of relief from withdrawal or negative outcome*. The individuals have a stress reactivity personality style.

- ***Obsessive Craving:*** It has been defined as lack of control over intrusive thoughts about drinking, resulting in impaired socio-occupational functioning. This type of craving results from a relative serotonin deficiency state. It correlates with either *urge to use alcohol, intent to drink alcohol,* or *lack of control over use* or *a combination* of all. The personality style of the individual is characterized by low constraint or disinhibition or a combination of both.

The three-pathway model describes the etiological and phenomenological differences of craving, which can have significant bearing on choosing the treatment strategies.

THEORIES OF CRAVING:

Researchers have proposed various models of drug craving which are essentially descriptive of the various dimensions which leads to craving and drug-taking behavior.

Conditioning theories:

1. ***Conditioned withdrawal model*** (Drummond et al, 1990)**:** This model provides a formulation of craving based on conditioning theory. The neutral environmental stimuli, due to repeated pairings with alcohol intake, over the time results in conditioned responses through a process of conditioned learning. According to this model conditioned craving is elicited as part of the conditioned withdrawal response.
2. ***Conditioned opponent process model*** (Siegel, 1989)**:** This model is based on the opponent process theory. Over the course of chronic alcohol consumption the body develops opponent processes which are homeostatic responses to counteract the effects of alcohol. The intake of alcohol results in a positive hedonic state whereas the homeostatic response produces a negative hedonic state. The opponent processes takes longer duration to develop resulting in the development of a negative hedonic craving state.
3. ***Conditioned drug-like model*** (Stewart et al, 1984)**:** They proposed that environmental cues following repeated pairing with alcohol intake and its pleasurable (unconditioned) effects can result in alcohol like conditioned responses (CRs). These positively hedonic CRs describes craving, which primes the individual to take more alcohol through a process of positive reinforcement.
4. ***Two process theory*** (Glautier & Remington, 1995)**:** According to this theory the positive or negative hedonic conditioned craving state will not necessarily lead to alcohol use. The motivational significance of cues or responses to cues cannot be presumed on their affective valence.
5. ***Incentive sensitization theory*** (Robinson & Berridge, 2001)**:** This model describes the addiction behavior more than craving. It has been proposed that the neural substrate (mesolimbic dopaminergic pathway) is responsible for alcohol seeking behavior, which becomes sensitized with repeated alcohol use. This pathway has been implicated for incentive motivation and reward. They made a distinction between 'liking' and 'wanting' alcohol; 'wanting' being associated with the sensitized incentive motivational system and 'liking' being synonymous with craving.
6. ***Cue–reactivity model*** (Drummond et al, 1995)**:** Within this model cue–reactivity can be autonomic (e.g. increased skin conductance, heart rate, salivation), cognitive–symbolic (e.g. subjective craving) or behavioral (e.g. alcohol seeking behavior). Cue-elicited craving has not been considered to be necessary for alcohol seeking or relapse. This theory does not assume an underlying conditioning mechanism, and thus provides a bridge between conditioning and cognitive theories.

Cognitive theories:

1. Cognitive social learning theory (Niaura, 2000)**:** Although this is predominantly a theory of relapse, it has relevance to understanding craving. The theory postulates that in a given 'high-risk situation' the likelihood of relapse will depend on the individual expectations. Efficacy expectations are the individual's confidence in his/her ability to resist the temptation to drink. Outcome expectations are the individual's beliefs about the consequences of

drinking or not drinking. Positive outcome expectancy means anticipation of positive effects of alcohol, whereas negative expectancy involves negative effects of drinking. Craving could be seen as a *'desire for positive drug effects'*. This theory describes four main types of craving:

(a) Craving in response to withdrawal symptoms (craving is the 'need to feel well again').
(b) Craving as a response to lack of pleasure (attempts to improve mood).
(c) Craving as a 'conditioned' response to drug cues and
(d) Craving as a response to hedonic desires.

2. *Cognitive labeling model* (Tiffany, 1990)**:** This model suggests that craving represents the cognitive labeling of physiological processes, such as those arising from alcohol withdrawal or conditioned responses to cues. A subject may interpret the internal physiological effects of exposure to cues associated in the past with alcohol use, as craving for alcohol. Thus craving during alcohol withdrawal may be a different phenomenon from craving in response to cue, but may be interpreted (cognitively) by the subject as the same. The potential importance of this model is that the subjects craving responses to cues could be, theoretically at least, diminished through therapeutic interventions aimed at cognitive reframing of craving.

3. *Dual affect model* (Baker et al, 1987)**:** According to this model alcohol intake is regulated by complex affective processing systems. Craving (or urges) may be elicited by either an appetitive response to alcohol cues ('positive affect urges') or a withdrawal based response ('negative affect urges'). Thus within one individual different cues could elicit either positive or negative urges. However, importantly, the two systems are hypothesized to interact with each other such that stimulation of the positive affect urge system will inhibit the negative affect system.

4. *Dynamic regulatory model* (Niaura et al, 1988)**:** This model argues that craving arises from a combination of conditioned responses to cues, and positive or negative affect. Alcohol use is mediated by coping and self efficacy, which is usually undermined by craving, thus increasing the likelihood of relapse. The initial alcohol use then serves to reinforce continuing its use through its pharmacological effects on affect, in a positive feedback loop. Self-efficacy has been considered as a mediating variable in the craving–relapse relationship.

5. *Cognitive processing model* (Tiffany, 1990)**:** This model posits that alcohol use is essentially an automatic process and is therefore carried out without conscious awareness or effort most of the time. Thus craving will not occur during alcohol use, although there will be accompanying physiological processes required to initiate and carry out alcohol consumption. However, if the subject's normal process of alcohol intake is impeded, a non-automatic, effortful cognitive process is elicited. In this model, craving is conceptualized as 'constellations of verbal, somatovisceral and behavioral responses supported by non-automatic cognitive processes'.

RELAPSE:

Relapse is defined as the time that elapses between a point in time (e.g., baseline, end of treatment) and the occurrence of a relapse episode. There is as yet no standard convention to define the time frame for relapse. In a sample of adolescent substance abusers, Maisto et al. (2003) found that time to relapse varied from 26 to 90 days, depending on whether the definition of relapse incorporated any use, heavy use, or a combination of use and negative consequences; however McKay et al. (2006) has extended the time frame for relapse up to 540 days. The standard definition of relapse is clearly different from a ***'lapse'*** by virtue of its severity and clinical significance. Marlatt & Gordon (1985) have proposed the ***Abstinence Violation Effect (AVE)*** which determines the way an initial lapse results in subsequent relapse.

Determinants of Relapse:

The more widely accepted theories of relapse (Donovan, 1996; Saunders & Houghton, 1996) postulate that relapse is a function of relatively enduring personal characteristics and background factors, which determine overall vulnerability to relapse; immediate precipitants, which trigger specific relapse episodes; and coping behaviors, which can counteract these factors and prevent relapse.

Psychosocial Factors: Marlatt & Gordon (1985) have classified determinants of relapse into two broad categories:

1. *Intrapersonal factors:* contributing to relapse includes negative emotional states (most common), negative physical states, positive emotional states and testing of personal control over urges and temptations.
2. *Interpersonal factors*: of relapse includes relationship conflicts and social pressure to use substance.

According to Daley (1989), relapse can be understood as resulting from a complex interaction between different variables:

1. *Affective variables*: includes negative or positive mood states.
2. *Cognitive variables*: involves the subject's attitude towards recovery, self perception of ability to cope with high risk situations.
3. *Behavioral variables*: comprises coping or social skill deficits, impulsivity.
4. *Environmental variables:* includes lack of family or social stability, social pressure variables to use substances, lack of recreational activities.
5. *Physiological variables*: involves craving, protracted withdrawal syndrome, chronic illness or pain symptoms.
6. *Psychiatric variables*: comprises any co-morbid psychiatric illness.
7. *Spiritual variables*: involves excessive guilt and shame related to inability in controlling substance intake.
8. *Treatment variables*: includes negative attitude toward caregivers or health care services.

Neurobiological factors:

Studies have shown that the ***prefrontal cortex*** and regions functionally and anatomically connected to it are substrates related to relapse in alcoholism. The ***mesolimbic cortical pathway*** or ***reward circuitry*** has been implicated in relapse. There are growing evidences that dysfunction in the ***dopaminergic system*** (receptor number or function) in specific brain regions may increase susceptibility for dependence and probability of relapse. Studies have revealed that low dopamine receptor (DA R) availability in limbic regions may confer biological vulnerability to relapse in alcohol abusers (Volkow et al., 1996).

There are two distinct ***neuroadaptations*** that increase vulnerability to alcohol relapse. First, there is a progressive loss of inhibitory control over conditioned or learned associations, which most likely is related to deficiencies in the prefrontal cortex. Second, reminders of drug use become increasingly more salient. Limbic structures such as the amygdala and ventral striatum (nucleus accumbens) are centrally involved in attributing salience to such stimuli (McKay et al, 2006).

Recent studies provide strong links between ***stress*** and relapse. A recent study found that reduced reactivity to stress, as indicated by lower cortisol levels after a laboratory stress inducing paradigm, predicted a greater likelihood of early relapse in alcoholic males (Junghanns et al., 2003).

ANTI-CRAVING STRATEGIES IN ALCOHOLISM:

Pharmacological approaches:

Various drugs have been used in the recent years which have been able to reduce craving in alcoholism by targeting specific neurochemical substrates of brain.

1. Naltrexone: It is a nonspecific opioid antagonist that blocks mu, delta, and kappa opioid receptors, with greatest affinity for the mu receptor. Naltrexone exerts its anti-craving properties by blocking opiate receptors and indirectly inhibiting dopamine release in the brain reward system. It is available in both oral and injectable forms.

Efficacy: The efficacy studies support the short and medium-term anti-craving efficacy of Naltrexone, with relatively few data available on its long-term efficacy. In a 12-week trial by Volpicelli et al (1992), 23% of patients treated with oral Naltrexone relapsed to heavy drinking versus 54% of patients treated with placebo; there was significant reduction in craving scores, mean number of drinking days and increase in the % of abstinent days, the time for the first relapse day, as compared with placebo. A meta-analysis of 27 randomized

controlled trials found that short-term (<12 weeks) treatment with Naltrexone decreased rates of relapse to heavy drinking by 36% and lowered the risk of treatment withdrawal. Medium-term treatment yielded decreased craving and increased time to first drink, but yielded no benefit for prevention of relapse (Srisurapanont & Jarusuraisin, 2005). It is suggested that a subgroup of alcohol-dependent patients with features of early-onset, male predominance, impulsivity and novelty-seeking, summarized as Cloninger type-2 could especially benefit from treatment with Naltrexone (Kiefer et al, 2008).

2. Nalmefene: It is another opioid antagonist which exerts its anti-craving effects predominantly through its selective action on mu and kappa opioid peptide receptors. It may alter the positive reinforcing effects of alcohol. It has been suggested that Nalmefene should be used as a part of alcohol treatment programme in combination with psychosocial interventions, such as support groups and psychotherapy (Swift, 2000). There are relatively few studies with regard to its anti-craving efficacy in alcoholism.

3. Acamprosate: It is the Ca2+ salt of N-acetyl Homotaurinate. Acamprosate inhibits glutamate overactivity by reducing the release of glutamate from the presynaptic nerve terminal and reducing the overactivation of postsynaptic NMDA receptors. This inhibition of glutaminergic system possibly blocks cue-induced craving, reduces withdrawal related dysphoric states and thus prevents relapse.

Efficacy: Acamprosate has been reported to exert good short- & medium-term, relatively better long–term anti-craving efficacy in alcohol dependence. In a 48- week trial of detoxified alcohol dependent patients, a significant higher continuous abstinence rates was observed in patients who received Acamprosate, as compared to those who received placebo (43% vs. 21% respectively). An additional 48-week follow-up period of patients no longer taking study medication showed that more Accamprosate treated patients remained abstinent than placebo-treated patients (Sass et al, 2004). Similarly, meta-analysis has revealed significant reduction in craving and higher abstinence rates in patients treated with Acamprosate (Boothby & Doering, 2005).

4. Disulfiram: It is an ***aversive agent*** which inhibits the metabolism of acetaldehyde into acetate by blocking the enzyme *aldehyde dehydrogenase (ADH)*, an action which precipitates the accumulation of acetaldehyde when alcohol is consumed, resulting in an unpleasant *disulfiram ethanol reaction (DER)*. Disulfiram is ***not exactly an anti-craving drug,*** but prevents the response to craving.

Efficacy: Fuller et al (1986) examined the abstinence rates and drinking days for 605 alcohol dependent subjects, who were treated daily with 250mg of Disulfiram (standard dose), 1 mg of Disulfiram (a low dose that would not elicit DER), or a vitamin (placebo); the subjects treated with 250mg/day of Disulfiram had fewer drinking days per year than those taking 1mg/day of Disulfiram or placebo. One study suggested that concomitant Disulfiram and Acamprosate treatment increased the number of abstinent days in comparison to when the drugs were used alone (Besson et al, 1998).

5. Carbamazepine & Oxcarbazepine: Carbamazepine is an iminostilbene derivative with anti-convulsant and mood stabilizing properties. Oxcarbazepine is the keto- derivative of Carbamazepine. Recent studies have established their anti-craving properties and efficacy in alcohol withdrawal states.

Efficacy: In a single-blinded and randomized pilot study, the efficacy and tolerability of Carbamazepine was compared with Oxcarbazepine in 29 subjects during alcohol withdrawal state; both the drugs produced reduction in craving, but the Oxcarbazepine group showed a significant decrease of withdrawal symptoms and reduction in craving for alcohol as compared to Carbamazepine group, with no significant differences in tolerability (Schik et al, 2005).

6. Topiramate: It is an anti-convulsant, a sulphamate fructopyrazone derivative, which antagonizes the rewarding effects of alcohol by inhibiting dopamine release in the reward circuit, with simultaneous facilitation of GABA and inhibition of the excitatory effects of glutamate at the AMPA & Kianate glutamate receptor sites.

Efficacy: In a 12-weeks randomized, double-blind study, involving 150 alcohol dependent patients, escalating dose of Topiramate (upto 300mg/day) was found to significantly reduce the number of drinking days & obsessive drinking scores and increased the number of abstinent days, as compared to placebo (Johnson et al, 2003). In an efficacy study, topiramate at the dose of 25-300mg/day was reported to produce significant reduction in craving, with 27.6% fewer heavy drinking and 26.2% more days of abstinence (Rubio et al, 2004).

7. Selective serotonin reuptake inhibitors (SSRIs): Several SSRIs like Fluoxetine, Fluvoxamine, Sertaline, Citalopram and Escitalopram have been examined for their ability to reduce craving in alcohol dependent patients (Naranjo et al, 2001). They are found to be particularly effective in treatment of alcohol dependence with co-morbid depression and anxiety. Cloninger's type-2 alcoholism characterized by impulsivity, suicidality, anti-social behavior and family history of alcoholism, have been reported to respond better to SSRIs (Stoltenberg, 2003).

Efficacy: In a review of studies in relation to the efficacy of different SSRIs in alcohol craving, Naranjo & Knoke (2001) found that Fluoxetine at dose of 40-80mg/day reduced craving and related parameters during the first week, but the overall short-term efficacy was poor; Fluvoxamine at 150mg/day in a 16 weeks trial, increased the rate of abstinence, but there was no significant effect on craving; Sertaline at dose of 200mg/day had less favorable outcome in craving control; Citalopram at 40mg/day for 12 weeks produced short-term reduction in craving and alcohol consumption in mild to moderate alcohol dependence. In a recent study, Escitalopram has been reported to bring significant reduction in alcohol craving (as measured by OCDS), with usefulness in the treatment of alcohol dependence with co-morbid major depression (Muhonen et al, 2008).

8. Other agents:

Several open-label studies, randomized controlled trials and case reports have revealed the anti-craving efficacy of drugs including Ondansetron, Buspirone, Ritanserin, Ca2+ channel blockers, Baclofen etc., in alcohol dependent patients (Lawrence, 2007). Studies have also demonstrated the anti-craving properties of dopamine antagonists like Ecopipam, Flupenthixol, Haloperidol and Olanzapine in alcohol dependence (Garbutt, 2006). Cannabinoid CB-1 receptors have been associated with the development of tolerance and dependence on alcohol. Rimonabant, a cannabinoid CB-1 receptor antagonist, has been shown to suppress alcohol seeking and to reduce voluntary alcohol intake in rats (Scheen et al, 2008). Animal studies involving novel agents like Corticotrophin-releasing factor agonists/antagonists & Neuropeptide Y (NYP) antagonists, have demonstrated reduction in alcohol consumption and motivation for alcohol self-administration; these agents are potential therapeutic targets for future research in humans (Garbutt, 2006).

Psychosocial approaches:

Various psychosocial approaches have been found to be effective in reducing craving and relapse in alcohol dependence:

Cognitive behavior therapy (CBT):

CBT is based on the basic principles of *social learning theory*, which means that behaviors are influenced by interpersonal & intrapersonal experiences & perceptions and in turn, these behaviors influence the environment. The core of CBT includes functional analysis of thoughts, feelings and behaviors that the patient has before, during and after using alcohol. The patient is asked to recognize the automatic thoughts surrounding the period of craving & relapse. The therapist tries cognitive restructuring of the patient's maladaptive automatic thoughts and substitute with more realistic and helpful ideas. The next step of CBT involves skills training, in which the subject is taught to manage the events and situations that commonly induce drinking behavior through problem solving, role playing and home work assignments (Kadden et al, 2007).

Motivational enhancement therapy (MET):

MET employs goal-directed, motivational psychology to elicit behavioral change in patients with alcohol dependence. It is based on the concept of natural recovery, a process through which individuals undergo a series of stages of change to make the necessary

behavioral modifications to overcome alcohol addiction. An individual goes through six stages of change including *precontemplation, contemplation, preparation, action, maintenance*, and possibly *relapse*, which then brings one back to the precontemplation stage to begin the cycle again. For certain stage of change, individuals accomplish established tasks with specific techniques, which have been devised to help them complete these stages. One such technique is motivational interviewing, that focuses on the rapid change of patient's harmful behavior through the examination of their ambivalence. The principles of motivational interviewing involves *expressing empathy, supporting patient's self-efficacy, avoid confrontation, roll with resistance*, and *develop discrepancy*, with the goal of establishing a therapeutic relationship, building patient's self-esteem, and encouraging autonomy (Rollnick & Miller, 1991).

Twelve-step Facilitation Therapy (TSF):

It is based on the concept that alcohol dependence is a disease and TSF attempts to facilitate the recovery process by actively engaging patients in *self-help groups*. The spiritual belief in a higher power and the support from other group members are considered to be the principal factors for maintaining sobriety. ***Alcoholic anonymous (AA)*** encourages patient to accept their illness of alcoholism, understand that the disease has no cure, admit that they are powerless over the substance, surrender themselves to a higher power, and have faith that this power can bring back stability in their lives. Although abstinence is encouraged, relapses are understood as part of the recovery process (Nowinski et al, 1994).

COMPARISON OF EFFICACY OF PSYCHOSOCIAL INTERVENTIONS:

Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity) was designed to compare the effectiveness of 3 common modes of psychosocial interventions in alcoholism i.e. **CBT**, **MET** and **TSF**. All the therapies were found to be effective in helping patients abstain from alcohol during the 3-year study period, with preliminary results from a 10-year follow-up, showing sustained improvement in abstinence and drinking intensity. Among the three treatment modalities, TSF was found to have maximum effectiveness in preventing relapse (Miller, 2005).

EFFICACY OF COMBINED TREATMENT MODALITIES:

Combining Pharmacological modalities:

a. Naltrexone & Acamprosate: Kiefer & Mann (2005) performed a randomized, double-blind, placebo-controlled study combining Naltrexone & Acamprosate in 160 patients with alcohol dependence, following detoxification. Patients received Naltrexone 50mg/day, Acamprosate 1998mg/day, Naltrexone plus Acamprosate, or placebo for 2 weeks; Naltrexone, Acamprosate and the combination regimen were all significantly more effective than placebo, in the measures of time to first drink, time to relapse, and cumulative abstinence time; Naltrexone showed the maximum efficacy in time to first drink & time to relapse, the combination of Naltrexone & Acamprosate was not found to be superior to Naltrexone alone.

b. Disulfiram & Acamprosate: One study suggested that concomitant Disulfiram and Acamprosate treatment increased the number of abstinent days in comparison to when the drugs were used alone (Besson et al, 1998).

2.7.2 Combining Pharmacological and Psychosocial modalities:

COMBINE study (Combined pharmacotherapies and behavioral interventions for alcohol dependence) - It is the largest randomized controlled trial on treatment for alcoholism. The study examined optimal combinations of pharmacotherapy (Naltrexone, Acamprosate, and combination of both) and manualized psychosocial treatment (medical management alone vs. medical management plus moderate intensity special alcohol dependence therapy) for 16 weeks. Eight treatment groups received medical management; 4 of these received Naltrexone (100mg/day), Acamprosate (3g/day), both Naltrexone & Acamprosate, or placebo drug and the other four groups mirrored those just described, but in addition received *combined behavioral intervention (CBI)*. The CBI therapy comprised of CBT, MET and techniques to enhance mutual-help group participation. A ninth group received CBI alone, without any medical management. Overall, the results showed that

patients regardless of the group assignments remained abstinent ranging from 25.2% to 73.1%; however, there were significant differences among the groups. Combining Acamprosate with Naltrexone did not enhance outcome more than that achieved with Naltrexone alone. Patients who received Naltrexone, CBI, or both demonstrated the best drinking outcomes after 6 weeks of treatment; the group that received CBI only without pharmacotherapy demonstrated the worst outcomes, suggesting that combination pharmacotherapy & behavioral treatment improved the outcomes in alcohol dependence (Anton & Randall, 2005).

CONCLUSION

The development of craving plays an important role in the development of alcohol dependence, maintenance of the alcohol taking behavior and has been implicated in relapse. Hence, the strategies to reduce craving plays a pivotal role in the management of alcohol related disorders.

BIBLIOGRAPHY

Anton, R.E., Randall, C.L. (2005) Measurement and choice of drinking outcome variables in the COMBINE Study. *Journal of Studies on Alcohol Supplement.* 7(15), 104-9.

Baker, T.B., Morse, E. & Sherman, J.E. (1987) The motivation to use drugs: a psychobiological analysis of urges, in: Rivers, P.C. (Ed.) The Nebraska Symposium on Motivation: alcohol use and abuse, pp. 257–323 (Lincoln, University of Nebraska Press).

Besson, J., Aeby, F., Kasas, A., Lehert, P., Potgieter, A. (1998) Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. *Alcohol, Clinical Experimental Research*, 22(3), 573-9.

Boothby, L.A., Doering, P.L. (2005) Acamprosate for the treatment of alcohol dependence. *Clinical Therapeutics*, 27(6), 695-714.

Daley, D. (1989) Five perspectives on relapse in chemical dependency. *Journal of Chemical Dependence Treatment*, 2, 23-26.

Donovan, D.M. (1996) Assessment issues and domains in the prediction of relapse. *Addiction*, 91 Suppl, S29-36au

Drummond, D.C. (2001). Theories of drug craving, ancient and modern. *Addiction*, 96 (1), 33-46.

Drummond, D.C., Cooper, T. & Glautier, S.P. (1990) Conditioned learning in alcohol dependence: implications for cue exposure treatment. *British Journal of Addiction*, 85, 725–743.

Drummond, D.C., Tiffany, S.T., Glautier, S.P. (1995) Cue exposure in understanding and treating addictive behaviours, in: Drummond, D.C., Tiffany, S.T., Glautier, S.P. & Remington, B. (Eds) Addictive Behaviour: cue exposure theory and practice, pp. 1–17 (Chichester, John Wiley).

Fuller, R.K., Branchey, L., Brightwell, D.R., Derman, R.M., Emrick, C.D., Iber, F.L., James, K.E., Lacoursiere, R.B., Lee, K.K., Lowenstam, I. (1986) Disulfiram treatment of alcoholism. A Veterans Administration cooperative study. *JAMA*, 256(11), 1449-55.

Garbutt, J.C. (2006) Medications for the treatment of alcohol dependence. *American Fam Physician*, 74(11), 1836.

.

Glautier, S.P. & Remington, B. (1995) The form of response to drug cues, in: Drummond, D.C., Tiffany, S.T., Glautier, S.P. & Remington, B. (Eds) Addictive Behaviour: cue exposure theory and practice, pp. 21–46 (Chichester, John Wiley).

Hillemacher, T. & Bleich, S. (2008) Neurobiology and treatment in alcoholism—recent findings regarding lesch's typology of alcohol dependence. *Alcohol & Alcoholism*, 43, 3, 341–346.

Johnson, B.A., Ait-Daoud, N., Bowden, C.L., DiClemente, C.C., Roache, J.D., Lawson, K., Javors, M.A., Ma, J.Z. (2003) Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet*, 361(9370), 1677-85.

Junghanns, K., Backhaus, J., Tietz, U., Lange, W., Bernzen, J., Wetterling, T., Rink, L., Driessen, M. (2003) Impaired serum cortisol stress response is a predictor of early relapse. *Alcohol and Alcoholism*, 38 (2), 189–193.

Kadden, R.M. (2001) Behavioral and cognitive-behavioral treatments for alcoholism: research opportunities. *Addictive Behaviour*, 26(4), 489-507.

Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.U., Kendler, K.S. (1994) Lifetime and 12-months prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry*, 51 (1), 8-19.

Kiefer, F. & Mann, K. (2005) New achievements and pharmacotherapeutic approaches in the treatment of alcohol dependence. *European Journal of Pharmacology*, 526 (13), 163-71.

Kiefer, F., Jiménez-Arriero, M.A., Klein, O., Diehl, A., Rubio, G. (2008) Cloninger's typology and treatment outcome in alcohol-dependent subjects during pharmacotherapy with naltrexone. *Addiction Biology*, 13 (1), 124-9.

Lawrence, A.J. (2007) Therapeutics for alcoholism: what's the future? *Drug Alcohol Review*, 26(1), 3-8.

Maisto, S.A., Pollock, N.K., Cornelius, J.R., *et al*. (2003). Alcohol relapse as a function of relapse definition in a clinical sample of adolescents. *Addictive Behaviors*, 28, 449– 459.
Marlatt, G.A., & Gordon, J.R. (1985). Relapse prevention: Maintenance strategies in the treatment of addictive behaviors. New York, Guilford Press.
McKay, J.R., Franklin, T.R., Nicholas, P., *et al*. (2006) Conceptual, methodological, and analytical issues in the study of relapse. *Clinical Psychology Review*, 26, 109– 127.
Messer, S.C., Liu, X., Hoge, C.W., *et al*. (2004) Projecting mental disorder prevalence from national surveys to populations-of-interest--an illustration using ECA data and the U. S. Army. *Social Psychiatry Psychiatric Epidemiology*, 39(6), 419-26
Miller, W.R. (2005) Are alcoholism treatments effective? The Project MATCH data: response. *BMC Public Health*, 5, 76.
Miller, W.R., Rollnick, S. (1991) Motivational interviewing: Preparing people to change addictive behavior. New York, NY: Guilford press.
Muhonen, L.H., Lönnqvist, J., Juva, K., *et al*. (2008) Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence. *Journal Clinical Psychiatry*, 69(3), 392-9.
Naranjo, C.A. & Knoke, D.M. (2001) The role of selective serotonin reuptake inhibitors in reducing alcohol consumption. *Journal of Clinical Psychiatry*, 62 Suppl 20, 18-25.
Niaura, R.S. (2000) Cognitive social learning and related perspectives on drug craving. *Addiction*, 95 (suppl. 2), S155–S164.
Niaura, R.S., Rohsenow, D.J., Binkoff, J.A., *et al*. (1988) Relevance of cue reactivity to understanding alcohol and smoking relapse. *Journal of Abnormal Psychology*, 97, 133–152.
Nowinski, J., Baker, S., Carroll, K. (1994) For the national institute on alcohol abuse and alcoholism. Twelve step facilitation therapy manual: a clinical research guide for therapists treating individuals with alcohol abuse and dependence. Project MATCH monograph series, vol.1,Rockville, Md: National institute of health; 1994. NIH publication no. 94-3722.
Robinson, T.E. & Berridge, K.C. (2001) Incentive sensitization and addiction. *Addiction*, 96, 103–11
Rubio, G., Ponce, G., Jiménez-Arriero, M.A., *et al*. (2004) Effects of topiramate in the treatment of alcohol dependence. *Pharmacopsychiatry*, 37(1), 37.
Saunders, B. & Houghton, M. (1996) Relapse revisited: a critique of current concepts and clinical practice in the management of alcohol problems. *Addictive Behaviour*, 21(6), 843-55.
Scheen, A.J., Seutin, V., Van Gaal, L.F., *et al*. (2008) Endocannabinoid system in the brain...and elsewhere. *Rev Med Liege*, 63(5-6), 364-71.
Schik, G., Wedegaertner, F.R., Liersch, J., *et al*. (2005) Oxcarbazepine versus carbamazepine in the treatment of alcohol withdrawal. *Addiction Biology*, 10(3), 283-8.
Schuckit, M.A. (2005) Alcohol related disorders, Comprehensive Textbook of Psychiatry, Sadock, B. J. & Sadock, V.A., 8th Edition, 1, 1168-1188.
Siegel, S. (1989) Pharmacological conditioning and drug effects, in: Goudie, A. J. & Emmett-Oglesby, M. W. (Eds) Psychoactive Drugs: tolerance and sensitization, pp. 115–180 (Clifton, NJ, Humana Press).
Singleton, E.G., Tiffany, S.T. & Henningfield, J.E. (2003). The Alcohol Craving Questionnaire (ACQ-NOW). In J.P. Allen & V.B. Wilson (Eds.), Assessing Alcohol Problems: A Guide for Clinicians and Researchers (2nd ed.; pp. 271-281). NIH Publication No. 03-3745. Bethesda, M.D.: National Institute on Alcohol Abuse and Alcoholism.
Srisurapanont, M., Jarusuraisin, N. (2005) Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. *International Journal of Neuropsychopharmacology*, 8(2), 267-80.
Stewart, J., Dewit, H. & Eikelboom, R. (1984) Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychological Review*, 91, 251–268.
Stoltenberg, S.F. (2003) Serotonergic agents and alcoholism treatment: a simulation. *Alcohol, Clinical Experimental Research*, 27(12), 1853-9.
Swift, R.M. (2000) Opioid antagonists and alcoholism treatment. *CNS Spectrums*, 5(2), 49-57.
Tiffany, S.T. (1990) A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. *Psychological Review*, 97 (7), 147–168.
Verheul, R., Brink, W.V.D., Geerlings, P. (1999) A three-pathway psychobiological model of craving for alcohol. *Alcohol and Alcoholism*, 34, 2,197-222.
Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Hitzemann, R., Ding, Y.S., Pappas, N., Shea, C., Piscani, K. (1996) Decreases in dopamine receptors but not in dopamine transporters in alcoholics. *Alcohol, Clinical Experimental Research*, 20 (9), 1594–8.
Volpicelli, J.R., Alterman, A.I., Hayashida, M., O'Brien, C.P. (1992) Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry*, 49 (11), 876-80.
World Health Organization (1992). The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, Switzerland: the Organization.