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Review Article

The growing problem of Alcoholism in Pakistan: An overview of current situation and treatment options

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Abstract
Alcoholism is turning in to a growing problem in Pakistan despite its status of a "dry land" where 96% of the population do not drink and alcohol drinking is prohibited by law. Out of estimated ten million alcohol abusers, one million develop alcohol use disorders. Stress is the prevalent factor responsible for alcohol abuse. Moreover, the recent trend of alcohol abuse at a young age of 14 years is of growing concern. Literature research conducted using PubMed, Google Scholar resulted in almost no research articles or reviews directly addressing this problem. Hence, this review is the first on this subject. In this context, this review would try to comprehend current scenario of alcoholism in Pakistan. The role of globally recognized and FDA approved treatment medications is also discussed together with raising importance of psychosocial support therapy for alcohol addicted patients. In addition to that underlying neurobiology and different stages of alcoholism are elucidated.

Keywords
Alcoholism, Pakistan, stress, anti-relapse drugs, psychosocial support

Introduction
Alcoholism, is a chronic relapsing mental disorder (Koob and Volkow, 2010), which is one of the most widespread forms of addiction globally (Bakti and Pennington, 2014). Alcohol consumption is classed as world's third largest risk factor for pre-mature mortality and loss of health (WHO report, 2011). Pakistan, an Islamic state, in which the alcohol sale and use is strictly prohibited by law is witnessing a surge in alcohol abuse and consequent alcohol use disorders in recent years (Haviland, 2013; Walsh 2010). Consequently, alcoholism is turning in to a growing problem in Pakistan.

Despite the rising trend of alcohol abuse, there is dearth of latest statistical data reporting the accurate number of illicit drug users, including alcohol abusers in Pakistan. For this review a literature research performed through PubMed/Medline and other data bases like Google scholar with terms such as "alcohol abuse in Pakistan" returned fewer publications, which were not relevant to the theme of searched criteria. Mostly, these research articles reported data collected through survey questionnaires only for relatively developed cities of the country like Karachi or Lahore, whereas, for rest of the country, the scenario remains completely obscured due to lack of data. Consequently, in order to comprehend the rising trend in alcohol abuse, data from sources like newspapers reports was also used in preparation of this review together with cross-sectional survey studies. In one such cross-sectional study conducted in Karachi city, alcohol was found to be the third most commonly abused substance after cocaine and amphetamine (Ali et al., 2011).

Moreover, alcohol-related diseases have risen by at least 10% in the past five years (Haviland, 2013). According to a report there are an estimated 10 million Pakistanis who drink alcohol, 1 million of whom develop alcohol associated problems (Walsh, 2010).

It's a grim reality that during last six years, a visible change is seen in the age at which drinking is initiated. Previously, drinkers were at least in their 20s but now some abusers admitted in rehabilitation centers are reported to be as young as of 14 years (Haviland 2013).

Factors contributing to alcohol abuse
Intriguingly, majority of drinkers do not drink for recreational purposes in Pakistan (Haviland, 2013). Although, it is a "drink of choice" in social gatherings and weddings organized by affluent stratum of society. The key factors which compel people to initiate drug abuse are psychological in nature, often associated with socioeconomic conditions of people. 45% of people in Karachi city are reported to commence drug use including alcohol due to problems associated with parental or marital relationship. Whereas, 47% people attributed it to social influence, whereas, 28% of people consider drugs as an escape from stress full and traumatic life events (Ali et al., 2011).

A recent cross–sectional survey study reported alcohol drinking as a stress coping strategy in order to decrease work load tension among final year medical students across six different medical colleges of Pakistan (Yousafzai et al., 2009).Moreover, the unstable law and order situation and escalating violence has contributed a great deal in instilling

sense of insecurity among people, making them susceptible to psychological disorders including addiction (Ahmed et al., 2014).

Although males make the biggest proportion of alcohol abusers, some Pakistani women, abuse alcohol as well (Haviland, 2013). Being an Islamic state, where 96% of people do not drink, alcohol drinking is considered forbidden and is a social stigma even for men. However, for women the concept of alcohol abuse is completely unacceptable and is a social taboo for women to abuse alcohol. Consequently, female alcohol addicts show reluctance in seeking treatments at rehabilitation centre (Haviland, 2013).

In context of growing problem of alcohol addiction in Pakistan, in this review pharmacological profile of current alcohol addiction treatment medications is discussed which can be of interest not only to the clinicians but also for general awareness. The efficacy of these treatment medications have been proved through several clinical trials. Additionally, the need for psychosocial intervention groups is highlighted for a society where stress is the major provoking factor for alcohol abuse. Moreover, from research point of view, our current understanding of the underlying neurobiology of alcohol addiction is discussed, with particular attention towards perturbation caused by alcohol intake in different neurotransmitter systems which after prolonged exposure to alcohol leads to the development of addiction sensitive neurocircuitries.

Neurobiology of alcoholism

An understanding of the underlying neurobiology of alcoholism is crucial for the development of effective pharmacotherapies. There are patients who remain abstinent for three or more years but can unintentionally relapse one day even after remaining sober for this long. This shows that during the development of dependence, alcohol-sensitive neurocircuitries and neuroadaptions take place which can make a person relapse after decades of abstinence (Koob and Volkow, 2010). Alcohol usually binds to hydrophobic pockets of proteins, as a consequence, the three-dimensional structure and function of these proteins is changed in the process. Generally these include ion channels, neurotransmitter receptors, and enzymes involved in signal transduction (Kenna et al., 2004). The small size of this molecule and absence of a specific receptor in the brain facilitates its interaction with many neurotransmitter systems. This accounts for the various pharmacological effects rendered by this molecule upon both short- and long-term exposure. More specifically, alcohol mediates its sedative effects by making non–specific interactions with the GABAergic system, while the dopaminergic system governs the positive pleasure enhancing effects and facilitates later transitions from social drinking to alcoholism. The deficits in learning and memory developed with chronic alcohol use are associated with perturbations in the glutametergic system (Koob, 2004). (See table 1).

Abused drugs, including alcohol, have the ability to interfere and influence the brain reward circuitry either by directly influencing the neurotransmitter dopamine, present within the system or by modulating the activity of other neurotransmitter such as γ-amino butyric acid (GABA) which exert a positive control over the mesolimbic dopaminergic system(Gilpin and Koob, 2008;Tomkins and Seller,2001). The brain reward circuitry is complex. Other than GABA, serotonin, acetylcholine, noradrenalin and endogenous opioids are some of the neurotransmitters that interact with this pathway at several points and influence its activity (Swift, 1999). Consequently, the acute reinforcing effects of alcohol are mediated by its interaction with several of these neurotransmitters and a continuous intake of alcohol results in neuronal alterations which form the basis of various components of the disease: sensitization, tolerance, dependence, withdrawal,relapse(Gilpin and Koob,2008). (See Figure 1).

Pharmacological treatment

Psychological therapies may aid in reducing alcohol consumption but the need for medications for the treatment of alcohol dependence is undeniable since 40-70 percent of patients resume drinking within 1 year of psychosocial treatment (Swift, 1999). This can be explained in context of development of dependence, during which alcohol-sensitive neurocircuitries and neuroadaptions take place, which can make a person relapse after decades of abstinence (Koob and Volkow, 2010). As stated earlier, alcohol lacks a specific receptor and the small size of the molecule allows it to bind with the hydrophobic pockets of proteins, specifically the, neurotransmitter receptors, consequently, the three-dimensional structure and function of these proteins are changed in the process (Kenna et al, 2004) Hence, nearly all the FDA–approved medications capitalize on blocking alcohol interaction with different neurotransmitters.

Naltrexone

Naltrexone, a μ-opioid antagonist, was approved by FDA in 1994 as an anti-relapse medication after a series of randomized clinical trials (O'Malley et al, 1992; Volpicelli et al 1992). At present, it is available in both oral and extended release injectable form. This drug became part of the alcoholism treatment regime after the origination of the theory that μ opioid receptors are involved in the rewarding effects of alcohol and their antagonism can prove to be of therapeutical significance (Froelich et al 1990;

Hubbel etal, 1986). Opioid peptides increase the rewarding effect of alcohol by interacting with an another neurotransmitter dopamine via μ-opioid receptors present in the ventral tegmental (VTA) part of reward circuitry (Swift, 1999). The release of dopamine in the nucleus accumbens (Nac) is said to be the key event in reinforcing alcohol dependence (Koob and Volkow, 2010).

Naltrexone and μ-opioid antagonists have been shown to block the release of dopamine in Nucleus accumbens (Nac) induced by alcohol intake (O'Malley et al, 1992; Volpicelli et al 1992) . Nearly, all clinical trials with naltrexone have reported only modest efficacy of this drug with higher treatment attrition rates due to compliance issues with the long term use (Garbutt ,2009; Kranzler and Kirk,2001), nevertheless, it is still the most widely researched drug, specifically in preventing relapse(Bujarski et al , 2012). Naltrexone has been reported to reduce the occurrence of heavy drinkingdays(Balldin et al,2003;Monti et al, 2001;Rubio et al,2002), additionally it also increases time to first relapse (Anton et al,1999 ;Keifer et al, 2003)and yields lower relapse rates(Heinala et al, 2001;Latt et al, 2002;Volpicelli, 1992). Unfortunately, no clinical studies have been reported of naltrexone with Pakistani subjects, this may be due to fewer no of alcohol dependents getting access to treatment and rehabilitation centers despite the growing problem of alcohol addiction in Pakistan.

Acamprosate

Acamprosate is a taurine analog. It is an anti-relapse drug widely used in the treatment of alcoholdependence.However, the pharmacological action of this drug has remained largely elusive (DeWitte, 2005). Interestingly, unlike naltrexone this drug does not has an exact cellular target to reduce alcohol intake. Inhibition of neuronal hyperexcitability either by blocking activity of excitatory amino acids or by blunting calcium ion fluxes is suggested to be the principal mechanism of action (Wilde and Wagstaff, 1997).

Acamprosate suppresses craving associated with alcohol withdrawal and hence facilitates abstinence from alcohol intake (Littleton, 1995). Acamprosate is demonstrated to have many potential benefits.It was shown that acamprosate apart from decreasing alcohol intake is devoid of any pharmacological interactions with other medications such as disulfiram or anti-depressants medications prescribed for the relief of psychoses and anxiety (Durbin et al, 1996) . Hence, acamprosate is ideal for alcohol dependent patients with co-morbid depression or psychosis. Additionally, unlike naltrexone, acamprosate is not metabolized extensively in the liver; therefore, patients with hepatic impairment can also gain the same therapeutic effects as patients without liver dysfunction (Wilde and Wagstaff, 1997). Overall, acamprosate therapy has been quite successful in maintaining abstinence for full 1 year after treatment compared with patients who received only placebo (Swift, 1999)

Disulfiram

The first FDA approved medication for the alcoholism treatment nearly 50 years ago was disulfiram. Unlike, other medications for alcohol treatment, disulfiram pharmacological action does not effect neurobiological systems underlying alcohol dependence, instead upon intake it produces aversive reactions such as flushing, throbbing, headache, nausea, vomiting, and chest pain (Swift, 1999) . Thereby, reducing alcohol intake in response to even low levels of alcohol consumption (Garbutt, 2009). Disulfiram works by preventing the metabolism of an alcohol by-product, acetaldehyde. High levels of acetaldehyde accumulates in the body after alcohol consumption causing unpleasant symptoms which provide a strong incentive to stop drinking (Swift, 1999). Consequently, treatment with disulfiram is suggested to be carried out in supervised setting with strict monitoring in order to achieve treatment effects. Over all, disulfiram treatment has yielded good treatment outcomes as evidenced by several controlled clinical trials, however, superior treatment outcomes can be obtained under supervision by fully educated and trained monitors to control evasion behaviors common in patients with alcohol dependence (Brewer,1992;Fuller et al, 1986). On the other hand, due to poor adherence to treatment, inconsistent results have also been reported which raise doubts regarding feasibility of this drug, however, adjunct therapy together with other alcohol treatment medications such as naltrexone and acamprosate can yield better treatment outcomes (Suh et al, 2006).

Nalmefene

Nalmefene, an opioid system anatgonist has emerged as a new treatment option for alcohol dependence. It is recently approved in Europe by the European medicine agency to be used in "as-needed" fashion for alcohol dependents with a high drinking risk level (Glen, 2014) and is introduced by the brand name "Selincro". Patients can take Nalmefene when they perceive the imminent risk of alcohol consumption in spite of taking it on daily basis as used for previously approved pharmacological therapies. Additionally, unlike naltrexone, acamprosate and disulfiram which are prescribed to prevent relapse in already abstinent patients, nalmefene is found to be effective in reducing alcohol consumption in alcohol-dependent patients with very high alcohol intakes, for whom complete abstinence is difficult to achieve (Keating,

2013)

The plight of alcoholism treatment is the lack of different treatment modalities. Relapse prevention is not an ideal and achievable goal and treatments at hand are only moderately effective in preventing relapse. Allowing for reduction in alcohol consumption is a much feasible goal. A clinical trial was conducted in 2013 with 604 subjects to evaluate the efficacy of as needed use of nalmefene in reducing alcohol consumption in patients with alcohol dependence (Mann et al, 2013). The trial was of eight months duration and a significant reduction in number of heavy drinking days was observed from the six month in the nalmefene group in comparasion to placebo group. Nalmefene is known as "universal antagonist" because of its ability to block all three types of μ opioid receptors, mu, kappa and delta (Culpepper-Morgan et al, 1995; Emmerson et al, 1994), unlike naltrexone which binds to just one type of receptor and may affect the other two only at high doses (Sawynok et al, 1975).

Nalmefene has a relatively safe profile and is well tolerated overall (Soyka, 2014). The only adverse effects reported are nausea, dizziness, and sleep disturbance, such as insomnia (Gual et al, 2013; Mann et al, 2013).Drug treatment needs to be combined with psychosocial therapy especially in order to improve treatment retention.

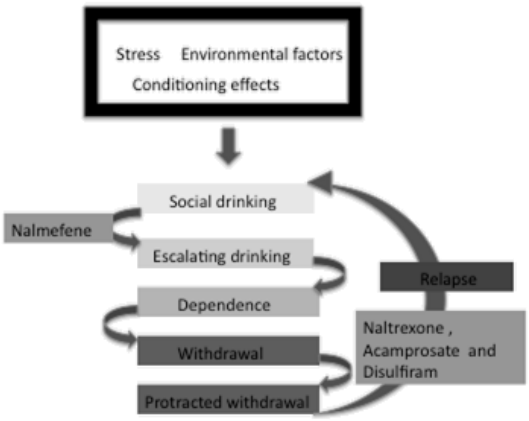

Figure 1: The cycle of alcohol addiction begins with low amounts of alcohol intake (social drinking). Stress, environmental factors and genes or the conditioned pleasure able and anxiolytic response gained from alcohol intake urge people to drink in large amounts (escalating drinking) and more frequently (more no of days). Nalmefene, at this stage can reduce alcohol consumption in individuals with a risk of high drinking. Increased alcohol intake leads to the development of dependence, a condition in which a person forms physical and psychological dependence on alcohol. Discontinuation of alcohol intake results in withdrawal, a body reaction against abrupt cessation of alcohol intake, its symptoms include distress, craving, anxiety, headaches, sweating and in severe cases seizures. Prolonged or protracted withdrawal is marked by changes in emotional and cognitive state of a person, when the signs of physical withdrawal are no longer apparent long after discontinuation of drinking. However, a person can relapse i.e. can resume escalated drinking if remain untreated. Treatment can be sought at this stage with anti- relapse medications naltrexone, acamprosate and disulfiram. Nac: Nucleus accumbens, Nacc: Nucleus accumbens core, μ-OR: mu-opioid receptor, δ-OR: delta-opioid receptor, VTA: ventral tegmental area, GABA: Gamma amino butyric acid, NMDA: N-methyl-D-aspartate receptor

Psychological and Psychosocial interventions for alcoholism

Psychological or Psychosocial interventions in conjunction with pharmacological treatment is the classical treatment approach for alcoholism. Usually, those subjects who have not yet developed alcohol addiction but experience alcohol misuse can be treated only with psychological interventions. These can be carried out in supervision of a therapist or counselor. Additionally, "Self-help" based interventions are also made into use with the help of DVDs, books, computer programmers or self-help manuals.

In countries like Pakistan, where the condition of health care system is quite adverse and many people do not have access to even, basic medical needs, the latter approach can be quite beneficial. Philanthropist organizations can play a vital in publication and dissemination of relevant literature and DVD's in alcohol abusing patients.

Psychological treatments are also beneficial for those subpopulation of alcohol dependent population suffering from co-morbid depression and anxiety. In the present scenario of unstable law and order situation and unabated violence, the existence of co-morbidities together with alcohol abuse does not seem to be out of question. The need of the hour is to make these treatment options accessible and affordable for all socioeconomic stratums of society. The 12-step facilitation programme by Alcoholics Anonymous society is practiced throughout in different countries and comprises of 12 steps towards getting rid of alcohol abuse. With the lifelong goal of abstinence from alcohol, 12 step is usually offered free of charge and have lifelong membership with the association. The patients are obligated to remain abstinent throughout, the 12 step meetings. A number of studies have reported, that the attendance in this programme is met with success (Ferri et al, 2006).

Neurotransmitter	Effect of acute alcohol intake on neurotransmitter	Ref
Dopamine	Elevates dopamine levels in NAcc , which produces pleasurable effects.	Dichiara et al, 1988; Weiss et al, 1993
Opioid system	After binding with μ -OR in VTA and δ- OR in Nac increases dopamine release in Nacc which enhances pleasure	Spanagel et al,1992,
GABA	Binds with $GABA_A$ receptors present in the cell membrane of the presynaptic neuron, activates them and causes neuronal inhibition, causing intoxication. By binding with $GABA_A$ in VTA it produces pleasure enhancing effects and anxiolysis.	Mihic and Harris 1995; Koob, 2003
Glutamate	Inhibits the excitatory activity of the NMDA receptor upon binding which causes cognitive dysfunction during intoxication. Alcohol withdrawal syndrome is also associated with the disruption of glutametergic system	Gonzales and Jaworski, 1997; Rosetti and Carboni, 1995
Serotonin	Serotonin functioning is increased during alcohol intoxication which results in anxiolytic response and motivates people for a continuous intake.	Lovinger, 1997

Table 1: Summary of interaction of alcohol with different neurotransmitters and alteration of their activity upon acute intake.

Conclusion

The problem of alcohol addiction is growing in Pakistan .The economic and medical impact of alcoholism is often enormous on societies. The abuse of alcohol as a "stress coping strategy" is found out to be the most common factor urging people to abuse alcohol. This appraises the need of psychosocial support groups, since unabated violence, together with unstable law and order situation has robbed people of sense of security and mental peace. Alcohol addiction is common in males but some women alcohol abusers have also been reported for whom seeking treatment is quite difficult due to double standard set by our society considering drinking as a "bigger social taboo" for women than for men. Therefore, under these unfortunate state of affairs, it's imperative to provide these patients an easy access to treatment centers. There is a need of increasing number of treatment clinics. In this respect a well-organized out –patient department (OPD) set in hospitals working in close association with a psychosocial support center would ideally be able to cater the treatment needs of patients of all types and at various stages of alcohol addiction.

Recommendation

Need is there to increase general awareness about health risk associated with alcohol abuse specially at young age, through seminars and workshop.

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