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Critical Review of Alcohol, Alcoholism and the Withdrawal Symptoms. II. Treatment Strategies

Singh Ashok K*

Department of Veterinary Population Medicine, University of Minnesota, USA

Abstract

Alcoholic beverages, socially accepted drinks around the world, are consumed (legally by adults and illegally by minors) to socialize, celebrate, and relax. However, persistent drinking results in the development of tolerance that necessitates a perpetual increase in alcohol drinking to achieve desired effects. In genetically predisposed subjects and in the presence of certain environmental cue, chronic alcohol drinking induces addiction, characterized by excessive uncontrollable drinking associated with rapid onset of the withdrawal symptoms. Currently there are only three medications approved by the U.S. FDA to treat alcoholism: disulfiram (alcohol metabolizing enzyme inhibitor), naltrexone (opiate receptor antagonist), topiramat and acamprosate (NMDA receptor inhibitor). Because pharmacotherapy alone or in combination with behavioral approaches is only modestly effective in treating alcoholism symptoms, there is an urgent need to develop effective and safe therapies. In the present review, we describe upcoming Biopsychosocial (BPS), pharmacologic, pharmacogenetic, pharmacogenomic, genomic and phyto medicinal approaches for the treatment of alcoholism.

Keywords

Acetaldehyde, Alcoholism, Addiction, Ethanol, Genomics, Herbal therapy, Pharmacogenomics, Pharmacotherapy, Tolerance, Withdrawal

Introduction

Alcoholism, a chronic disorder with often devastating health and economic consequences [1-3] has multiple causes with psychological, social and biological factors (Figure 1), also known as the Biopsychosocial (BPS) factor [4], determine the course of an individual's health-related outcomes [4]. Therefore, a single approach such as pharmacotherapy and/or behavioral counseling may not effectively treat the complex nature of the disorder [5,6]. In addition, every individual is not equally affected by each cause, necessitating a comprehensive individual assessment in order to adequately determine the individual's treatment needs. According to a 2016 National Institute of Drug Abuse (NIDA) report, a comprehensive alcoholism therapy must include a combination of behavioral therapy, psychosocial counseling, pharmacotherapy, exercise, relapse prevention and other services to meet the needs of the individual patient to accommodate issues as age, race, culture, sexual orientation, gender, pregnancy, parenting, housing, and employment, as well as physical and sexual abuse (Figure 2).

The comprehensive therapy proposed by NIDA, although effective, is expansive and require extensive re-

sources and time commitment that may not be generally available in primary care settings. Therefore, novel strategies are needed that will effectively treat alcoholism and prevent relapse without some of the disadvantages listed above. Currently, many diverse approaches including the psychosocial therapies, non-traditional pharmacotherapy, Pharmacogenetics, pharmacogenomics, gene therapy and herbal therapy are being developed and tested for clinical use [7-11].

Despite considerable development in the quality of health care for people suffering from alcoholism, many deficiencies remain. Two major deficiencies are discussed below.

Corresponding author: Singh Ashok K, Associate Professor, Department of Veterinary Population Medicine, College of Veterinary Medicine, University of Minnesota, Twin Cities, St Paul, MN 55108, USA, Tel: 763-234-9655, E-mail: Singh001@umn.edu
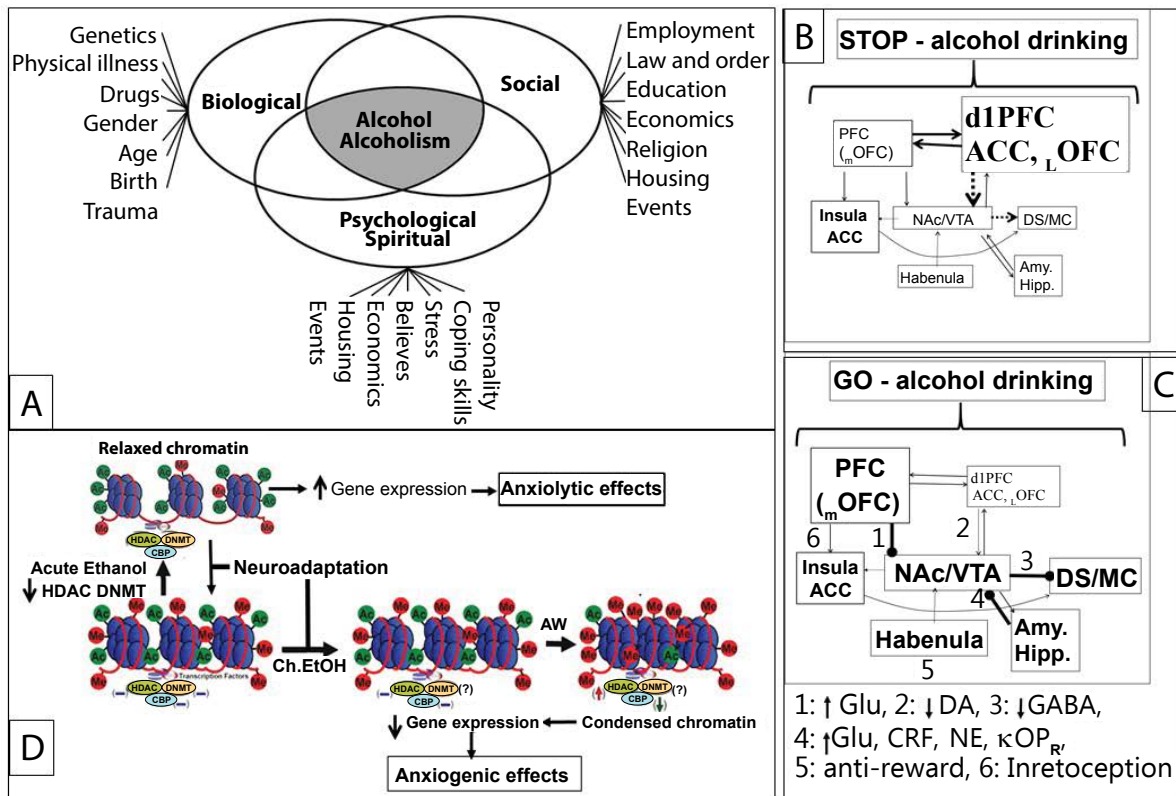
Figure 1: Alcoholism is a multifaceted disorder in which psychosocial (Figure 1A) and biological (Figure 1B, Figure 1C and Figure 1D) psychological factors (also known as the Biopsychosocial (BPS) theory) combine and interact to produce addiction disorder [4]. Different components of the psychological and social contexts are listed in Figure 1. The biological deficits include (i) Differential sensitivities of various brain regions to alcohol in non-alcoholic (Figure 1, dlPFC (ACC, $_L$OFC) > PFC (mOFC), Insula, AAc, VTA, Amy, Hipp, DS, MS, and Habenula) and alcoholic (Figure 1, PFC (mOFC), AAc, VTA, Amy, Hipp, DS, MS, and Habenula > dlPFC (ACC, $_L$OFC)) subjects and (ii) Opposing effects of acute (causes anxiolytic effects by relaxing chromatin and enhancing gene expression) and chronic (caused anxiogenic effects by condensing chromatids and suppressing gene expression) alcohol exposures on epigenetic regulation of gene expression (Figure 1). Because of the heterogeneity in the population of alcohol abusers, a comprehensive individual assessment is essential in order to adequately determine the patient's treatment needs [54,200].

ACC: Anterior Cingulate Cortex; dPFC: Dorsolateral Prefrontal Cortex; DS: Dorsal Striatum; OFC: Lateral Orbitofrontal Cortex; MO: Motor Cortex; NAc: Nucleus Accumbens; VTA: Ventral Tegmental Area; VS: Ventral Striatal; DA: Dopamine; GABA: γ-amino Butyric Acid; CRF: Corticotrophin Releasing Factor; κ-OP$_R$ *kappa* Opioid Receptors.
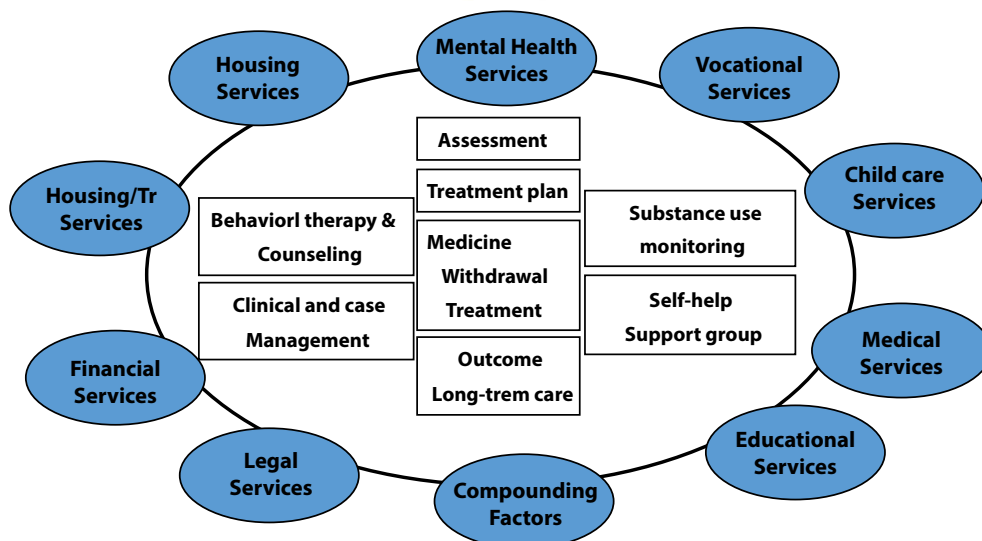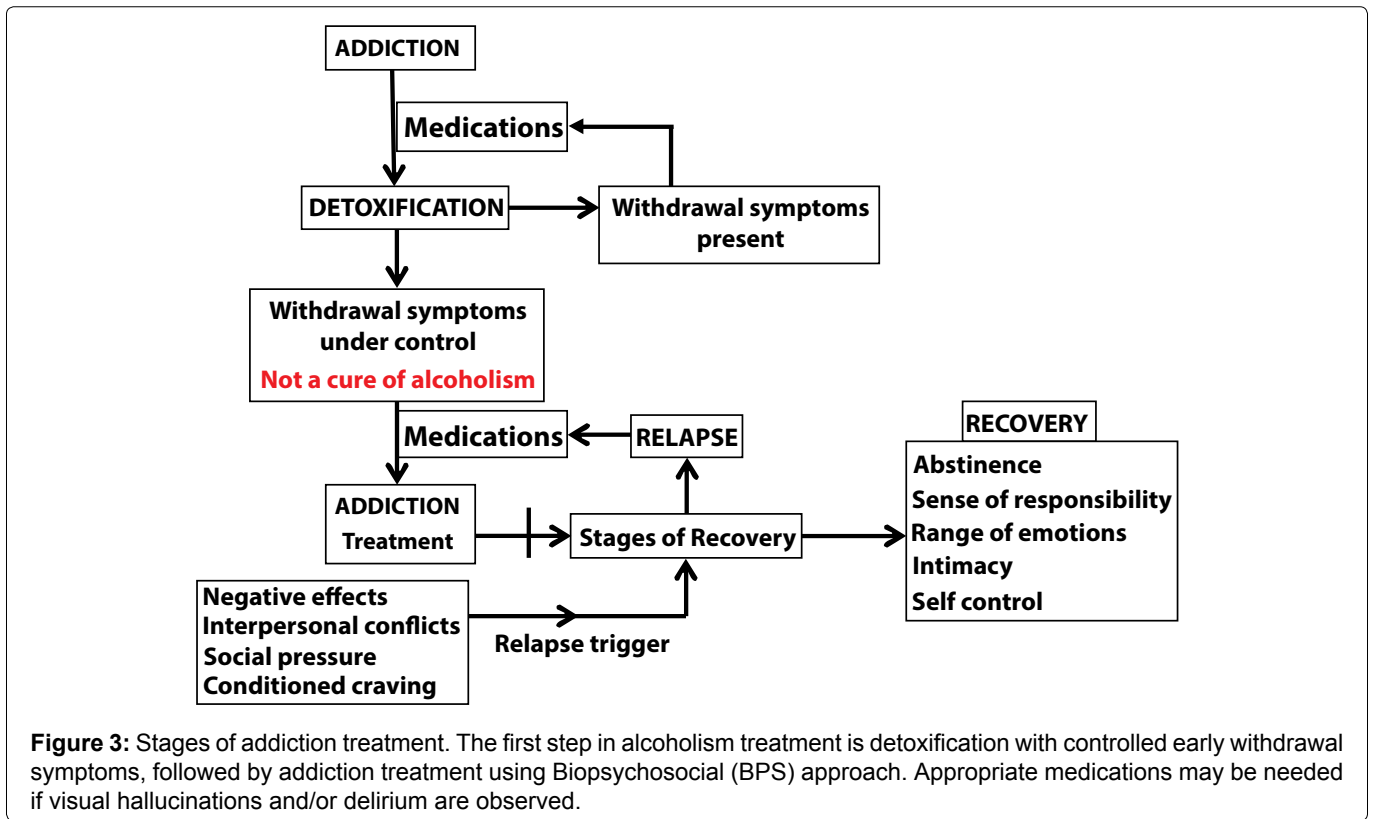

Figure 2: A comprehensive approach for treatment of alcoholism devised by the National Institutes of Drug Abuse and National Institutes of Health.

Figure 3: Stages of addiction treatment. The first step in alcoholism treatment is detoxification with controlled early withdrawal symptoms, followed by addiction treatment using Biopsychosocial (BPS) approach. Appropriate medications may be needed if visual hallucinations and/or delirium are observed.

• According to a National Institute of Alcohol Abuse and Alcoholism report (2015) [12], only about 40% of the 7.9 million people suffering from alcohol dependence seek and/or receive treatment in the United States, possibly because people lack insurance or have limited financial resources, intimidated by the therapeutic agent's side effects and/or need for long-term commitment by the patients.

• Studies have shown that the chances of relapse (alcoholic reinstating alcohol consumption) are extremely high (approximately 54% relapse rate in the United States) in a large proportion of people who are in treatment program or have undergone available treatments [13]. Major precipitating factors for relapse include drug craving and stress, pre-attentive automatic reactions, and attention bias related to previous drug experiences [14-18].

For alcoholism therapy to be entirely successful, these deficiencies must also be addressed.

The overall aim of this review article is to elucidate current and upcoming approaches for treatment of alcoholism and other alcohol-related disorders. In general, alcoholism therapy is a three-step process: (1) Management of the withdrawal symptoms to facilitate abstinence and (2) Pharmacologic and non-pharmacologic treatments of the disease and (3) Prevention of relapse (Figure 3).Withdrawal management is not by itself an addiction treatment, but it is management of the with-

drawal's aversive symptoms so that abstinence can be maintained. Relapse and even death from alcohol overdose may occur if the patients do not successfully transition to treatment and/or support program (Figure 3).

Management of the alcohol withdrawal symptoms

Cessation of alcohol drinking is the first step in treatment of alcoholism and other alcohol related disorders. Unfortunately, in alcoholics, self-detoxification is problematic because abrupt alcohol withdrawal results in rapid onset of symptoms such as agitation, anxiety, fever, tremors, seizures, and in some cases, hallucinations, Delirium tremens (DT) and, if not treated, death [19] (Figure 4).

Alcoholics seek alcohol to get relief from the withdrawal symptoms. Thus, for detoxification, the withdrawal symptoms must be controlled as part of a comprehensive treatment program to increase the likelihood of successfully altering their drinking behavior [20]. Prior to deciding a treatment strategy, the severity of the withdrawal symptom is assessed using one of the assessment-protocols such as the Clinical Institute Withdrawal Assessment, CIWA-Ar [21]. Patients with CIWA-Ar score less than 8 (in some cases less than 15 in the absence of any co-morbidity such as psychiatric, cognitive or poly substance use problems) could successfully complete detoxification in an outpatient setting with managed supportive therapy and some pharmacological intervention [22]. Patents with CIWA-Ar score greater
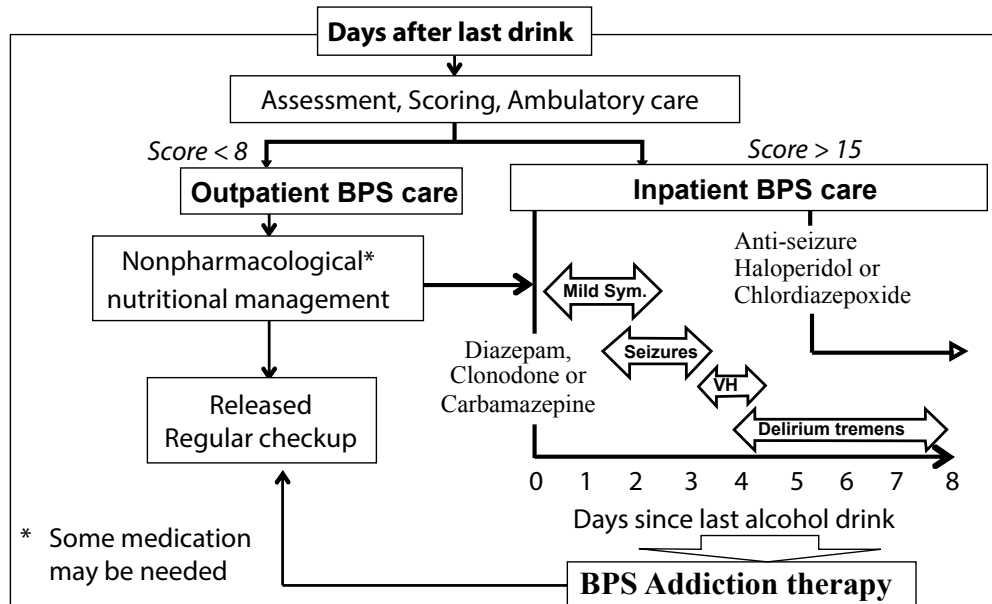
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Figure 4: Time-course of the evolution of alcohol withdrawal symptoms and treatment strategies (BPS: Biopsychosocial approach, VH: Visual hallucinations). If withdrawal severity score < 8 (or, in some cases, < 15 without any seizures, hallucinations, delirium and/or comorbidity), patient may receive non-pharmacological (medication may be given if necessary) and nutritional treatments as outpatient. If the severity score is > 15, a comprehensive inpatient treatment may be needed. If treatment is not received in time, the patient may exhibit a clinical syndrome of acute onset characterized by altered sensorium with disorientation, perceptual abnormalities in the form of illusions and hallucinations and confused or disordered thinking, psychomotor agitation (or retardation) with disturbed sleep-wake cycle.

than 15 (or < 15 with co-morbidity such as recent surgery, psychiatric problems, pregnancy and lack of social support) may require hospitalization for more tests and treatments. In the following sub-sections, various pharmacological and non-pharmacological approaches of withdrawal management will be discussed.

Pharmacological management of alcohol withdrawal symptoms: Pharmacotherapy involves disease treatment with pharmaceuticals that act on a specific target, enzyme or receptor [23]. The interest in pharmacotherapy is growing because of identification of novel neurotransmitter systems that initiate and sustain alcohol drinking, synthesis of neurotransmitter analogues that may alter dependence, use of phyto-pharmacologic agents that reduce alcohol consumption, and medications that have improved the treatment of other addictive disorders, such as nicotine and opioid dependence [24]. The following drugs are approved for managing the withdrawal symptoms:

• *Benzodiazepines*: Benzodiazepines bind to the Gamma-amino-butyric acid $(GABA)_A$ receptors at a site distant from the GABA-binding site and enhance the GABA-induced chlorideinflux [25,26]. Two commonly used benzodiazepines are chlordiazepoxide and diazepamthat, in addition to having anticonvulsant capabilities (diazepam >> chlordiazepoxide), also reduces everity of the withdrawal symptoms. However, its chronic use results in deterioration of cognitive functioning, physical

dependence and tolerance [27-30]. Thus, in benzodiazepine treated patients, the drug-withdrawal may induce withdrawal symptoms that may be resistant to other drugs listed above.

• *Carbamazepine*: Carbamazepine is a GABA receptor agonist and has potency to suppress seizures, neuropathic pain and manic-depressive illness [31]. The drug has also been shown to be efficacious and can be chosen as an alternative to benzodiazepines in treatment of the withdrawal symptoms.

• *Chlormethiazole*: This drug is a positive allosteric modulator at the barbiturate/picrotoxin site at the $GABA_A$ receptor [32]. It effectively treats and/or prevents DTs in alcoholism patients, if given at an early stage.

• *Buspirone, a non-benzodiazepine anxiolytic*: Buspirone may reduce anxiety with less side effects and addiction potential than benzodiazepines [33-36].

• *Adjuvant treatments*: Adjuvants such as atenolol, propranolol and clonidine may be used in conjunction with benzodiazepines in patients with coexisting conditions such as coronary artery disease [19]. Bromocriptine (a dopamine agonist) and chlormethiaxole (a CNS depressant) have also been used in supportive treatment of alcohol withdrawal [36]. Acupuncture can also be used as an adjunctive treatment to the alcohol withdrawal symptoms in combination with other medication

[37,38]. Further investigation of this treatment modality appears to be warranted.

Application of herbal remedies in withdrawal management: There have been promising results from different research groups studying the therapeutic effects of plant extracts on the withdrawal symptoms.

- *Passiflora incarnata* Linneaus and a tri-substituted Benzoflavone moiety (BZF) isolated from the extract may counter the dependence produced by benzodiazepine or other addiction-prone substances like morphine, nicotine, and alcohol [39-42].

- Poyares, et al. [43] showed that valerian, a naturally occurring root, decreased WASO (wake time after sleep onset) with the mild anxiolytic effect in patients experiencing withdrawal symptoms in response benzodiazepine withdrawal after receiving 2-week of treatment.

- The aqueous extract of kudzu root or purified puerarin, in addition to suppressing alcohol intake, also suppressed the severity of alcohol withdrawal symptoms [44-46]. More clinical studies are warranted to identify the active ingredients and decipher the underlying mechanisms for the beneficial effects of herbal extracts in humans.

Management of addiction and relapse

As discussed earlier [47], a journey from responsible alcohol drinking to alcoholism involves the following stages: (i) Positive (pleasure seeking) and negative (pain avoidance) reinforcements, (ii) Tolerance, (iii) Physical addiction or alcoholism and (iv) Physical signs of withdrawal from alcohol abstinence [48,49]. Although substantial evidence support that the brain genomic, metabolic, cellular, and molecular processes play a critical role in the development of alcoholism and other alcohol-related disorders, an integrated and unified mechanism has not been established, thus hindering development of effective and safe therapeutic approaches. As discussed earlier, alcoholism is a multifaceted disease with complex biological, psychological and social interactions (Figure 1), thus requiring a multifaceted treatment approaches. In following sub-sections, current upcoming strategies for treatment of alcoholism and prevention of relapse have been discussed.

Non-pharmacological psychosocial management of alcoholism: Psychosocial approaches are based on an interrelation of social factors with individual thought and behavior including a patient's mental, emotional, social, and spiritual health. As shown in Figure 1, an interaction between the genetic and environment factors plays a critical role in the development of alcoholism in people abusing alcohol. Pharmacotherapy, Pharmacogenetics, pharmacogenomics and gene therapies (discussed in section 3.2) may address the only the biological abnormalities, not the psychological, social and economic issues. In the following sub-sections, psychosocial and behavioral approaches have been discussed.

- *Involvement of a social worker*: Abnormal alcohol consumption and alcoholism management can have adverse social and economic consequences on the individual, his family and society as a whole in terms of resources required for criminal justice, health care and other social institutions. A social worker, not the clinic or hospital, many assist the patients and the family to deal with social and/or economic issues.

- *Biopsychosocial (BPS) Therapy/Interventions*: The 'Bio' part of BSP therapy involves pharmacotherapy and gene therapy that are discussed later. The Psychosocial therapy deals with an individual's psychological development in and interaction with their social environment. The therapy includes structured counseling, motivational enhancement, care coordination, psychotherapy, and relapse prevention. To improve the patient's motivation to change, he/she is subjected to (i) Brief motivational intervention (BMI) and (ii) Motivational interviewing (MI) [50]. MI improves motivation to change, self-efficacy, and social support for abstinence. BMI, via 1 to 4 short sessions (10- to 60-minute), provides information and advice on the negative consequences of alcohol abuse with the goal to reduce alcohol intake rather than abstinence [51].

The Cognitive behavioral therapy (CBT) improves the patients' cognitive and behavioral skills for changing their drinking behavior. In general, CBT is based on a model developed by [52] of relapse prevention, and often includes the following strategies: (1) Identifying triggers for relapse (intrapersonal and interpersonal), (2) Coping-skills training, (3) Refusal skills training, (4) Functional analysis of substance use, and (5) Fostering non-use-related activities [53].

Although mechanisms for regulation of alcohol drinking is not fully understood, [54] have proposed key roles of (1) Dorsal prefrontal cortex (dlPFC) that sends a STOP alcohol drinking signal to VS, (2) Medial orbitofrontal cortex (mOFC) that sends GO drink alcohol signal to VS, and (3) Ventral striatum (VS) that integrates the dlPFC and mOFC and regulates incentive motivation for alcohol seeking behavior. In healthy subjects, dlPFC is more active than mOFC, thus social alcohol drinking activates dlPFC, but not mOFC, and sends an inhibitory signal to the VS and ensuing incentive motivation to consume alcohol (Figure 5i). This reduces alcohol drinking. In patients during the early phase of alcoholism re-
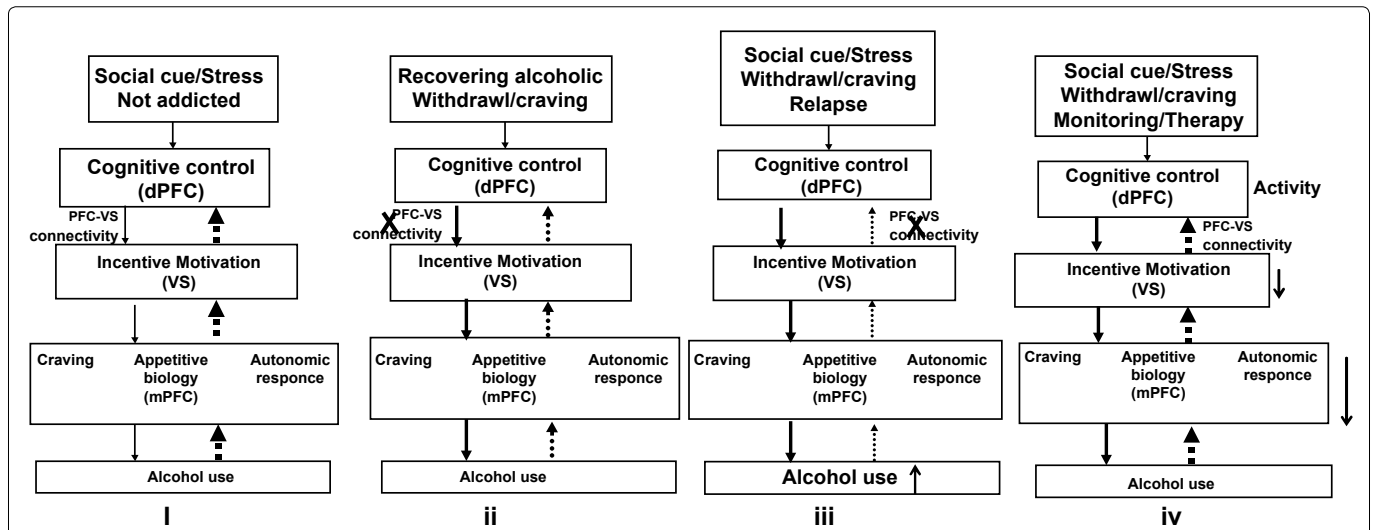
Figure 5: A simplified sketch showing possible roles of dPFC, medial OFC (mOFC) and Ventral striatum (VS) areas of the brain in regulation of craving and alcohol drinking in non-addicts and addicted subjects. In non-addicted person, a social cue and/or stress initiates alcohol drinking that activate sdPFC and suppresses mOFC, thus signaling VS to suppressing incentive motivation, craving and alcohol drinking (Figure 5). In addicted person, mPEF activity may be greater than Dpef activity that may signal VS to enhance incentive motivation, resulting in an increase in craving (Figure 5). If alcohol is available, person will begin drinking to transiently suppress the craving and restores the inhibitory state, indicating the beginning of 'relapse'. When patients receiving behavioral therapy that restores dlPFC-VS-mOFC balance, the inhibitory balance is restored associated with suppressed incentive motivation, craving and alcohol drinking (Figure 5).

covery, mOFC is more active then dlPFC, and sends a positive signal to VS, resulting in an increase in craving and incentive to consume alcohol (Figure 5ii). Alcohol consumption transiently activates dlPFC that suppress the withdrawal symptoms, beginning of the 'relapse' process (Figure 5iii). The behavioral/motivational exercises that activate dPFC and restores the dlPFC-VS cross-talk may suppress craving and incentive motivation to drink alcohol, thus preventing relapse (Figure 5iv).

Pharmacological management of alcohol addiction: Table 1 lists the currently approved and experimental therapeutic agents at various stages of development. At present, disulfiram, topiramate, naltrexone and acamprosate, alone or in combination, are commonly used to treat alcoholism [55,56], although studies have shown variability in their efficacy. [57,58] conducted a multi-state project sponsored by the NIAAA, to evaluate the efficacy of naltrexone, acamprosate, or both, with or without additional non-pharmacological treatment of alcoholism. They reported that patients receiving medical management with naltrexone, behavioral therapy, or both fared better on drinking outcomes, while acamprosate was ineffective. Therefore, more research is needed to evaluate the efficacy of drug combination in alcoholism pharmacotherapy. [59,60] provided clinical and experimental evidence that Varenicline, a partial agonist of nicotinic Acetylcholine receptor (nAChR), reduced self-reported alcohol reactivity, decreased alcohol self-administration and modulated DA mediated activities. This suggests that nAChRs play an important role

in the behavioral effects of alcohol. [61] suggest that endocannabinoids acting at Cannabinoid receptor 1 (CB1) contribute to ethanol preference and caused an age-dependent decline in the appetite for both ethanol and food by decreasing coupling of CB1 to G proteins in the limbic forebrain by mechanisms other than altered receptor or G protein levels. Voronin, et al. (2008) [62] showed that aripiprazole reduced the amount of drinking (reducing drinks per day and increasing days abstinent) during a natural observation period. However, some of these studies are experimental and require more studies.

Herbal therapy of alcoholism: Although pharmaceuticals are commonly used for treatment of alcoholism and other alcohol-related disorders, they have limited efficacy and, in some cases, severe side effects. This limitation has led to an exploration of complementary treatment approaches such as traditional herbal medicines that is relatively new to western medicine, but used extensively in traditional therapies in China, India, Egypt and other countries [63]. As summarized in Table 2, crude extracts and/or purified ingredients from St. John's wort, ibogaine, kudzu root and other plants suppressed alcohol intake and severity of the withdrawal symptoms in animal models of excessive drinking. Although the mechanisms of action of these compounds on alcohol intake are not fully understood, these compounds may exert their effects by modulating several neuronal systems implicated in drinking behavior. Their role in the future of pharmacotherapy for alcoholism will depend upon the outcome of carefully conducted clinical trials.

Table 1: Properties and efficacy of commonly used and upcoming anti-addiction drugs.

NT system	Existing and potential pharmacotherapies	References
Dopamine system • Normalization of DA$_{ergic}$ response • Alcohol drinking • Adjuvant treatment for the Withdrawal symptoms (WS)	Dopamine receptor partial agonists • *Aripiprazole - D$_2$ receptor partial agonists* • *Bromocriptine* - WS adjuvant therapy	Brunetti, et al. Kenna, et al. Williams and McBride [147-150].
	Dopamine receptor antagonists • *GSK 598809 - D$_3$ receptor antagonists*	Te Beek, et al. [151].
GABA system • Prevents relapse • Suppresses the WS	GABA receptor modulators • *Gabapentin - GABA$_B$ receptor modulator* • *Benzodiazepines*	Karam-Hage and Brower, Holbrook, et al. [152,153].
5-HT systems • Decrease in craving and drinking	Selective serotonin uptake inhibitor • *Fluoxetine, Sertraline,* Citalopram • 5-HT antagonist *ondansetron*	Naranjo, et al. Gerra, Babor and Caetano, Dundon, et al. Johnson [154-159].
Brain stress system • Stress management • Manage alcohol drinking • Prevents relapse • Reduce alcohol drinking • Adjuvants for the WS	CRF-related targets • *Antalarmin, pexacerfont - CRF receptor antagonists*	Hwa, et al. Zorrilla, et al. [160,161].
	Non-CRF-related targets • *Prazosin* - α1 Adrenergic receptor antagonist • *Naltrexone/β-Funaltrexamine* - μ opioid receptor antagonists • *Norbinaltorphimine* - κ opioid receptor antagonist • *Naltrindole* - opioid receptor antagonist • *Nalmefen* - μ and δ opioid receptor antagonist	Rasmussen, et al. Volpicelli, et al. Kranzler, et al. Matsuzawa, et al. Krishnan-Sarin, et al. Froehlich, et al. [162-168].
	• Neuropeptide Y receptor agonist • (*Leu^{31}Pro^{34} NPY*) • Substance P receptor antagonist • *L-760735*	Brothers and Wahlestedt, Haddjeri and Blier [169,170].
Glutamate system • Increases duration of • Abstinence • Reduces drinking and facilitates • Abstinence • Alcohol dependence and • Drinking	Glutamate receptor agonists and antagonists • *Acamprosate - N*-methyl-D-aspartate (NMDA) receptor partial agonist • *Topiramate* - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist • *3-[(2-methyl-1,3-thiazol-4-yl) ethynyl] pyridine (MTEP)*mGluR5 antagonist.	Kranzler and Gage, Kranzler, et al. Johnson, et al. Johnson, Weiss and Porrino, Blednov and Harris [34,171-176].
Stress management and alcohol craving	• LY-379,268 - mGluR2 and mGluR3 agonist • (1S,2R,5R,6R)-2-amino-4-oxabicyclo[3.1.0]hexane-2,6-dicarboxylic acid	Zhao and Wu [177].
Antipsychotic activity	Aripiorazole	Wang, et al. [61].

Pharmacogenetics, Pharmacogenomics and Genomic Therapy of Alcoholism

Investigating the role of genetics in predicting treatment outcomes is one of the promising areas of research, since a genetic basis for alcoholism (heritability rate, 50 to 60%) is well established in the literature [64-66]. With the completion of the Human Genome Project and rapidly falling costs of genetic analysis, genetics is providing a better understanding of diseases including alcoholism. With increased understanding of disease etiology comes greater potential to match patients with treatments. In general, three gene-based treatment strategies are developing: pharmacogenetics that involves development of

Table 2: Anti-addiction effects of herbal preparations.

Herb	Mechanisms	Effects	References
St John's Wort Hypericin Quercetin, rutin	Decreased 5-HT and GABA reuptake Decreased DA degradation Synergist to OPR, DA receptor agonist	Decrease in alcohol intake and craving	De Vry, et al. Panocka, et al. Perfumi, et al. Rezvani, et al. [178-182].
Kudzu root Puerarin, diadzein	Decreased 5-HT and DA degradation BZD-GABA$_A$ synergist 5-HT$_{2c}$ and GABA$_A$ agonist	Decrease in alcohol intake, craving and withdrawal symptom Increase in alcohol degradation Anxiolytic	Benlhabib, et al. Overstreet, et al. Keung, et al. Heyman, et al. [44-46,183,184].
Tabernanthe iboga Ibogaine (toxic) 18-methoxycoro Naridine (non toxic)	Decreased DA$_{ergic}$, DA levels, κ-OPR signaling, DA release NMDA mediated GABA release	Decrease in craving and alcohol drinking	Rezvani, et al. Sweetnam, et al. Sershen, et al. Leal and de Gusmao [185-189].
Ginseng Ginsenosides	Not understood	Decrease in alcohol toxicity	Harun, et al. [190].
Kava (*Piper methysticum Forst*)	Decrease in NE and DA reuptake, and Glu release	Decrease in stress and brain DA levels	Steiner, Cairney, et al. Baum, et al. [191-193].
Voacanga africana	Increase in GABA$_{ergic}$ activity	Decrease in craving and withdrawal symptoms	Kombian, et al. [194].
Ashwagandha *Withania* A	Decrease in GABA binding to GABA$_A$ receptor and Ca^{2+} channels.	Decrease in craving	Kulkarni and Ninan 1997 Andrade, et al. Sudhir, et al. [195-197].
Salvia miltiorrhiza Tanshinones I, II Miltrone	BZD-GABA$_A$ synergist Increase in DA release	Decrease in alcohol intake	Colombo, et al. Imanshahidi and Hosseinzadeh [198,199].

pharmaceuticals that selectively target people with certain gene alleles, pharmacogenomics that considers the entire genome to select appropriate pharmaceuticals, and gene therapy that involves direct manipulation of selected genes to achieve desired therapeutic effects.

Pharmacogenetics

Although pharmacotherapy is commonly used to treat alcoholism, currently available drugs have modest efficacy, high individual variability in treatment outcomes, and severe side effects listed below [67,68] limit positive outcomes of the treatments.

- Benzodiazepines themselves are addictive and generate severe withdrawal symptoms similar to alcohol addiction.

- Carbamazepine has a rather narrow therapeutic window, warranting the need to monitor serum levels, and its hepatotoxic effects.

- Naloxone may potentiate the acute withdrawal syndrome and cause catecholamine release, ensuing pulmonary edema and cardiac arrhythmias.

- The side effects of topiramate include anxiety, ataxia, confusion, diarrhea, diplopia, dizziness, drowsiness, dysphasia, fatigue, etc.

Thus, the pharmaceuticals currently being used may be poorly tolerated, especially when used for relatively longer term. The high variability may be due to a close association between the genetic makeup of the brain and the susceptibility to different pharmacotherapeutic agents. For example, the effectiveness of naltrexone treatment was determined by the patients having *OPRM1*-Asp 40 heterozygous OPRM1-Asn 40 homozygous proteins [58]. The frequency of the homozygous and SNP alleles differs considerably in different societies, so is their response to naltrexone (Figure 6) [69].

However, the experimental studies and clinical trials have yielded variable results regarding association between naltrexone and OPRM1 (A118G polymorph, Asp 40 protein substation) since a positive association [70-78] and lack of association [79-84] have both been reported between naltrexone and OPRM1-Asp 40. In addition to OPRM1, other pharmacogenetic targets that may differentially respond to therapeutic drugsare OPRK1 (G36T and C843T), OPRD1 (G8T (Cys27Phe)), GRIK1 (C > A) and SLC6A4 5), polymorphisms in alcohol metabolism, the 'reward pathway' (5HT, DA, GABA, Glu and β endorphin) and the behavioral stress response system (CRF and NPY).
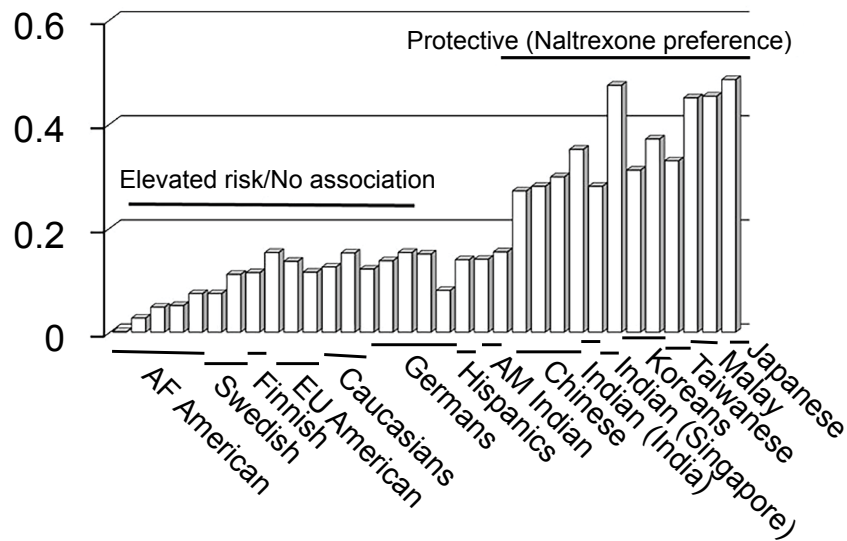
A key advantage of pharmacogenetic approach is

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Figure 6: Distribution of the Asp40 heterozygous OPMR1 in different human populations (AF: Africans, AM: Americans, EU: Europeans).
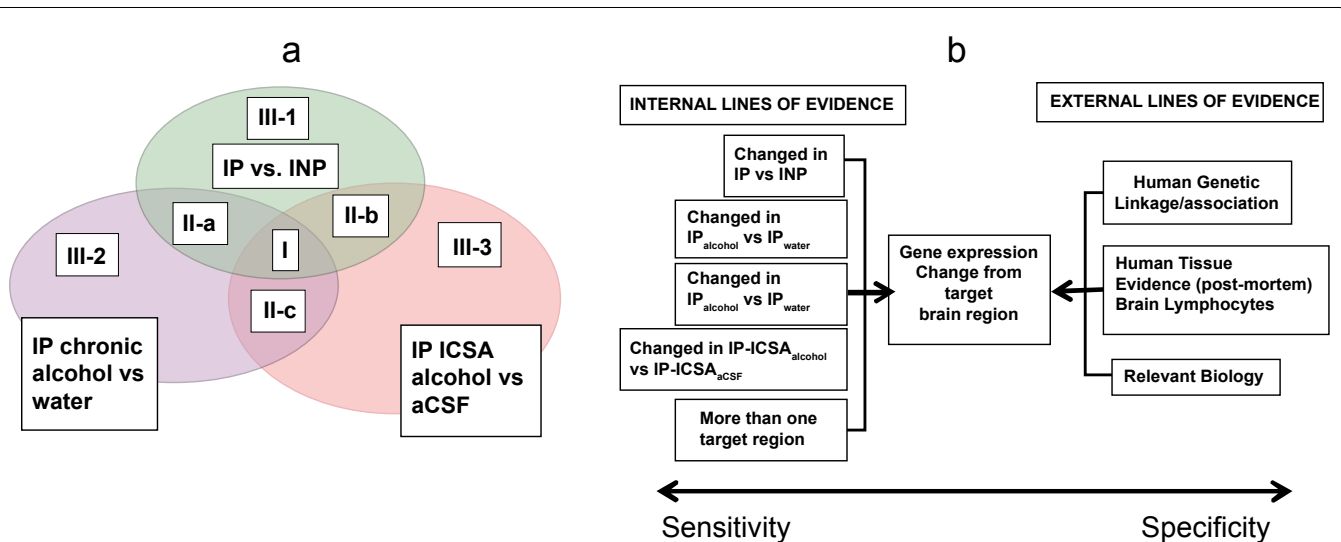

Figure 7: (a) Experimental strategy to study Convergent functional genomics (CFG) in Alcohol preferring (IP) and Alcohol non-preferring (INP) rats self-administering ethanol [68]. The three experimental paradigms (1, 2 and 3, described in text) are shown in green, purple and red colors. 'I' represents genes that changed in all three paradigms. 'II' represents genes that changed intwo of the three paradigms (II-a: changed in both 1 and 2, II-b: changed in both 1 and 3, and II-c: changed in 2 and 3). 'III' represents genes that changed only in one paradigm; (b) Contribution of internal and external evidences in CFG.

possible development of a personalized therapy that may provide better outcome [9,85]. Following are some of the genetic approaches currently being tested:

1. Naltrexone is more effective in patients possessing a polymorphic OPMR1 of the μ-opioid receptor gene than in patients lacking the polymorph [58,74,86].

2. Karpyak, et al. [87] have shown that patients containing single nucleotide polymorphism of GATA-binding protein 4 (GATA4) experiences very few relapses when treated with acamprosate [87].

3. 5-HTTLPR, a polymorph of the serotonin transporter (5-HTT) gene modulate the severity of alcohol consumption and predict a therapeutic response to the 5-HT(3) receptor antagonist, ondansetron. Individuals with this specific genotype had a higher percentage of abstinent days than all other genotype and treatment groups [88-90].

4. Enoch, et al. [91] have shown additive effects of a functional *HTR3B* rs1176744 SNP and the 5-HTTL-PR polymorphism on alcohol and drug dependence. The genotype combinations of *HTR3B* variants and
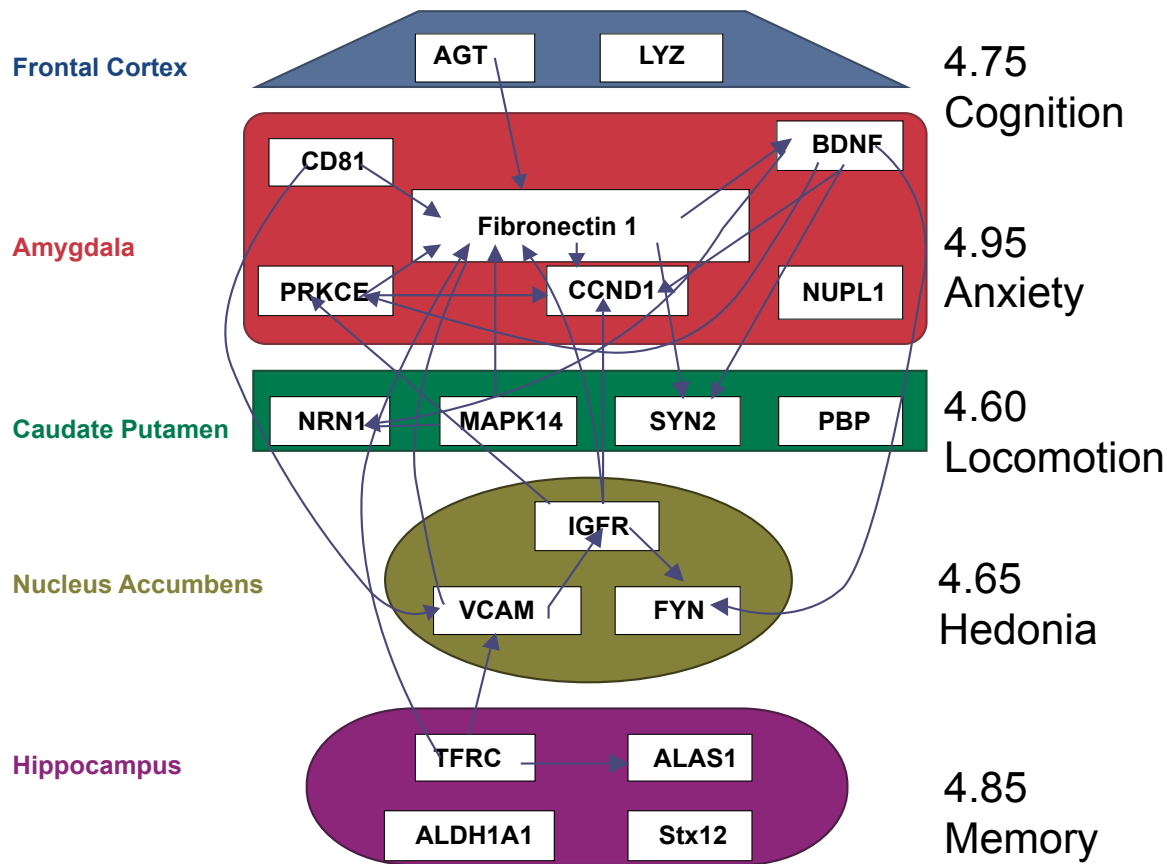
Figure 8: The interacting pathways in different brain regions deciphered by [90]. Out of top 20 differentially expressed genes, 14 interacted in a network with Fibronectin 1 core. The details are discussed in the text.

the 5-HTTLPR polymorphism may identify subgroups of alcoholics with varying response to ondansetron [92,93].

5. Franklin, et al. [94] proposed that the purinergic receptor P2X4R that binds adenine nucleotides [95] represents a novel target for drug development to prevent and/or treat alcoholism and other alcohol-related disorders. They hypothesized that there is an inverse relationship between P2X4R activity and ethanol consumption. Ivermectin, a positive modulator of P2X4Rs, antagonized ethanol-mediated inhibition of P2X4Rs *in vitro* and reduced ethanol intake in rodents.

Research is in progress to screen more pharmacotherapeutic alleles that can potentially be used to treat alcoholism.

Pharmacogenomics

Pharmacogenomics examines overall inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict an individual's response to a drug [96]. Translation of the inherited variations in a gene gives rise to different proteins that may be functionally different. An alcoholic individual may possess different proportions of the gene alleles and

exhibit different sensitivity to a particular pharmacotherapy. An example of this is the genes encoding Alcohol dehydrogenase (ADH) for which variations in the gene sequences leads to the expression of different enzyme isoforms such as ADH1B, ADH1A, ADH1C and ADH4. People having different proportions of these isoenzymes may exhibit different degree of alcohol metabolism and alcoholism susceptibility [97,98].

Earlier Rodd, et al. [99] applied a Convergent functional genomics (CFG) approach to elucidate the genomics of alcoholism-related disorders. The three paradigms used were: (1) Innate neurological differences in basal gene expression in two rat-lines (IP and INP) selected for divergent propensity to consume alcohol, (2) The genetic alterations produced by chronic alcohol consumption in IP rats, and (3) Changes in gene expression following Intracranial self-administration (ICSA) of alcohol into the posterior VTA that should primarily be the result of the reinforcing actions of alcohol in this region (Figure 7). Based on the patterns of change, genes were labeled in three categories shown in Figure 7. Rodd, et al. [99] showed that, out of top 20 differentially expressed genes, 14 interacted in a network with FN1 core that interacted with the following networks (Figure 8):

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Table 3: Top candidate genes in our data sets that encode targets of existing pharmacological agents (Ingenuity analysis) from [87].

Symbol - description	Brain region (Paradigm) fold-change/P-value		Family	Drug group
ALDH1A1 AF001898	PFC(1)1.34/0.00211 HIP(1)1.22/0.02931	CP(2)1.21/0.028 HIP(3)1.39/0.00103	Enzyme	1
PPP3CA D90035	PFC(3)1.29/0.00282 AMY(3)1.26/0.01712 NAC(1)-1.11/0.0311	AMY(1)1.23/0.02995 CP(3)1.17/0.01792	Phosphatase	2
SCN1A M22253	PFC(1)1.46/0.01392 NAC(1)1.78/0.00133 CP(3)1.17/0.0254	AMY(1)1.69/0.03608 CP(2)-1.25/0.00874 HIP(1)1.44/0.01154	Ion channel	3
NR3C1 M14053	PFC(2)1.47/0.0497 HIP(1)-1.22/0.04664	AMY(1)1.37/0.018	Ligand-dependent nuclear receptor	4
CHRM3 M16407	AMY(1)1.24/0.0131	HIP(3)-1.18/0.03711	G-protein coupled receptor	5
ALDH2 AI172017	AMY(2)1.13/0.03773	NAC(1)1.19/0.03525	Enzyme	1
THRA M31174	AMY(3)1.23/0.04192 HIP(3)1.27/0.01358	CP(1)1.63/0.01932	Ligand-dependent nuclear receptor	6
GABRA1 L08490	AMY(3)1.40/0.02694		Ion channel	7
LPL AI237731	CP(1)-1.58/0.04801 HIP(1)1.32/0.02446	NAC(3)-1.81/0.02148	Enzyme	8
GABRB1 NM_012956	CP(1)-2.65/0.02562	HIP(1)1.57/0.00735	Ion channel	7
GABRD M35162	CP(1)-2.11/0.0258 HIP(2)-1.14/0.01673	CP(1)-1.72/0.03088	Ion channel	7

Abbreviations: ALDH1A1**:** Aldehyde dehydrogenase family 1, member A1; PPP3CA: Protein phosphatase 3; SCN1A: Catalytic subunit, alpha isoform, sodium channel, voltage-gated, type 1, alpha polypeptide; NR3C1: Nuclear receptor subfamily 3, group C, member 1; CHRM3: Cholinergic receptor, muscarinic 3; ALDH2: Aldehyde dehydrogenase 2; THRA: Thyroid hormone receptor alpha; GABRA1: Gamma-aminobutyric acid receptor, subunit beta 1; LPL: Lipoprotein lipase; GABRB1: Gamma-aminobutyric acid receptor, subunit beta 1; GABRD: Gamma-aminobutyric acid A receptor, delta.

Target-associated pharmacological agents: 1: Disulfiram, 2: Cyclosporine, Fk506, 3: Lamatrogine, lidocaine, phenytoin, prilocaine, procaine, ropivacaine, zonisamide, 4: Beclomethasone dipropionate, betamethasone, dexamethasone/tobramycin, fluticasone, fluticasone/salmeterol, methylprednisolone, mometasone furoate, prednisolone, prednisone, triamcinolone acetonide, 5: Ipratropium, olanzapine, tolterodine, 6: Amiodarone, thyroxine, 7: Clonazepam, diazepam, fioricet, lorazepam, muscimol, olanzapine, sevoflurane, temazepan, zaleplon, zolpidem, 8: Gemfibrozil, nicotinic acid.

- *cell adhesion and signaling* - VCAM1 in nucleus accumbens [100] and CD81 in amygdale [101],

- *iron-heme metabolism* - TFRC [102] and ALAS1 [103] in hippocampus,

- *cardiovascular regulation* - AGT in frontal cortex [104] and PRKCE in amygdala [105],

- *cell proliferation and differentiation*-insulin-like growth factor 1 receptor - IGF1R [106] BDNF [107], CCND1 [108], FYN [109] and MAPK14 [110] in different brain regions, and

- *synaptic transmission and neurite outgrowth* - SYN2 [111] and NRN1 [112] in caudate putamen.

Some of the candidate genes in the data sets encode for proteins that are modulated by existing pharmacological agents (Table 3), which may potentially be applicable in alcoholism therapy.

Gene transfer therapy of alcoholism

As discussed above, pharmacogenomics therapy is based on how variations in the human genome affect the response to medications. However, the genomic therapy involves direct modulation (activation or suppression) of a gene to achieve desired therapeutic effects. Recombinant viral vectors (Adenoviruses (AdV), Adeno-associated viruses (AAV), and retroviruses including the leukemia virus and the human immunodeficiency virus) containing the gene of interest are administered to deliver genes for increasing protein expression. Conversely, antisense oligo nucleotides are used to block or destroy the mRNA, thus reducing the protein expression. The 3rd generation viral vectors allow the expression of the therapeutic gene for periods exceeding 1 year [113,114]. Earlier studies [115-119], using AAV or AdV vectors, have shown increased expression of the target genes in the brain reward centers such as the Ventral segmental
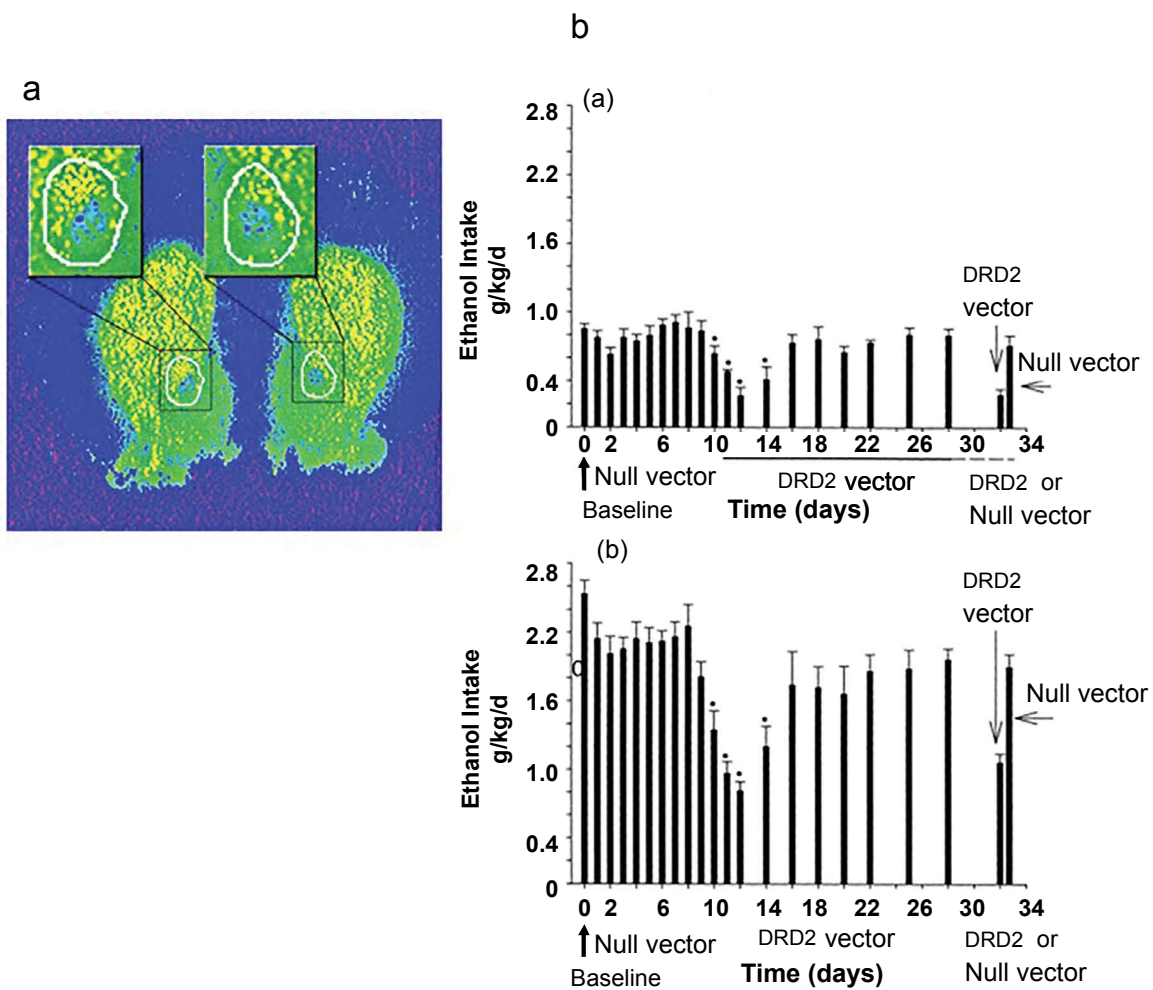
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Figure 9: *Left* - Increased expression of DRD2 in left nucleus accumbens directly administered the DRD2 vector. Right - Ethanol self-administration in alcohol preferring (a) and non-preferring (b) rats administered a null vector followed by a DRD2 vector that gradually decreased ethanol administration for up to 12 days, then ethanol drinking increased gradually as the brain DRD2 expression return to the baseline. A second DRD2 vector administration, but not Null vector administrator again decreased ethanol drinking.
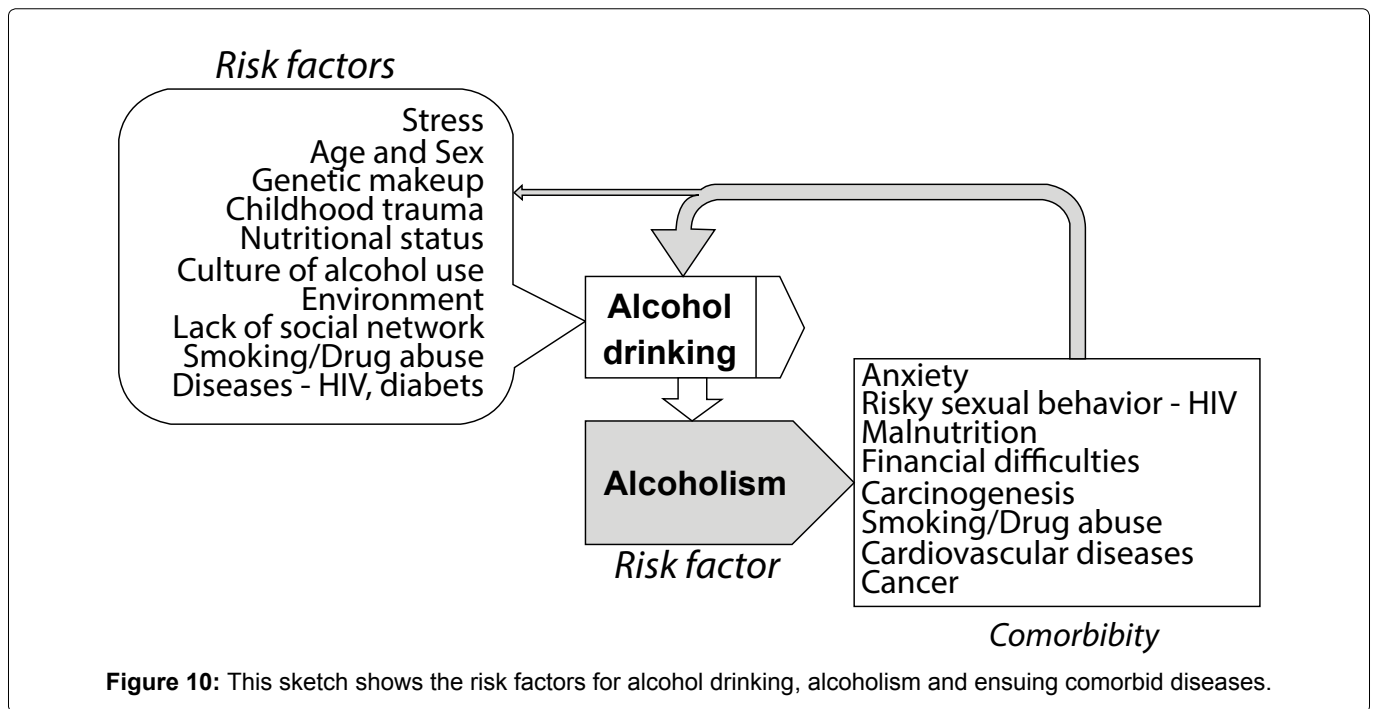
area (VTA), Nucleus accumbens (NuA), and other corticolimbic structures, including the extended amygdala. [120,121] have described an AdV gene delivery vector that addresses the role of oxidants in alcohol-induced liver injury. [122-124] used antisense phosphorothioate oligonucleotides to inhibit TNF α synthesis in Kupffer cells and Aldehyde dehydrogenase (ALDH2) and ethanol consumption in rodents [125] showed that an antisense oligonucleotide directed against a GGGA motif in rat mitochondrial ALDH2 markedly inhibited the synthesis of this enzyme, leading to a significant increase in acetaldehyde levels and decreases in alcohol consumption by rats.

Rivera-Meza, et al. [126] administered an adenoviral vector (AdV-ADH/asALDH2) encoding both a fast rat ADH and an antisense RNA against rat ALDH2 in rats and showed a 176% increase in liver ADH activity and 24% decrease in liver ALDH2 activity in control rats. Upon ethanol administration, their arterial acetaldehyde

levels were 400% higher than those of animals Administered control vector (AdV-C) with 60% reduction in their voluntary ethanol intake versus controls. Thus, the simultaneous increase of liver ADH and a reduction of ALDH activity by gene transfer could constitute a potential therapeutic strategy for the treatment of alcoholism.

Thanos, et al. [127] administered an AdV-dopamine D2 receptor (DRD2) gene vector into the Nucleus accumbens (NAc) of rats previously trained to self-administer alcohol, and assessed if DRD2 levels regulated alcohol intake in preferring (Figure 9a) and non-preferring (Figure 9b) rats.

They showed that a 52% increase in NAc DRD2 caused 43% reduction in alcohol preference (43%), and 64% reduction in alcohol intake of ethanol preferring/non-preferring rats, which recovered as the DRD2 returned to baseline levels. This was the first evidence that over expression of DRD2 reduces alcohol intake and

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Figure 10: This sketch shows the risk factors for alcohol drinking, alcoholism and ensuing comorbid diseases.

suggests that high levels of DRD2 may be protective against alcohol abuse. Later [128], showed that animals receiving bilateral microinjections of a viral vector producing 5-HT$_{1B}$ over expression (HA1B/GFP) in nucleus accumbens consumed twice as much ethanol as the control groups, possibly because increased 5-HT$_{1B}$ expression led to either greater reward or reduced aversive effects. [129,130], by administering a null vector or a genetically modified adenoviral vector containing the rat D2R cDNA into the NAc of wild-type (*Drd2+/+)*, heterozygous (*Drd2 +/−)*, and receptor-deficient mice *(Drd2−/−)* mice showed significant decrease in ethanol intake by *Drd2+/+* and *Drd2+/−* animals, but increase in ethanol intake in *Drd2−/−* animals. Ethanol intake and preference were then determined using the two-bottle choice paradigm. These observations provide proof of concept that gene manipulation can be a novel means to treat alcohol-related disorders, provided the functional genomics of the disorders are fully understood. With respect to alcohol and health outcomes, the strong association between alcohol drinking and smoking is often important because smoking has important relations to many medical conditions.

Risk Factors and Comorbidity

Risk factor is a factor that increases a person's chances of developing a disease, while comorbidity is presence of two or more illnesses, simultaneously or sequentially, in the same person. Figure 10 shows the risk factors for alcohol drinking and alcoholism and ensuing co morbid diseases.

Some of the key risk factors are dietary habits and nu-

tritional deficiency [131], habitual smoking [132] cancer risk [133-135], cardiovascular diseases, liver diseases, etc. [136,137]. Some other risk factors are discussed below:

- *Stress and Circadian Rhythms:* Studies have shown that acute and chronic stress plays an important role in the motivation to abuse addictive substances including alcohol [15,138,139]. Conversely, alcohol drinking both reduces negative affect and increase positive effect, thereby reinforcing an effective, albeit maladaptive, coping strategy [138]. Stress management, therefore, is an important component of alcoholism therapy.

- *Sex differences:* Given the same amount of alcohol consumed, men and women can have differing morbidity and mortality from alcohol-related chronic disease and conditions, possibly because of pharmacokinetic and hormonal differences [140]. Women may attain higher blood alcohol concentrations than men after drinking an equivalent amount of alcohol [141-143].

- *Age differences:* Lazebnik, et al. [144] have suggested that the age of the drinker may determine possible pathology of alcohol-related ischemic heart disease and that differences may exist in the risk of ischemic heart disease in different age groups. However, additional research is needed to assess if age modifies the risk relationships between alcohol and other diseases.

- *Genetic differences:* Previous studies have shown that people carrying the ALDH Lys487 allele are at an elevated risk of cancer and digestive diseases from alcohol consumption [145]. This allele is more prevalent in Asian populations than in America, European or African populations [146].

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Conclusions and Future Research

Currently there are only three medications approved by the U.S. Food and Drug Administration (FDA) for use in the treatment of alcohol abuse and alcoholism: disulfiram (alcohol aversion), naltrexone (opiate inhibitor), and acamprosate (NMDA receptor inhibitor). At present, pharmacotherapy alone or in combination with behavioral approaches is modestly effective in treating alcoholism symptoms in genetically diverse population. Thus, there is substantial room for improvement. Following are some of the important future research issues:

1. Potential use of new drugs such GABAB receptor agonists, cholinergic receptor partial agonists, corticotrophin-releasing factor and cannabinoid CB1 receptor antagonists [61], nociception receptor ligands, and the novel antipsychotic aripiprazole.

2. Further development of Biopsychosocial (BPS) approaches to integrate biological, psychological, social and cultural issues will improve service to the patients. There is an urgent need to develop a comprehensive individual assessment to adequately determine the individual's treatment needs. Successful integration of non viral vectors containing specific gene's cDNA into one's genome will be an important improvement in gene therapy.

3. Although interest in herbal therapy is increasing, there is still a major problem of standardized herbal preparation and treatment protocols. Efforts are needed to improve the bioavailability of the herbs. A new approach is development of nano particle coupled herbs.

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