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基于炎症抑制与肠道菌群控制的酒精性肝损伤治疗和
预防策略

Treatment and Prevention of Alcoholic Liver Disease
Based on Engineered Cells

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1 背景

酒精是多个世纪以来在多种文化中得到广泛使用的具有产生依赖特性的精神活性物质。酒精使用在许多文化中都非常普遍，而酒精的有害使用会导致巨大的疾病、社会和经济负担。世界卫生组织(WHO)《酒精与健康全球状况报告》显示，全世界每年因有害使用（“有害使用”的定义为，对饮酒者本人、饮酒者周围的人和整个社会造成损害健康和社会后果的饮酒行为，以及使有害健康后果风险增加的饮酒模式。(Organization 2014)）酒精导致 300 万例死亡，占有死亡数的 5.3%。我国酒精使用的情况也不容乐观，人均酒精消耗量逐年上升，酒精所致的健康问题也日趋严重。(World Health Organization 2018)

酒精性肝病（包括脂肪肝、肝硬化、肝纤维化，乃至肝癌等）的产生，发病的直接原因是酒精过量摄入造成的肝脏损伤，但究其根本，人群酒精过量摄入背后有多种社会原因。(Fuster and Samet 2018) 当前医疗机构收治酒精性肝病患者数量也在不断增加，所以酒精性肝病患者也已经受到了当前社会的广泛关注。(Baser et al. 2011) 随着酒精性肝病患者对自身疾病的认知程度的不断提高，他们也越来越意识到戒酒的重要性，但是能够引起疾病发生的患者，其自身都有着长期酗酒的习惯，所以往往很难戒掉。事实上，很多人由于特定社会压力不能直接戒酒，其他的患者如存在心理或精神问题的患者，从生理特点上决定了其不能直接戒酒。此外患者往往对酒精分解类药物存在过度乐观的信任，从而导致了患者的报复性饮酒。(Becker 2017)

1 Background

Alcohol is a psychoactive substance with dependence-producing properties that has been widely used in many cultures for centuries. Alcohol use is very common in many cultures, and the harmful use of alcohol can cause huge disease, social and economic burdens. The World Health Organization (WHO) Global Status Report on Alcohol and Health shows that harmful use ("harmful use" is defined as the harm to the health and social consequences of the drinker himself, the people around the drinker, and the society as a whole) every year worldwide Drinking behaviors and drinking patterns that increase the risk of harmful health consequences. (Organization 2014)) Alcohol caused 3 million deaths, accounting for 5.3% of all deaths. The situation of alcohol use in my country is not optimistic. Per capita alcohol consumption is increasing year by year, and the health problems caused by alcohol are becoming more serious. (World Health Organization 2018)

Alcoholic liver disease (including fatty liver, cirrhosis, liver fibrosis, and even liver cancer) is directly caused by liver damage caused by excessive alcohol intake, but at the root, there are many reasons behind the excessive alcohol intake of the

population Social Causes. (Fuster and Samet 2018) At present, the number of patients with alcoholic liver disease admitted to medical institutions is also increasing, so patients with alcoholic liver disease have also received extensive attention from the current society. (Baser et al. 2011) With the continuous improvement of alcoholic liver disease patients' awareness of their own diseases, they have also become more and more aware of the importance of abstinence, but patients who can cause the disease have their own long-term The habit of alcoholism is often difficult to quit. In fact, many people cannot quit drinking directly due to specific social pressures. Other patients, such as those with psychological or mental problems, determine that they cannot quit drinking directly due to their physical characteristics. In addition, patients often have excessively optimistic trust in alcohol-decomposing drugs, which leads to retaliatory drinking. (Becker 2017)

2 我国酒桌文化与压力下的过量饮酒

2.1 酒桌文化的起源和发展

在中国，酒的历史几乎与人的历史一样久远。早在汉字成熟之前，中国人就已经掌握了酿酒技术。很多典籍中都有关于酒和饮酒文化的记载，酒文化深入中国人的血脉深处。酒被赋予了礼仪、社交、休闲等含义，体现了特定的宗法秩序以及人伦关系。许多典籍专门讲酒，如西周的《酒诰》，西汉的《酒赋》《酒箴》，东晋的《酒诫》和初唐的《酒经》《酒谱》等等。可见，酒很早就成了中国文化的重要元素。

酒文化的扩展有一个循序渐进的过程，随着技术进步与经济的发展，慢慢自上而下渗透。统治集团形成的政治性酒文化慢慢向社会各阶层蔓延，影响深远。从最初的政治统治中难以忽视的角色，到普通大众的消费品，酒与酒文化经历了漫长的发展过程，深入到中国人心中。可以说，当代的酒文化是古代政治文化演化过来的，有着政治权力下强制性的阴影。作为世界上最早用酒曲酿酒的国家，喝酒早已成为中国社会中一种难以忽视的社交工具。

2 Drinking culture and excessive drinking under pressure in China

2.1 The origin and development of drinking culture

In China, the history of wine is almost as old as human history. Long before the Chinese characters matured, the Chinese had already mastered the winemaking technique. There are records about wine and drinking culture in many ancient books, and wine culture goes deep into the blood of Chinese people. Liquor is endowed with the meanings of etiquette, social interaction, and leisure, reflecting the specific patriarchal order and human relations. Many classics specialize in wine, such as "Jiu Gao" in the Western Zhou Dynasty, "Jiu Fu" and "Jiu Zhen" in the Western Han Dynasty, "Jiu Jing" in the Eastern Jin Dynasty, and "Jiu Jing" and "Wu Pu" in the early Tang Dynasty. It can be seen that wine has long become an important element of Chinese culture.

The expansion of wine culture has a gradual process. With technological progress and economic development, it slowly penetrates from top to bottom. The political wine culture formed by the ruling group slowly spread to all classes of society, with far-reaching influence. From the role that was difficult to ignore in the initial political rule to the consumer goods of the general public, wine and wine culture have gone through a long process of development and have penetrated into the hearts of Chinese people. It can be said that contemporary wine culture evolved from ancient political culture and has a shadow of compulsion under political power.

As the first country in the world to use koji to make wine, drinking has long become a social tool that cannot be ignored in Chinese society.

2.2 应酬聚会：社会权力下的压力

餐桌与权力到底有何关系?在法国历史学家马克·阿尔贝写的《权力的餐桌》一书中,从古希腊时代的公众宴会,到路易十四的豪华餐桌,直至如今爱丽舍宫的第五共和国晚宴,餐桌的变迁被视为是一个权力控制与驯服的过程——“菜”不仅仅是菜,“吃”也不是个人的事儿,因为在吃的“规矩”和“意义”背后,总有需要达成的目的。对应到我们当下,也可以说,在官员的酒桌上,“酒”也不仅仅是酒,“喝”也不是个人的事。

在权力的酒桌上,喝酒不只是助兴,而是一种考验。事情能不能办,看你喝多少、怎么喝;自己能不能提拔,更要看你喝多少、怎么喝。对于一些人而言,酒量大可能就意味着前途朗朗。有送命之虞的酒桌,固然有传统酒桌文化的催化作用,但在根本上,问题还是源于权力文化的助兴。喝什么酒,如何敬酒,乃至如何挡酒,都是要被精细拿捏分寸的权力文化。这种文化,归根结底不过是一种权力秩序的外延,它构成支撑权力的现实注脚,并以微妙的方式,显示一种权力的在场。

大多数生意上的成功仍然是取决于工作的表现。但嗜酒者在尚未戒酒时或许以为,在生意中取得成功的关键是魅力、机智和乐天派的性格。这些品质无疑有助于饮酒适度的人,但是对嗜酒者来说并非如此,因为后者在饮酒时往往过于强调这些品质的重要性。不过,能喝酒并不是什么值得夸耀的事,相反,喝酒带来的危害比我们认为的要大得多。

根据全球疾病负担研究(2017)的统计,2017年中国饮酒致死人数达到了67.03万人,是1990年的1.82倍,其中有97%是男性。(Jiang et al. 2020)

酒桌上的“权力基因”是酒桌“恶俗”文化的源头。社会不仅需要反思所谓的“酒桌文化”这一表象,更需要在权力约束这一源头上寻找突破口。

2.2 Social gatherings: Pressure under power

What is the relationship between the dining table and power? In the book "The Dining Table of Power" written by French historian Marc Albert, from the public banquet in ancient Greece, to the luxurious dining table of Louis XIV, to the first place in the Elysee Palace. For the dinner of the Five Republics, the change of the table is seen as a process of power control and tame-"dishes" are not just dishes, "eating" is not a personal matter, because behind the "rules" and "meanings" of eating, There is always a purpose that needs to be achieved. Corresponding to our present moment, it can also be said that at the official wine table, "wine" is not just wine, and "drinking" is not a personal matter.

At the wine table of power, drinking is not just a pleasure, but a test. Whether you can handle things depends on how much and how you drink; whether you can be promoted depends on how much and how you drink. For some people, heavy drinking may mean a bright future. A wine table in danger of death certainly has a catalytic effect on the traditional wine table culture, but fundamentally, the problem stems from the power culture. What kind of wine to drink, how to toast, and even how to stop the wine, are all power cultures that have to be fine-tuned. This kind of culture, in the final analysis, is just an extension of the order of power, which constitutes a footnote supporting the reality of power, and in a subtle way, it shows the presence of power.

Most business success still depends on job performance. But when alcoholics have not stopped drinking, they may think that the key to success in business is charm, wit, and optimistic character. These qualities undoubtedly help people who drink in moderation, but not for alcoholics, who tend to overemphasize the importance of these qualities when drinking. However, being able to drink is not something to boast about. On the contrary, the harm caused by drinking is much greater than we think.

According to the Global Burden of Disease Study (2017), the number of deaths caused by drinking in China reached 670,300 in 2017, 1.82 times that of 1990, and 97% of them were men. (Jiang et al. 2020)

The "power gene" on the wine table is the source of the "vulgar" culture on the wine table. Society not only needs to reflect on the appearance of the so-called "drinking table culture", but it also needs to find a breakthrough at the source of power constraints.

2.3 亲友聚会：人情下的压力

酒文化源于政治文化，是封建社会政治统治的道具，后来下移到社会普通大众生活中。这个过程极为漫长，但也影响深刻，最终高度异化了中国人的人际情感。在中国，除了皇家法律系统外，社会与家庭的伦理和礼仪也具有高度的强制性。宗法社会下，每个人在家中、社会上都有自己的位置，以等级来区分，社会上并没有平等的大多数。人与人之间的关系多数是不对等的，所有不对等的关系之间一旦互动，就会产生强制性。家庭伦理、社会伦理都是这样。

劝酒则不一样，劝酒一般都是被动的，有很多是负面的，劝酒的酒不是你自愿在喝，而是别人在强迫你喝。因为你不好意思拒绝，拒绝可能会伤人情，因此有了“宁可伤身体，不可伤感情”一说。喝酒本为助兴，婚丧嫁娶、逢年过节，席上都少不了酒。但在中国，酒桌常常成为展示权力与地位的地方。事实上，谁都清楚喝酒的健康危害，那为什么有人依旧闭眼干到底呢？因为谁都知道不喝的后果。在中国，“不喝就是不给我面子！”对很多人而言，太重了。

2.3 Gathering of relatives and friends: Pressure from human relations

Wine culture originated from political culture and was a prop for feudal society and political rule, and later moved down to the lives of ordinary people. This process is extremely long, but it also has a profound impact, and ultimately highly alienated the Chinese people's interpersonal emotions. In China, in addition to the royal legal system, the ethics and etiquette of society and family are also highly mandatory. In the patriarchal society, everyone has his own place in the family and in society, distinguished by hierarchy, and there is no equal majority in society. The relationships between people are mostly unequal. Once all unequal relationships interact, they will be compulsory. Family ethics and social ethics are like this.

Persuading alcohol is different. Persuading alcohol is generally passive, and many of them are negative. You are not voluntarily drinking the alcohol you persuade, but others are forcing you to drink. Because you are embarrassed to refuse, and refusal may hurt people, so there is the saying "I would rather hurt your body than your feelings". Drinking is originally for fun, weddings, funerals, and holidays, and wine is indispensable at the banquet. But in China, the wine table often becomes a place to show power and status. In fact, everyone knows the health hazards of drinking, so why do some people still close their eyes and dry it? Because everyone knows the consequences of not drinking. In China, "not drinking is not giving me face!" To many people, it is too heavy.

2.4 困境和变局

随着社会的进步，酒桌文化的阴暗面逐渐被更多人重视。通过宣传以及对围绕酒的法律法规（包括贿赂、酒后驾车等）的严格执行，风气有得到一定程度的遏制。

但是我们应该清楚的明白，酒桌文化已经对中国人产生了如此深远的影响，改变不可能是瞬间发生的。这需要更广泛意识觉醒。

专家认为我们认为当前我国限制有害饮酒的工作应该重点从以下几方面入手。一是，加强酒类生产、销售和流通环节的管控，通过企业自律、法规宣贯、家长和学校健康教育限制未成年人的酒类产品的可获得性；二是，在医疗卫生体系中填补限酒/戒酒适宜技术和服务的空白，提供酒精依赖快速筛查、简短戒酒干预等服务；三是，加强酒类广告的限制措施，尽快出台新媒体（如网络、社交媒体）酒类产品营销活动规范；四是，针对酒税问题开展科学研究和评估，定期审查与通货膨胀和收入水平相关的酒类价格。(Jiang et al. 2020)

2.4 Difficulties and changes

With the progress of society, the dark side of wine table culture is gradually being valued by more people. Through publicity and strict enforcement of laws and regulations surrounding alcohol (including bribery, drunk driving, etc.), the atmosphere has been curbed to a certain extent.

But we should clearly understand that the wine table culture has had such a profound impact on the Chinese people, and the change cannot happen instantaneously. This requires a broader consciousness awakening.

Experts believe that we believe that the current work of restricting harmful drinking in my country should focus on the following aspects. One is to strengthen the management and control of alcohol production, sales and circulation, and to restrict the availability of alcoholic products for minors through corporate self-discipline, law publicity, parent and school health education; To limit the gaps in the appropriate technologies and services for alcohol restriction/abstinence, provide services such as rapid alcohol dependence screening, brief alcohol withdrawal interventions, etc.; third, strengthen restrictions on alcohol advertising and introduce new media (such as the Internet, social media) Product marketing activities are standardized; fourth, scientific research and evaluation are carried out on alcohol tax issues, and alcohol prices related to inflation and income levels are regularly reviewed. (Jiang et al. 2020)

3 酒精戒断综合症

据统计，全球每年约有 1200 万例患者因为过度饮酒住院，住院治疗期间由于停止饮酒，80%患者有可能会出现酒精戒断综合症(alcohol withdrawal syndrome, AWS)。(Farooq and Bataller 2016)

根据世界卫生组织《2018 年酒精与健康全球状况报告》，中国的人均酒精消费量已从 2005 年的 4.1 升，增长到了 2016 年的 7.2 升，几乎翻了一番。而终身戒酒率则从 2005 年的 50.9%跌至 2016 年的 42.1%。(World Health Organization 2018) 2018 年，医学杂志《柳叶刀》公布了全球疾病负担研究中的酒精负担调查数据：在 2016 年，中国男性的饮酒率为 48%，女性为 16%，两者间的比值达到了 3:1，而全球 195 个国家和地区的男女平均饮酒率就没有那么悬殊，两者分别为 39%和 25%。(Fuster and Samet 2018) 随着健康观念的不断加深，人们开始注意自觉地控制日常饮酒量或者选择戒酒。但是，伴随而来的酒精戒断综合症却对此造成一定的干扰。据统计，酒精摄入减少的人群中 AWS 的发生率可达到 30%。(Kattimani and Bharadwaj 2013)

3 Alcohol withdrawal syndromes

According to statistics, about 12 million patients are hospitalized due to excessive drinking every year. During the hospitalization period, 80% of patients may suffer from alcohol withdrawal syndrome (AWS) because they stop drinking. (Farooq and Bataller 2016)

According to the World Health Organization's "Report on the Global State of Alcohol and Health in 2018", China's per capita alcohol consumption has increased from 4.1 liters in 2005 to 7.2 liters in 2016, almost doubled. The lifetime abstinence rate dropped from 50.9% in 2005 to 42.1% in 2016. (World Health Organization 2018) In 2018, the medical journal The Lancet published the survey data of the burden of alcohol in the Global Burden of Disease Study: In 2016, the drinking rate of Chinese men was 48%, and women's was 16%. The ratio reached 3:1, while the average drinking rate of men and women in 195 countries and regions around the world is not so different, the two are 39% and 25% respectively. (Fuster and Samet 2018) With the deepening of health concepts, people began to pay attention to consciously controlling their daily drinking or choosing to abstain from drinking. However, the accompanying alcohol withdrawal syndrome has caused some interference. According to statistics, the incidence of AWS in people with reduced alcohol intake can reach 30%. (Kattimani and Bharadwaj 2013)

3.1 药物治疗

3.1.1 戒断症状的药物治疗

BDZ 类药物(Benzodiazepines, BZDs)是各指南推荐治疗酒精戒断综合征的首选药物。多个安慰剂对照研究支持 BZDs 的临床疗效,可有效减轻酒精戒断综合征的主要症状,如焦虑和自主神经亢进症状(如出汗、震颤、心悸),并减轻整体戒断症状的严重程度,降低谵妄和癫痫的发生率。美国心理协会(APA)建议 BZDs 仅适用于治疗酒精戒断综合征,或者共病其他符合该药物适应症时使用。世界生物精神病学联盟提到最常使用的 BZDs 有地西泮、氯氮卓、奥沙西泮、劳拉西泮、阿普唑仑等。国内指南同样提到苯二氮卓类药物是目前公认有效、安全、研究充分的药物,但具体的选择需要考虑多方面因素,如药动学参数、起效时间、成瘾潜力以及患者的躯体健康和耐受情况等。目前暂无证据显示长效或短效药物的优劣,但临床医生更倾向使用长效药物,因其给药次数少,依从性更好,并且患者症状缓解更为平稳。一般情况下,首选口服给药方式,但对于严重精神错乱或躯体不适的患者,尤其是震颤谵妄的患者,静脉注射安定更合适。(Kattimani and Bharadwaj 2013)

APZ 属于 BDZ 类药物,其进入体内后会对脑内的 β -肾上腺素受体产生作用,可以有效地减轻 AWS 病人的精神异常症状,产生抗焦虑、抗抑郁、镇静、催眠、抗惊厥以及肌肉松弛等作用。需要注意的是,服药的少数病人会发生倦怠、头晕、口干、恶心、便秘、视力模糊、精神不集中等不良反应,而且久用后停药有戒断症状,因此应该避免长期使用。如果需要停止服用,则需要逐渐减量而非立刻中断。

数据分析的结果显示,AWS 病人会在精神状态以及胃肠道方面出现不适感,主要形式为谵妄、抑郁、易激惹、腹泻、恶心呕吐。在诸多的临床表现中,谵妄症状的发生率较高。谵妄,又被称为急性脑综合征。该病的主要临床表现为意识障碍、行动的目的不明确、注意力无法集中等。该病通常起病急,而且起伏波动明显。目前多针对此类病人的精神症状给予相关的精神类药物进行治疗(如氟哌啶醇)。为了防止药物的使用加深意识障碍,应优先选择小剂量、短期治疗的方法。(Singal et al. 2018)

3.1 Drug therapy

3.1.1 Drug therapy for withdrawal symptoms

BDZ drugs (benzodiazepines, BZDs) are the drugs of choice for the treatment of alcohol withdrawal syndrome recommended by various guidelines. Controlled studies of multiple sedatives support the clinical efficacy of BZDs, which can effectively alleviate the main symptoms of alcohol withdrawal syndrome. For example, as recommended by the American Psychological Association for Worry and Autonomy (APA), BZDs are only suitable for the treatment of alcohol withdrawal syndrome, or otherwise overall Relieve the severity of withdrawal symptoms and reduce the incidence of delirium and seizures. Use when other comorbidities meet the drug indications. The World Federation of Biological Psychiatry mentioned that the most commonly used BZDs are diazepam, chlordiazepoxide, oxazepam, lorazepam, alprazolam, etc. Domestic guidelines also mention that benzodiazepines are currently recognized as effective, safe, and well-researched drugs, but the specific selection needs to consider many factors, such as pharmacokinetic parameters, time of onset, addiction potential and patients Physical health and tolerance status. There is currently no evidence to show the pros and cons of long-acting or short-acting drugs, but clinicians are more inclined to use long-acting drugs because they occur less frequently, have better compliance, and patients have more stable symptoms. Under normal circumstances, oral weight loss is the preferred method, but for patients with severe mental confusion or physical discomfort, especially patients with delirium tremor, intravenous diazepam is more suitable. (Kattimani and Bharadwaj 2013)

APZ belongs to the BDZ class of drugs. After entering the body, it reorganizes the β -adrenergic receptors in the brain to produce effects, which can effectively alleviate the mental abnormalities of AWS patients, and produce anti-anxiety, anti-depression, sedation, hypnosis, anti-convulsions and muscle relaxation. And so on. It should be noted that a small number of patients taking the drug will experience fatigue, dizziness, dry mouth, nausea, constipation, blurred vision, lack of concentration and other adverse reactions, and withdrawal symptoms after stopping the drug for a long time, so long-term use should be avoided . If you need to stop taking it, you need to gradually reduce the dose without interrupting it immediately.

The results of data analysis show that AWS patients will experience discomfort in mental state and insulin tract, the main forms are delirium, depression, irritability, diarrhea, nausea and vomiting. Among the many clinical manifestations, the incidence of delirium symptoms is relatively high. Delirium is also known as acute brain syndrome. The main clinical manifestations of the disease are consciousness disorder, the purpose of action is not clear, and attention cannot be concentrated. The disease usually has a rapid onset with obvious fluctuations. At present, it is mostly aimed at preventing the use of drugs from deepening consciousness barriers,

and low-dose, short-term treatment should be preferred. (Singal et al. 2018)

3.1.2 酒精使用障碍的药物治疗

纳曲酮(Naltrexone)作为一种阿片受体拮抗剂(受体拮抗剂指能与受体结合,并能阻止激动剂产生效应的一类配体物质),对 μ -、 δ -、 κ -阿片受体均有阻断作用,能够减少酒精引起的奖赏回路的激活,减少伏隔核中多巴胺的释放,从而减少了酒精的奖赏效应和饮酒渴求。APA 指南推荐纳曲酮或阿坎酸(1B级)适用于以减少酒精使用或戒酒为目标、更倾向于药物治疗或对非药物治疗无效,且无该药物禁忌症的中度至重度酒精使用障碍患者。阿坎酸(Acamprosate)属于GABA受体激动剂,能有效降低患者的酒精渴求,然而其缺点是口服给药时生物利用度较低,常需较高的药物剂量,禁用于严重肾功能损害者。欧洲成瘾学会联合会(FAS/EUFAS)指南中推荐纳曲酮治疗可有效减少酒精消耗及复饮,与阿坎酸比较,纳曲酮对降低酒精渴求及减少高水平饮酒天数的疗效更显著,但对维持较长时间戒酒状态疗效较差(C级)。国内指南中也提及阿坎酸的疗效可能主要在于维持戒酒的效果而非减少未戒酒者的饮酒量。(Singal et al. 2018)

3.1.2 Drug therapy for alcohol use disorders

As an opioid receptor antagonist, Naltrexone blocks the μ - , δ - , κ -opioid receptors, reducing the activation of alcohol-induced reward circuitry and the release of dopamine in the nucleus accumbens, thereby reducing the rewarding effect of alcohol and alcohol craving. APA guidelines recommend naltrexone or alcanic acid (level 1B) for moderate to severe alcohol use disorders with the goal of reducing alcohol use or abstinence, a preference for drug therapy or failure to respond to non-drug therapy, and no contraindications to the drug. Acamprosate belongs to GABA receptor agonist, which can effectively reduce patients' alcohol craving. Its disadvantage is that prosate has low bioavailability and often requires high drug dose when orally administered, and is forbidden for people with severe renal impairment. Naltrexone is recommended in the FAS/EUFAS guidelines to reduce alcohol consumption and rehydration. Compared with arcanic acid, naltrexone is more effective in reducing alcohol craving and reducing the number of days with high levels of alcohol consumption, but less effective in maintaining a longer period of abstinence (grade C). The national guidelines also mention that the effect of acarbate may be primarily to maintain the effect of abstinence rather than to reduce the amount of alcohol consumed by non-abstainers. (Singal et al. 2018)

3.1.3 心理学治疗

由于患者是属于长期酗酒才导致自身身体状况出现，所以患者在接受长期治疗过程当中，自身的心理情绪波动将会产生十分明显的变化，而且部分患者在进入医院进行治疗之前就已经接触过很多其他方法的治疗，所以在接受医院的治疗是很多患者对医院的治疗成功率信心并不大，在接受治疗过程当中，部分患者会带有严重的负面情绪。(Leggio and Lee 2017) 有的患者在接受治疗过程当中，除了有严重的焦虑以外，也会产生一部分抑郁情感，在接受护理和治疗过程当中，并不会主动与护理工作人员和主治医生进行沟通。有的患者甚至由于长期酗酒，导致存在植物神经功能紊乱症状，再进行治疗过程当中就会为主治医生带来更多的麻烦，所以护理工作人员在关心患者的同时也一定要提供良好的常规护理工作，保证护理工作质量与患者进行友好的交流沟通，与患者之间建立信任联系，激励患者。

3.1.3 Psychological therapy

Because the patient is a long-term drinking of alcohol to cause his own physical condition, the patient's psychological and emotional changes will have very obvious changes during the long-term treatment, and some patients have been exposed before entering the hospital for treatment. There are many other methods of treatment, so when receiving treatment in the hospital, many patients are not confident in the success rate of the hospital's treatment. During the treatment process, some patients will have serious complications. (Leggio and Lee 2017) In the process of receiving treatment, some patients, in addition to serious deficiencies, will also develop a part of depression. During the process of receiving care and treatment, they will not take the initiative to contact the nursing staff and the attending doctor. Communicate. Some patients even have symptoms of autonomic dysfunction due to long-term drinking, and the main treatment doctor will cause more trouble during the treatment process. Therefore, the nursing staff must provide good routines while caring for the patient. Nursing work, to ensure the quality of nursing work, communicate with patients friendly, establish trust relationship with patients, and motivate patients.

3.1.4 综合手段

治疗酒精使用障碍的目标是提高患者的生活质量。根据患者的具体情况，治疗包括针对其身心健康、人际关系、社会和职业适应、司法状况以及其他成瘾或危险行为等多方面进行干预。为了真正改善患者的状况，彻底改变其酒精使用的模式至关重要。一直以来大家都认为戒酒是最佳的治疗目标，尤其是对于严重酒精依赖或滥用，且并发重大躯体或精神疾病的患者。但酒精不同于阿片类、苯丙胺类等非法物质，将戒酒作为所有患者治疗的唯一目标是有争议的。因此，APA、NICE 及 FAS/EUFAS 的指南中均提出另一供选择的治疗目标，即减少酒精消耗量，保持低风险的饮酒模式。饮酒模式风险有限且不伴有重大躯体疾病的患者可建议此治疗目标，对于风险较高、伴有重大躯体疾病或精神障碍的患者无法接受完全戒酒目标，也可以把此作为一个可行的治疗目标。(Singal et al. 2018)

治疗目标应该由医患双方共同决定，APA 建议患者和临床医生之间需明确酒精使用障碍的初步目标并达成一致意见，其目标包括戒酒、减少酒精使用或减少伤害等，并需要记录在病历中，在此基础上制定以患者为中心的个性化治疗方案，包括基于循证依据的非药物治疗及药物治疗等多种干预方式。

酗酒已经成为了当前饮酒患者的重要特征之一，所以在进行酒精性肝病患者治疗过程当中，要想保证治疗工作有序进行，就必须保证患者戒酒。酒精性肝病患者不仅仅是自身肝脏的功能受到一定的损害，同时也对患者自身的神经系统造成了更为严重的影响，在接受治疗时，患者普遍存在暴动，贫血，四肢无力等症状，而在护理工作开展过程当中，开展心理护理，饮食护理包括其他条件的护理，能够更好地保证患者在治疗过程当中拥有平稳的心态。综上所述，在护理工作开展过程当中，密切观察患者的身体状况，包括病情的变化，为患者设计科学合理的护理计划，能够对促进酒精性肝病酒精戒断综合症患者的康复。(Schuckit 2009)

综上所述，酒精使用障碍的治疗是以戒酒或降低饮酒风险及酒精消耗为目标，结合社会心理治疗、药物治疗及其他生物学治疗等多种治疗手段。未来，不论是心理治疗、药物治疗，抑或是 rTMS 等其他生物学治疗方面仍有待进一步的研究，使酒精使用障碍患者在躯体健康、心理健康、社会功能恢复等多方面取得更大的获益。

3.1.4 Comprehensive means

The goal of treating alcohol use disorder is to improve the patient's quality of life. According to the patient's specific situation, treatment includes interventions in various aspects such as physical and mental health, interpersonal relationships, social and occupational adaptation, judicial status, and other addictive or dangerous behaviors. In order to truly improve the patient's condition, it is essential to completely change the pattern of alcohol use. Everyone has always believed that abstinence is the best treatment goal, especially for patients with severe alcohol dependence or abuse, and complicated by major physical or mental illness. However, alcohol is different from illegal substances such as opioids and amphetamines, and it is controversial to regard abstinence as the sole goal of treatment for all patients. Therefore, the APA, NICE and FAS/EUFAS guidelines all propose another alternative treatment goal, that is, to reduce alcohol consumption and maintain a low-risk drinking pattern. Patients with limited risk of drinking patterns and not accompanied by major physical diseases can recommend this treatment goal. For patients with higher risk, major physical diseases or mental disorders who cannot accept the goal of complete abstinence, this can also be used as a feasible treatment aims. (Singal et al. 2018)

Treatment goals should be jointly decided by both doctors and patients. APA recommends that patients and clinicians clarify the initial goals of alcohol use disorder and reach an agreement. The goals include abstinence from alcohol, reducing alcohol use or reducing injuries, etc., and need to be recorded in medical records. On this basis, individualized patient-centered treatment plans are formulated, including evidence-based non-drug treatment and drug treatment and other intervention methods.

Alcoholism has become one of the important characteristics of current drinking patients. Therefore, in the process of treatment of patients with alcoholic liver disease, if the treatment is to be carried out in an orderly manner, it is necessary to ensure that the patients stop drinking. Patients with alcoholic liver disease not only damage their own liver function to a certain extent, but also cause more serious effects on the patient's own nervous system. When receiving treatment, patients generally have symptoms such as rashes, anemia, and limb weakness. In the process of nursing work, carrying out psychological nursing, diet nursing including nursing of other conditions, can better ensure that patients have a stable mentality during the treatment process. In summary, during the development of nursing work, close observation of the patient's physical condition, including changes in the condition, and designing a scientific and reasonable care plan for the patient can promote the recovery of patients with alcoholic liver disease and alcohol withdrawal syndrome. (Schuckit 2009)

To sum up, the treatment of alcohol use disorder aims to stop drinking or reduce the risk of drinking and alcohol consumption, combined with a variety of treatment methods such as psychosocial therapy, drug therapy and other

biological treatments. In the future, whether it is psychotherapy, drug therapy, or other biological treatments such as rTMS, further research is still needed to enable patients with alcohol use disorder to achieve greater benefits in many aspects such as physical health, mental health, and social function recovery.

3.2 社会团体: Alcoholics Anonymous

Alcoholics Anonymous 是一个同舟共济的团体，所有成员通过相互交流、相互支持和相互鼓励而携起手来，解决他们共同存在的问题，并帮助更多的人从嗜酒中毒中解脱出来。AA 并没有在科学范围内被认可，但在群体中有一部分已经很长时间没有复饮。这一部分详见访谈。

我们通过文献调研和访谈了解到，完全戒酒不是很多人能够接受的选项，并且减少酒精消耗量，保持低风险的饮酒模式是科学研究证实可行的方案。这样一定程度上缓和了部分人群完全戒酒和社交饮酒方面的不兼容性，缓和了部分人群在当下社会氛围下一定的社会压力，是一个能够被更大群体接受的辅助治疗的手段。

3.2 Social group:Alcoholics Anonymous

Alcoholics Anonymous is a group of individuals who work together to solve their common problems and help more people escape from alcoholism by communicating, supporting and encouraging each other.AA is not scientifically recognized, but there is a segment of the population that has not been drinking again for a long time.Please refer to the interview for this part.

Through literature research and interviews, we know that complete abstinence from alcohol is not an acceptable option for many people, and that reducing alcohol consumption and maintaining a low-risk drinking pattern are feasible solutions confirmed by scientific research.In this way, the incompatibility of complete abstinence and social drinking among some people is alleviated to a certain extent, and the social pressure of some people under the current social atmosphere is alleviated, which is an auxiliary treatment that can be accepted by a large number of people.

4 项目背景

过量的酒精摄入会诱发乙醛堆积、氧化应激、细胞线粒体功能障碍等，造成肝脏细胞损伤，诱导炎症因子的释放；同时高浓度酒精会损伤小肠上皮，导致大量内毒素进入血液；双重作用下，肝脏局部产生炎症反应，如不能在损伤期及时戒断，则可能进一步发展为脂肪肝，酒精性肝炎，肝硬化乃至肝癌。炎症反应是酒精性肝病的主要促因。

酒精性肝病 (Alcoholic Liver Disease, ALD) 是长期大量饮酒所致的肝脏疾病，包括脂肪肝，酒精性肝炎，酒精性肝硬化，从可逆的酒精性肝损伤逐渐演化为不可逆的肝脏病理损伤，是肝癌发生的重要原因之一。

目前为止，酒精性肝炎治疗的基石仍然为戒酒、营养支持和皮质激素治疗，但效果均不理想。肝移植是包括 ALD 在内的终末期肝病的唯一治愈性措施。美国食品药品监督管理局 (FDA) 尚未批准任何新的靶向性治疗药物。

本项目针对处于酒精性肝损伤前中期，有一定的饮酒习惯并无法接受完全戒酒目标，寻求低风险饮酒模式的人群以及寻求循序渐进的戒酒措施，综合改善酒精引起的心理健康问题及酒精性肝损伤并规避严重的酒精戒断综合征的人群。本产品对患者在生活中面临的实际困境给予了充分考虑，为医生提供了一种可及并可控的 ALD 发展阻断方法。我们致力于通过切实可信且可行的方式，提升 ALD 患者的健康水平，并最终帮助患者提升生活质量。

除此之外，一直有理论认为酒精性肝病的发生发展与肠道菌群密切相关。最新研究表明，粪肠球菌 (*Enterococcus faecalis*, *E. faecalis*) 的存在与酒精性肝损伤患者的肝病严重程度和死亡率相关，粪肠球菌会产生多种毒素，损伤肠黏膜。肠黏膜损伤后，粪肠球菌进入血液迁徙至肝细胞附近，产生溶细胞素杀伤肝细胞，导致酒精性肝损伤的发生。临床数据表明，溶细胞素呈阳性的酒精性肝病患者在入院后 180 天内死亡率近 90%；而溶细胞素呈阴性的酒精性肝病患者死亡率仅为 4%，证明粪肠球菌存在与酒精性肝病的死亡率和不良预后呈现明显的正相关关系。

基于此背景，抑制肝脏局部炎症与控制粪肠球菌数量是两类可尝试的、前景可观的酒精性肝病的治疗和预防措施。基于此思路，我们设计了工程化的大肠杆菌系统，其分别感应乙醇浓度信号与群体感应信号，可执行以下功能：

1. 感受乙醇信号后，分泌可穿小肠上皮膜吸收的抑炎因子，抑制肝脏局部炎症；
2. 感受群体感应信号后，分泌靶向粪肠球菌的杀菌肽，下调肠道内粪肠球菌数量；
3. 感受群体感应信号后，通过细菌接合，将携带 CRISPR-Cas9 系统 / microRNA 干扰系统的穿梭质粒转入粪肠球菌，干扰粪肠球菌种群溶细胞素的表达 / 干扰粪肠球菌的生存关键基因，以合适速率下调肠道内粪肠球菌的数量。

同时，我们非常倡导能够将我们的辅助疗法和心理学治疗结合，达到共同减轻对酒精的依赖，实现减少酒精消耗量，保持低风险的饮酒模式或者循序渐进的戒酒以规避严重的酒精戒断综合征的效果。

4 Project Background

Excessive alcohol intake will induce acetaldehyde accumulation, oxidative stress, cellular mitochondrial dysfunction, etc., causing liver cell damage and inducing the release of inflammatory factors. At the same time, high concentration of alcohol can damage the epithelium of small intestine and lead to a large amount of endotoxin entering the blood. Under the dual action, local inflammatory response occurs in the liver. If the patient cannot be stopped in time during the injury period, it may develop into fatty liver, alcoholic hepatitis, cirrhosis and even liver cancer. Inflammation is a major contributor to alcoholic liver disease.

Alcoholic Liver Disease (ALD) is a chronic Alcoholic Liver Disease caused by excessive drinking, including fatty Liver, Alcoholic hepatitis and Alcoholic Liver cirrhosis. It gradually evolves from reversible Alcoholic Liver injury to irreversible Liver pathological injury and is one of the important causes of Liver cancer.

So far, the cornerstone of treatment for alcoholic hepatitis remains abstinence, nutritional support and corticosteroid therapy, but the results are not satisfactory. Liver transplantation is the only cure for end-stage liver disease including ALD. The US Food and Drug Administration (FDA) has not approved any new targeted therapeutic drugs. This project is aimed at people who are in the pre-middle stage of alcoholic liver injury, have certain drinking habits and cannot accept the goal of complete abstinence, seek low-risk drinking patterns, and seek gradual measures to stop alcohol, and comprehensively improve mental health problems and alcoholism caused by alcohol Liver damage and avoid people with severe alcohol withdrawal syndrome. This product gives full consideration to the practical dilemmas faced by patients in real life, and provides doctors with an accessible and controllable method to block the development of ALD. We are committed to improving the health of ALD patients through practical and feasible methods, and ultimately helping patients improve their quality of life.

In addition, it has been theorized that the occurrence and development of alcoholic liver disease are closely related to intestinal flora. Recent studies have shown that *Enterococcus faecalis* (*E. faecalis*) is associated with the severity of liver disease and mortality in patients with alcoholic liver injury. *Enterococcus* produces a variety of toxins and damages the intestinal mucosa. After intestinal mucosal injury, *enterococcus faecalis* enters the blood and migrates to the vicinity of hepatocytes, producing cytolytic cytoplasm and killing hepatocytes, leading to alcoholic liver injury. Clinical data showed that nearly 90% of patients with alcoholic liver disease who were cytolytic positive had a mortality rate within 180 days after admission. However, the mortality rate of the patients with alcoholic liver disease with negative cytolytic cytokines was only 4%, indicating that the presence of *enterococcus faecans* was positively correlated with the mortality and poor prognosis of alcoholic liver disease.

In this context, inhibition of local inflammation in the liver and control of *enterococcus faecalis* are two promising therapeutic and preventive measures for alcoholic liver disease. Based on this idea, we designed an engineered *E. coli*

system, which senses the ethanol concentration signal and the quorum sensing signal respectively, and can perform the following functions:

1. After sensing the ethanol signal, it secretes anti-inflammatory factors that can be absorbed through the epithelial membrane of small intestine to inhibit local inflammation of the liver;

2. After sensing quorum sensing signal, secreted bactericidal peptides targeting enterococcus faecalis, and down-regulated the number of enterococcus faecalis in the intestinal tract;

3. After sensing quorum sensing signals, the crisPR-Cas9 system /microRNA interference system shuttle plasmids were transferred to enterococcus faecalis through bacterial bonding, which interfered with the expression of cytins in enterococcus faecalis population/interfered with the survival key genes of Enterococcus faecalis, and down-regulated the number of enterococcus faecalis in the intestinal tract at an appropriate rate.

At the same time, we strongly advocate the ability to combine our adjuvant therapy and psychotherapy to jointly reduce dependence on alcohol, reduce alcohol consumption, maintain a low-risk drinking pattern or steadily quit alcohol to avoid serious alcohol withdrawal.

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