



DDS Perspective: Time to Get Serious About the Global Pandemic

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For many years now, the world has experienced a global pandemic—a disease that can be asymptomatic for some and for others account for significant morbidity and mortality. Indeed, this deadly pandemic's culprit is responsible for nearly 400 deaths daily in the United States (US) alone [1]. Thirty-eight million adults in the US remain at risk of being affected [1]; and hospitalizations due to this pandemic have doubled in just a few years resulting in an estimated \$23 billion in hospital costs [2]. And increasingly, young people and women are at risk [1]. While the World Health Assembly has recommended a global strategy to combat this pandemic [3], countries have only incompletely adhered to guidance. For example, preventive strategies in the US have been offered to only 8% of those most vulnerable to disease [4]. Perhaps these statistics appear familiar because of the COVID-19 pandemic we have battled since 2019; however, what I've outlined is the global pandemic that is alcohol-associated liver disease, or alcohol-related, liver disease (ALD). Eliminating the ALD pandemic will require a multifaceted approach involving robust public health policies, enhanced technology and education, and a shift toward therapies that address the early metabolic consequences of the disease.

US Public Health Policy and ALD

ALD is a preventable, treatable, and reversible condition until the liver fails. Its spectrum extends from the largely asymptomatic, but pathologic, stage of hepatic steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. A subset of patients can also develop alcohol-associated hepatitis, a subacute syndrome characterized by rapid liver injury and dysfunction with associated high short-term

mortality. Although there have been several efforts to determine effective treatments for alcohol-associated hepatitis, trials dedicated to chronic ALD are sparse and have largely focused on cirrhotic-stage disease. Investments in preventive public health mitigation strategies have also not kept pace.

Review of both the Centers for Disease Control and Prevention (CDC)'s 2020 pre-COVID-19 pandemic and 2023 intra-COVID-19 pandemic budget requests (\$7 and \$10 billion, respectively) revealed several priority areas; however, none related to alcohol despite the CDC's data demonstrating a threefold increase in mortality from ALD over the past 20 years [5]. The 2023 budget includes a focus on viral hepatitis, opioid overdose, and suicide prevention, but alcohol and its related health consequences are not mentioned. In the field of gastroenterology, national targets have been set for colorectal cancer screening and hepatitis C elimination, thus highlighting the existence of structures that can mobilize public digestive health goals. That only 8% of US individuals who suffer from alcohol use disorder are receiving treatment even though 20% of 15–49-year-olds die prematurely of alcohol-related deaths [4] speaks volumes about our national priorities. Moreover, the alcohol content of beer, wine, and spirits has increased over the past two decades (4.65% to 4.74% for beer; 11.6% to 12.3% for wine; and 36.9% to 38.3% for spirits) [6] without additional public health policy safeguards, potentially increasing the risk of ALD for individuals who report the same alcohol consumption pattern over this time period.

ALD and Digital Platforms

The World Health Organization (WHO) warned recently that direct digital marketing is a key strategy to increase alcohol use among young social media users and advised countries to develop policies to address cross-border alcohol advertisements [7]. This announcement is alarming, because rates of alcohol use disorder, ALD, and alcohol-associated cirrhosis are increasing most significantly for individuals aged 25–34 [8], the age group that is also the

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largest demographic on most social media platforms [9]. Despite the WHO's guidance, however, nearly half of countries have not regulated marketing of alcohol on social media. Fortunately, social media platforms themselves have established some guidelines in their attempts to self-regulate [10], but it is unclear how long they will remain in place or how adherent they are to those guidelines.

Although the limited regulations of alcohol marketing on social media could lead to an increase in consumption among young people, the widespread availability of social media is also an effective tool for dissemination of health education. Networks such as #Livertwitter and organizational and institutional accounts from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), American Association for the Study of Liver Diseases, American Liver Foundation, and Global Liver Institute present up-to-date guidance on risk factors and management of liver diseases, inclusive of ALD. Because these organizations increasingly interface directly with patients and the public at large, it is likely that these educational strategies can counteract some of the impact of social media marketing of alcohol.

ALD Education and Training of Medical Professionals

Globally, the majority of individuals with alcohol use disorders remain untreated. Treating these disorders is akin to eradicating the hepatitis C virus (HCV) as the primary strategy for management of HCV-induced liver disease. In a global survey of 408 hepatologists and gastroenterologists, 77% report having received only limited addiction education, and 84% reported being uncomfortable with management of alcohol use disorder [11]. Among residents and fellows, there is no standard addiction curriculum and few formal training opportunities for those who seek additional instruction [12]. For medical students, few are comfortable with hepatology knowledge upon graduating [13]. Developing a professional workforce competent in the primary prevention of ALD through management of alcohol overuse and addiction disorders is critical to combatting the ALD pandemic. In my view, focusing these efforts only on transplant hepatology programs is unlikely to be sufficient given the dearth of programs, their location only at tertiary care centers, declining fellowship enrollment, and emphasis on patients who already have advanced disease. Instead, education should begin in pre-clinical programs (physician and non-physician) and continue through internal and family medicine residencies and general GI fellowships in order to ensure that we have an adequate workforce to implement a preventive strategy for ALD.

Prevention of Advanced ALD Will Require a Focus on Alcohol Dysmetabolism

Because ALD is a systemic metabolic disease stemming from overconsumption of alcohol, strategies that target both the dysmetabolic effects of alcohol and the behavioral component (i.e., alcohol overuse) of the disease are warranted. For example, in the related disorder nonalcoholic fatty liver disease (NAFLD), management includes nutritional guidance as well as pharmacologic strategies aimed at reversing obesity and insulin resistance that are present in the majority of individuals with NAFLD.

In ALD, there is profound lipid and glucose dysmetabolism, and the latter increases the likelihood of advanced disease [14]. Moreover, concomitant obesity exacerbates ALD [15]. Preclinical studies suggest that in addition to alcohol avoidance, dietary fat consumption modulates disease [16]. These data indicate a consequential metabolic component of ALD that may be exploited for novel therapeutic strategies outlined below.

PPARs

Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)- γ agonist approved as a therapeutic for biopsy-proven nonalcoholic steatohepatitis (NASH). The pan-PPAR agonist lanifibranor is under investigation, with promising phase 2 results for improvement in steatosis, inflammation, fibrosis, and dyslipidemia in NASH [13]. There are no human data for these agents in ALD; however, pioglitazone was associated with reduced alcohol consumption one year after it was prescribed in a small observational study of patients with alcohol use disorder [17]. In a rodent model, the combination of pioglitazone and naltrexone reduced the rate of relapse more than either medication alone [18]. Pioglitazone and other PPAR agonists also prevent liver injury in rats despite ongoing alcohol consumption [19]. These studies provide proof-of-principle that a PPAR-class of ALD therapeutics could be used for individuals unable to achieve sobriety.

Incretins

The incretin class of diabetes therapeutics is being investigated for treatment of NAFLD and has been examined in pre-clinical ALD studies. Glucagon-like peptide 1 (GLP1) is an incretin that slows gastric emptying, stimulates insulin secretion, and inhibits glucagon secretion after a carbohydrate meal. GLP1 also regulates the brain's reward center in humans [20]. In rodents, the GLP1-agonist liraglutide not only reduces food intake and weight gain as demonstrated in humans with diabetes and NAFLD, but also reduces alcohol

intake [21]. Although there are no studies to date of incretins in ALD, a phase 1 study of the effects of the GLP-1 agonist exenatide on alcohol consumption in humans was launched but ultimately interrupted due to the COVID-19 pandemic [22].

FXR Agonism

Farnesoid X receptor (FXR) agonists and fibroblast growth factor (FGF)19 analogs are other categories of medications under investigation to address dysmetabolism in NAFLD. FXR is a nuclear receptor that regulates bile acid synthesis. Preclinical data demonstrate that FXR deficiency (in particular, intestinal FXR deficiency) exacerbates ALD [23] and, conversely, that FXR agonism remedies steatosis, inflammation, and oxidative stress [24]. A phase 2 study of obeticholic acid in patients with alcohol-associated hepatitis began in 2014, but was halted in 2017 because of post-marketing reports of hepatitis [25]. The registration of this study demonstrates that targeting dysmetabolism in ALD may indeed be part of the armamentarium of strategies in the future.

Lipid Modulation

Several pre-clinical studies and human association studies have linked ALD risk with dietary fat consumption. Our lab has extended this literature by examining the role of intracellular lipids on the pathogenesis of ALD during steatosis. Namely, we have identified the sphingolipid class ceramide as promoting ALD through its regulation of lipid droplet organelles [26]. Uncovering novel molecular targets that can be modulated early in the disease regardless of abstinence is a practical preventive strategy, as only a minority of individuals are successfully treated for alcohol overuse disorders.

In summary, combatting the global pandemic of ALD requires a paradigm shift toward public policy harm reduction strategies; optimizing alcohol education and treatment among pre-clinical professionals, residents, and fellows; amplifying digital strategies; and shifting therapeutics toward early-stage disease. It is time to get serious about this longstanding pandemic with a deployment of resources commensurate with the impact of this disease.

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