Notes on the Basic Pharmacology of Substance Use Disorders:

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WHO on Psychoactive substances

Psychoactive substances are substances that, when taken in or administered into one's system, affect mental processes, e.g. cognition or affect. This term and its equivalent, psychotropic drug, are the most neutral and descriptive term for the whole class of substances, licit and illicit, of interest to drug policy.

The bare facts

We know what can and needs to be done to help reduce the burden of psychoactive substance use. Therefore, WHO is committed to assisting countries in the development, organization, monitoring and evaluation of treatment and other services.

- The harmful use of alcohol results in 3.3 million deaths each year.
- On average every person in the world aged 15 years or older drinks 6.2 litres of pure alcohol per year.
- Less than half the population (38.3%) actually drinks alcohol, this means that those who do drink consume on average 17 litres of pure alcohol annually.
- Some 31 million persons have substance use disorders.
- Almost 11 million people inject drugs, of which 1.3 million are living with HIV, 5.5 million with hepatitis C, and 1 million with both HIV and hepatitis C

Alcohol

Alcohol is a psychoactive substance with dependence-producing properties that has been widely used in many cultures for centuries. The harmful use of alcohol causes a large disease, social and economic burden in societies. Environmental factors such as economic development, culture, availability of alcohol and the level and effectiveness of alcohol policies are relevant factors in explaining differences and historical trends in alcohol consumption and related harm.

Alcohol-related harm is determined by the volume of alcohol consumed, the pattern of drinking, and, on rare occasions, the quality of alcohol consumed. The harmful use of alcohol is a component cause of more than 200 disease and injury conditions in individuals, most notably alcohol dependence, liver cirrhosis, cancers and injuries. The latest causal relationships established are those between alcohol consumption and incidence of infectious diseases such as tuberculosis and HIV/AIDS.

A wide range of effective global, regional and national policies and interventions are in place to reduce the harmful use of alcohol, with a promising trend over the past few decades.

1. Alcohol consumption:
- Worldwide consumption in 2010 was equal to 6.2 litres of pure alcohol consumed per person aged 15 years or older, which translates into 13.5 grams of pure alcohol per day.
- A quarter of this consumption (24.8%) was unrecorded, i.e., homemade alcohol, illegally produced or sold outside normal government controls. Of total recorded alcohol consumed worldwide, 50.1% was consumed in the form of spirits.
- Worldwide 61.7% of the population aged 15 years or older (15+) had not drunk alcohol in the past 12 months. In all WHO regions, females are more often lifetime abstainers than males. There is a considerable variation in prevalence of abstention across WHO regions.
- Worldwide about 16.0% of drinkers aged 15 years or older engage in heavy episodic drinking.

- o In general, the greater the economic wealth of a country, the more alcohol is consumed and the smaller the number of abstainers. High-income countries have the highest alcohol per capita consumption (APC) and the highest prevalence of heavy episodic drinking among drinkers.
2. Health consequences
- o In 2012, about 3.3 million net deaths, or 5.9% of all global deaths, were attributable to alcohol consumption.
- o There are significant sex differences in the proportion of global deaths attributable to alcohol, for example, in 2012 7.6% of deaths among males and 4% of deaths among females were attributable to alcohol.
- o In 2012 139 million net DALYs (disability-adjusted life years), or 5.1% of the global burden of disease and injury, were attributable to alcohol consumption.
- o There is also wide geographical variation in the proportion of alcohol-attributable deaths and DALYs, with the highest alcohol-attributable fractions reported in the WHO European Region.
3. Policies and interventions
- o Alcohol policies are developed with the aim of reducing harmful use of alcohol and the alcohol-attributable health and social burden in a population and in society. Such policies can be formulated at the global, regional, multinational, national and subnational level.
- o Delegations from all 193 Member States of WHO reached consensus at the World Health Assembly in 2010 on a WHO Global stratgy to reduce the harmful use of alcohol.
- o Many WHO Member States have demonstrated increased leadership and commitment to reducing harmful use of alcohol over the past years.
- o A significantly higher percentage of the reporting countries indicated having written national alcohol policies and imposing stricter blood alcohol concentration limits in 2012 than in 2008.

Other psychoactive substances

It is estimated that 275 million people used illicit drugs, such as cannabis, amphetamines, opioids, and cocaine, in 2016 which translates into an annual prevalence of illicit drug use of 5.6%. Cannabis is most used with 192 million users. Some 31 million of people who use drugs suffer from drug use disorders. It is estimated that there are almost 11 million people who inject drugs.

UNODC 2018 World Drug Report

275 million people worldwide, which is roughly 5.6 per cent of the global population aged 15-64 years, used drugs at least once during 2016. Some 31 million of people who use drugs suffer from drug use disorders, meaning that their drug use is harmful to the point where they may need treatment. Initial estimations suggest that, globally, 13.8 million young people aged 15-16 years used cannabis in the past year, equivalent to a rate of 5.6 per cent. Roughly 450,000 people died as a result of drug use in 2015, according to WHO. Of those deaths, 167,750 were directly associated with drug use disorders (mainly overdoses). The rest were indirectly attributable to drug use and included deaths related to HIV and hepatitis C acquired through unsafe injecting practices.

Drug treatment and health services continue to fall short: the number of people suffering from drug use disorders who are receiving treatment has remained low, just one in six. Some 450,000 people died in 2015 as a result of drug use. Of those deaths, 167,750 were a direct result of drug use disorders, in most cases involving opioids. These threats to health and well-being, as well as to security, safety and sustainable development, demand an urgent response.

Opioids continued to cause the most harm, accounting for 76 per cent of deaths where drug use disorders were implicated. PWID - some 10.6 million worldwide in 2016 - endure the greatest health risks. More than half of them live with hepatitis C, and one in eight live with HIV. The headline figures for drug users have changed little in recent years, but this stability masks the striking ongoing changes in drug markets. Drugs such as heroin and cocaine that have been available for a long time increasingly coexist with NPS and there has been an increase in the non-medical use of prescription drugs (either diverted from licit channels or illicitly manufactured).The use of substances of unclear origin supplied through illicit channels that are sold as purported medicines but are destined for non-medical use is also on the increase. The range of substances and combinations available to users has never been wider.

Criteria for a Substance Use Disorder (SUD) in DSM 5
The Diagnostic and Statistical Manual of the American Psychiatric Association, the 5th version

You have a substance use disorder if your substance use is causing significant problems in your life, like health issues or disability that are related to your substance use and/or not meeting your responsibilities at work, home, or school.

Substance use disorders are classified as mild, moderate, or severe, depending on how many of the diagnostic criteria you meet. The 11 DSM-5 criteria for a substance use disorder include:

1. **Hazardous use:** You've used the substance in ways that are dangerous to yourself and/or others, i.e., overdosed, driven while under the influence, or blacked out.
2. **Social or interpersonal problems related to use:** Your substance use has caused relationship problems or conflicts with others.
3. **Neglected major roles to use:** You've failed to meet your responsibilities at work, school, or home because of your substance use.
4. **Withdrawal:** When you've stopped using the substance, you've experienced withdrawal symptoms.
5. **Tolerance:** You've built up a tolerance to the substance so that you have to use more to get the same effect.
6. **Used larger amounts/longer:** You've started to use larger amounts or use the substance for longer amounts of time.
7. **Repeated attempts to control use or quit:** You've tried to cut back or quit entirely, but haven't been successful.
8. **Much time spent using:** You spend a lot of your time using the substance.
9. **Physical or psychological problems related to use:** Your substance use has led to physical health problems like liver damage or lung cancer, or psychological issues, such as depression or anxiety.

1. **Activities given up to use:** You've skipped activities or stopped doing activities you once enjoyed in order to use the substance.
2. **Craving:** You've experienced cravings for the substance.

Substances that Cause SUD in the DSM 5

1. Alcohol
2. Caffeine
3. Cannabis
4. Hallucinogen
5. Inhalant
6. Opioid
7. Sedative, hypnotic or Anxiolytic
8. Stimulant
9. Tobacco
10. Other or Unknown

Pharmacological Treatments: HHS Public Access Dec 2018

Alcohol:

The opioid antagonists naltrexone and nalmefene are approved for persons diagnosed with alcohol use disorders. Naltrexone is approved as a daily oral formulation, and also as a monthly depot injection.

Acamprosate (calcium acetyl homotaurinate) is approved for maintenance of abstinence from alcohol in several countries. The mechanism of action of acamprosate is not well understood, and may involve GABA or glutamate neurotransmitter systems.

Disulfiram (an inhibitor of aldehyde dehydrogenase and dopamine-β-hydroxylase (DBH) has been long-approved for this indication, and causes aversive effects (e.g., nausea) if a person taking disulfiram ingests alcohol.

The overall usage of the aforementioned medications, has remained relatively modest, for a variety of medical, socio-cultural and reimbursement factors

Tobacco:

Nicotine patches, lozenges and gum (and other formulations) are approved for tobacco use disorder (i.e., with an "agonist-based" approach). These are often used for extended periods (although the knowledge base for extended use is limited) and can decrease the probability of relapse.

The other main medications approved for this disorder are bupropion and varenicline, which is a partial agonist at the α4β2 nicotinic receptor subtype.

There is little information on the pharmacotherapeutic management of abuse of "e-cigarettes" (which typically vaporize nicotine solutions). There is little evidence in support of the use of e-cigarettes as aids to smoking cessation, whereas there is emerging data showing that adolescent use of e-cigarettes increases the probability of cigarette smoking behaviors

Heroin and abused μ -agonists:

There are two main medications approved for the medical management of severe opioid use disorders. These are methadone or buprenorphine / naloxone, taken on a daily basis.

Methadone is a selective and long-lasting μ-agonist (although it also functions as an NMDA antagonist), whereas buprenorphine is a μ-partial agonist that also has κ-antagonist or partial

agonist effects. The antagonist naloxone is added to this buprenorphine formulation, as an abuse deterrent (i.e., to avoid diversion and injection). There are extensive long-term data showing considerable therapeutic benefit of chronic methadone and buprenorphine / naloxone maintenance, when used in high quality programs, providing sufficient doses of these medications

The short-acting antagonist naloxone has been approved for decades as a parenteral injection, for the acute reversal of μ-agonist overdose. An intranasal formulation of naloxone was recently approved for this purpose, and may be especially helpful to laypersons and first responders [.

α_2 adrenergic agonists such as clonidine (or lofexidine, in some countries) are used primarily to manage short-term symptoms of sympathetic over-activation that occur during withdrawal from chronic μ-agonists.

More recently, a monthly depot-formulation of naltrexone has been approved in the U.S., to prevent relapse in persons diagnosed with opioid dependence who have undergone detoxification

Undergoing opioid detoxification and induction onto the depot naltrexone formulation is a challenge that can limit the applicability of such antagonist-based approaches, as many patients have difficulty in this transition. Optimized use of depot naltrexone, including adjunctive treatments, its long-term clinical impact, and reimbursement are areas of recent interest. Overall, usage of this naltrexone depot formulation remains considerably smaller than that of methadone and buprenorphine/naloxone.

A six-monthly implant of buprenorphine has been approved in 2016 in the U.S., as an option for persons who had previously been on stable buprenorphine/naloxone maintenance.