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Treatment-refractory substance use disorder: Focus on alcohol, opioids, and cocaine

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ABSTRACT

Substance use disorders are common, but only a small minority of patients receive adequate treatment. Although psychosocial therapies are effective, relapse is common. This review focusses on novel pharmacological and other treatments for patients with alcohol, opioid, or cocaine use disorders who do not respond to conventional treatments.

Disulfiram, acamprosate, and the opioid antagonist naltrexone have been approved for the treatment of alcoholism. A novel, "as needed" approach is the use of the mu-opioid antagonist and partial kappa agonist nalmefene to reduce alcohol consumption. Other novel pharmacological approaches include the GABA-B receptor agonist baclofen, anticonvulsants such as topiramate and gabapentin, the partial nicotine receptor agonist varenicline, and other drugs. For opioid dependence, opioid agonist therapy with methadone or buprenorphine is the first-line treatment option. Other options include oral or depot naltrexone, morphine sulfate, depot or implant formulations, and heroin (diacetylmorphine) in treatment-refractory patients. To date, no pharmacological treatment has been approved for cocaine addiction; however, 3 potential pharmacological treatments are being studied, disulfiram, methylphenidate, and modafinil. Pharmacogenetic approaches may help to optimize treatment response in otherwise treatment-refractory patients and to identify which patients are more likely to respond to treatment, and neuromodulation techniques such as repeated transcranial magnetic stimulation and deep brain stimulation also may play a role in the treatment of substance use disorders.

Although no magic bullet is in sight for treatment-refractory patients, some novel medications and brain stimulation techniques have the potential to enrich treatment options at least for some patients.

1. Introduction

ICD-10 and DSM-IV follow a categorical approach and classify substance use disorders (SUDs) as abuse (harmful use) or dependence. Substance abuse/harmful use is characterized by somatic or psychiatric problems (and social problems in DSM-IV but not ICD-10). These classifications define dependence by a cluster of somatic, psychological, and behavioral symptoms (APA, 2000; WHO, 1992). The recently published DSM-5 has abandoned the categorical distinction between abuse and dependence and introduced a dimensional approach (APA, 2013). Substance-related and addictive disorders are specified by 11 symptoms: 6 or more positive symptoms constitute a severe substance use disorder; 4 or 5, a moderate one; and 2 to 3, a mild one. SUDs are associated with high psychiatric and somatic morbidity, a substantial global burden of morbidity and premature death (Gowing et al., 2015).

Numerous studies indicate that SUDs, in particular alcoholism, are common. A recent report on global statistics of addictive behaviors (Gowing et al., 2015) states that 4.9% of the world adult population have an alcohol use disorder (7.8% of men and 1.5% of women), 22.5% of the adult population smoke tobacco products, and 3.5% use cannabis. The use of other illegal psychoactive drugs is less than 1% for each class. The prevalence estimates are 0.2% for opioid use and 0.5% for both cocaine and amphetamines. Recent European data suggest that 1.9% of young Europeans (15–34 years old) have used cocaine at least once in the last 12 months, and 1% of this group have used amphetamines (EMCDDA, 2015). Opioid use is reported in 0.4% of adults (15–64 years old).

Earlier studies estimated the prevalence of alcoholism to be 7%–10% in Europe and the USA (Grant et al., 2004; Kessler et al., 2005; Pirkola et al., 2006; Rehm et al., 2005). Using DSM-5 criteria, the US National Epidemiologic Survey on Alcohol and Related Conditions II reported a 12-month and lifetime prevalence for alcohol use disorders of 13.9% and 29.1%, respectively (Grant et al., 2015). Only 19.8% of affected people had ever been treated. Globally, prevalence estimates of alcoholism range from 0% to 16% (WHO, 2011).

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Opioid dependence is a chronic relapsing disorder with a significant mortality rate (Degenhardt et al., 2011, 2013; Peles et al., 2010). Epidemiological studies indicate that the worldwide prevalence of opioid use disorders is about 0.4% in individuals aged 15–64 years and that there are 15.5 million opioid-dependent people worldwide (United Nations Office on Drugs and Crime, 2006). Epidemiological data suggest that in the European Union prevalence rates for opioid consumption have declined in recent years (EMCDDA, 2014); however, still about 1.3 million individuals in the EU have problematic opioid use, with a prevalence of about 0.4%. The drugs of choice have shifted somewhat from heroin towards other opioids, including methadone, buprenorphine, and fentanyl (EMCDDA, 2014). In the USA, some 3.7 million individuals have used heroin at least once in their lives, and 750,000 to 1 million individuals are currently heroin dependent (Kessler et al., 2012; Kleber et al., 2007). The World Health Organization (WHO) estimates that the burden of harm from opioid use is 11.2 million disability-adjusted life years (DALYs; WHO, 2004). The Global Burden of Disease study estimated that the burden of harm from opioid dependence is 9.2 million DALYs (Degenhardt et al., 2013, 2014). In addition, the USA in particular has an epidemic of opioid prescription drug use and has recorded multiple deaths associated with an overdose of opioid pain killers, including many accidental poisonings in children (Imtiaz et al., 2014).

Cocaine abuse is becoming increasingly prevalent in western countries. Cocaine is the second most common illicit drug (after marihuana) in both the USA and in almost all western industrial societies. The 12-month prevalence for cocaine use is 1% in Europe, and the lifetime prevalence is 4.6% (EMCDDA, 2015).

In contrast to other psychiatric disorders, "treatment-refractory" SUDs have no clear or operationalized definition. In a recent review on heroin treatment in treatment-refractory heroin addiction, Strang et al. (2015) reported studies in patients who "repeatedly failed in orthodox treatment." This definition may serve well for this review. Usually, treatment of SUDs has 2 goals: (1) complete and continuing abstinence, or (2) reduction of substance use (harm reduction strategy). Agonist drug maintenance plays an important role in the latter, especially in opioid dependence. For pharmacological and other reasons, agonist maintenance treatment is not suitable for all drugs of abuse. A recently published excellent and insightful comment on this topic is provided by Darke and Farrell (in press). Since alcohol, opioid, and cocaine use plays the most important role in substance use treatment and causes significant psychiatric and somatic complications, this narrative will focus on these types of drugs and in particular on new or emerging treatment options. We identified relevant publications from the years 2005–2015 through a Medline/PubMed search with the terms "pharmacotherapy," "therapy," and "brain stimulation."

2. Alcoholism

2.1. Neurobiology

The neurobiological basis of alcoholism is complex and has been the subject of intensive research in recent years (for a review see Noronha et al., 2014). In brief, the neural substrates and neurocircuitry of alcohol dependence and other drugs of abuse include the limbic system (ventral tegmentum and nucleus accumbens) and orbito- and prefrontal cortices. Dopamine (DA) release in the nucleus accumbens mediates reinforcing effects of drugs of psychoactive drugs (reward processing); the prefrontal cortex is of relevance for cognitive control and the orbitofrontal cortex for motivation (Nutt and Nestor, 2013).

Other variables mediating the vulnerability for alcohol dependence are stress or sensitivity to stress and neuroendocrine function, especially the hypothalamic-pituitary-adrenal (HPA) axis and the central nucleus of the amygdala, the main structure of the brain stress system (Heilig and Koob, 2007; Spanagel et al., 2014a; Stephens et al., 2014)

Alcohol has different molecular targets and a low affinity to many neuroreceptors. There is no specific alcohol receptor or molecular target. Neurotransmitters affected by alcohol include inhibitory gamma-aminobutyric acid (GABA), the opioid endorphin system, glutamate, the endocannabinoid system, noradrenaline, DA, and serotonin (Koob et al., 2014; Spanagel and Vengeliene, 2013).

There are 3 major classes of opioid receptors: mu (μ), kappa (κ), and delta (δ) (Gianoulakis, 2004). Recent research has viewed the opioidergic system as a "hedonic" system. It is implicated in the development of alcohol use disorders (Nutt, 2014) and mediates the reinforcing effects of alcohol by indirectly modulating DA release (Gianoulakis, 2004; Koob et al., 2014), especially via the mu-opioid receptor subtype (Narita et al., 2001).

Alcohol stimulates the release of the endogenous opioid receptor ligands beta-endorphin, enkephalins, and dynorphin (Dai et al., 2005; Marinelli et al., 2004, 2005, 2006). Opioid receptors on GABAergic neurons interact with dopaminergic neurons and thus mediate DA release (Koob et al., 2014). Functional neuroimaging data suggest a negative correlation between mu-opioid receptor binding and alcohol craving (Bencherif et al., 2004; Heinz et al., 2005).

2.2. Approved medications

Beside psychosocial therapies, medications can be used to lower relapse risk to heavy drinking, although pharmacotherapy for alcoholism is still a widely neglected area and few pharmacotherapies have been approved for treatment of alcoholism to date (Heilig and Egli, 2006; Soyka et al., 2011a; Soyka and Rosner, 2010; Spanagel and Kiefer, 2008).

2.2.1. Disulfiram

For decades, the acetaldehyde dehydrogenase inhibitor disulfiram was the only available drug to treat alcohol dependence. Disulfiram is described as an aversively-acting agent and induces negative states through an unpleasant alcohol–disulfiram reaction, mediated by acetaldehyde inhibition of hepatic aldehyde dehydrogenase (Ehrenreich and Krampe, 2004; Mutschler et al., 2011; Soyka et al., 2011a; Soyka and Lieb, 2015). However, evidence for efficacy is limited, at least in non-supervised settings; supervised treatment with disulfiram produces high effect sizes, making it an effective and well-established form of pharmacotherapy for relapse prevention in alcohol dependence (Skinner et al., 2014). The use of disulfiram has become controversial for various reasons, including the safety profile of the drug, patient adherence to treatment, methodological limitations of former studies, and mainly the psychologically aversive nature of the treatment approach itself (Mutschler and Kiefer, 2013).

2.2.2. Acamprosate

In the 1990s, the putative N-methyl-D-aspartic acid (NMDA) modulator acamprosate (Maisel et al., 2013; Rosner et al., 2010a) was introduced into clinical practice for the treatment of alcoholism. The mechanism of action of acamprosate is not fully understood, but some data suggest that modulation of the glutamatergic NMDA receptors is of relevance (Littleton and Zieglgansberger, 2003). Recent data indicate that the calcium part of the molecule is the only active compound, but these findings need to be replicated (Spanagel et al., 2014b). The efficacy of acamprosate was hypothesized to be linked to glutamatergic hyperactivity in the CNS (Gueorguieva et al., 2011).

Clinically, acamprosate is usually safe and well tolerated. A Cochrane analysis suggests that the only frequent side effect is diarrhea (Rosner et al., 2010a). Acamprosate is given as 3 tablets of 333 mg 3 times a day in patients with a bodyweight ≥60 kg and 2 tablets twice a day in patients weighing ≤60 kg. The comparatively high number of tablets needed may limit the acceptance of acamprosate treatment. Numerous randomized controlled trials (RCTs) on acamprosate have been performed in more than 4000 patients in total (Rosner et al., 2010a). Furthermore, several recent meta-analyses have evaluated acamprosate (Jonas et al., 2014; Rosner et al., 2010a), including 1 Cochrane analysis (Rosner et al., 2010a). Although there are some important negative