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Review Article

THERAPEUTIC USES OF DEPENDENCE CAUSING AGENTS: THE PAST AND THE PRESENT

YASHASVI SUVARNA, M. C. SHIVAMURTHY

Department of Pharmacology, M S Ramaiah Medical College, Bangalore 560054
Email: yashasvisuvarna@gmail.com

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ABSTRACT

A lot is known about substance dependence and abuse, but very few studies have explored the use of potential dependence causing drugs as therapeutic agents. This could be attributed to stringent regulations and restricted availability of these agents. But, in the last decade, resurgence in the use of these agents as research tools has been observed. This review focuses on both the past and present therapeutic uses of dependence causing agents like amphetamine, nicotine and opioids to name a few.

Keywords: Drug dependence, Therapeutic uses, Amphetamine, Nicotine

INTRODUCTION

A lot of emphases have been laid on the harm caused by dependence causing agents. But, little is known about its beneficial therapeutic effects which were of considerable importance in the bygone era. Due to stringent regulations and the social stigma associated with these agents, they have not been used much in the recent years for therapy or research. Today, thanks to the perseverance of certain researchers, many new beneficial effects are being discovered. This review focuses on both the past and present therapeutic uses of dependence causing agents.

Alcohol

Alcohol, produced by fermentation of sugar, is a very valuable therapeutic agent. But, its use has considerably declined over the past twenty to thirty years. In the past, alcohol has been used as a treatment for infection, an anesthetic, and a sedative. Alcohol exerts its beneficial effects on the body by stimulating $GABA_A$ receptor-mediated synaptic inhibition, inhibiting NMDA excitatory amino acid receptor and stimulating $5\text{-}HT_3$ receptors [1].

Alcohol is known as a pain suppressant and was used for hundreds of years for treating people with injuries and for those needing surgery. It was used to treat typhus as recently as the 1920s [2]. Research in the 1990s showed that moderate amounts of alcohol could help reduce the risk of heart attacks but, conversely, alcohol abuse has been connected to heart disease [2].

In certain acute diseases like pneumonia and diphtheria, administration of alcohol 1/16 to 1 ounce every 2 to 4 h is found to improve the general health of the patient. In elderly patients with chronic heart disease and bronchitis, a little whisky or brandy is often used as a home remedy as it acts as a stimulant and promotes sleep. In protracted convalescence from acute

diseases, a little whisky as much as much as 1 ounce may improve the tone of digestion and accelerate the rate of recovery particularly in influenza [3].

However, the uses of alcohol today are primarily restricted to the external application and as a vehicle for liquid preparations used internally. It is used as an antiseptic; as a rubefacient and counterirritant for sprains and muscle pains; to prevent the formation of bedsores; injections are used to treat intractable neuralgias; retrobulbar injections are used to treat optic neuritis, and through the nasogastric tube to treat methanol poisoning. It has also been used as an appetite stimulant [4].

Nicotine

This is a cheap, common, and mostly safe drug that has been in daily use for centuries but has only lately been investigated for its therapeutic potential. It is an alkaloid obtained from *Nicotiana tabacum* plant and exerts its effects on the human body by acting on the nicotinic acetylcholine receptors [5].

The primary therapeutic use is in smoking cessation as nicotine replacement therapy via gums, lozenges, patches, electronic cigarettes and nasal sprays which deliver controlled levels of nicotine [6]. In cases of mild to moderate degree of ulcerative colitis, the addition of transdermal nicotine to conventional therapy (usually mesalazine) for up to 6 w results in clinical improvement and may also represent a therapeutic alternative when corticosteroids cannot be employed [7]. A plausible mechanism of action in these cases may be by virtue of its anti-inflammatory and vasoconstrictive effects.

Tobacco smoke has been shown to contain compounds capable of inhibiting MAO, which is responsible for the degradation of dopamine in the human brain and thus may be beneficial in Parkinsonism [8]. Nicotine patches may be of benefit to some individuals with a defined mutation in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) whose seizures are refractory to standard antiepileptic therapy [9]. While acute/initial nicotine intake causes activation of nicotine receptors, chronic low doses of nicotine use leads to desensitisation of nicotine receptors (due to the development of tolerance) and results in an antidepressant effect, with research showing low dose nicotine patches being an effective treatment of Major depressive disorders in non-smokers [10]. Nicotine (in the form of chewing gum or a transdermal patch) is being explored as an experimental treatment for Obsessive Compulsive Disorder. Small studies show some success, even in otherwise treatment-refractory cases [11].

Nicotine has been demonstrated to enhance parietal cortex activation using functional MRI imaging techniques thus, helping in improving attention. It has also been found to increase significantly activation in the occipital cortex during both the control and rapid visual information processing tasks, suggesting a general modulation of attention. But, nicotine increased activity in the parietal cortex occurs only during rapid visual information processing, suggesting a specific modulation on task performance. Because of these properties, nicotine is being viewed as a potential cotherapeutic agent in schizophrenia and as therapeutic agents in Attention Deficit Hyperactivity Disorder. Nicotine has also been hypothesized to replete neurotransmitter levels and proves beneficial in Alzheimers' and Parkinsons' disease [11].

Nicotine has exhibited potential analgesic activity in animals and also is found to be involved in the regulation of leptin signalling,

suggesting that leptin and its receptor play a role in the anorectic effects of nicotine on food intake and body weight in rats [12]. Nicotine is also being investigated as an analgesic in humans [13]. Flood P *et al.* completed a pilot study of 20 women undergoing gynecological surgery. All the women had access to unlimited morphine and also got either a single 3-mg dose of nicotine nasal spray or a placebo. The placebo group had peak numerical analog pain scores of eight out of a possible ten in the first hour after surgery. Women who got nicotine averaged a pain score of five. Despite the small sample size, the results were highly significant [13]. Subsequently, many studies were done yielding conflicting results with some studies reporting increased pain in the first hour following surgery with use of nicotine [14].

Nicotine has thus been thoroughly researched upon for different pharmacological properties and beneficial effects; it has very little actual therapeutic use. Probably in the future, this may rise as a potential therapeutic agent rather than a substance of abuse.

Opioids

Opioids, obtained from the *Papaver somniferum* plant, have been used for thousands of years to treat pain and continue to be one of the most commonly prescribed medications for pain [15]. They relieve pain predominantly by acting on the peripheral μ receptors and both spinal μ2 receptors and supraspinal μ1 receptors, particularly on the limbic system. Thus, they target both the nociceptive and affective component of pain. While opioids are preferred in acute pain such as that post surgery, its efficacy in chronic cancer pain is debatable. The efficacy of opioids for chronic non-cancer pain has been demonstrated in only short-term trials, which includes opioids for neuropathic pain, but, evidence on the efficacy and effectiveness of these agents for a long duration of treatment which is typical for chronic non-cancer pain is limited [16-18].

In addition, numerous concerns have been raised about adverse effects including the development of psychologic addiction or abuse, or both, that may arise with long-term use [19].

Amongst the opioids, morphine is the opioid of choice for the treatment of moderate to severe cancer pain according to guidelines from the World Health Organization (WHO) [20]. Patients who experience inadequate pain relief or intolerable side can be switched to an alternative opioid. Oxycodone is a suitable alternative to morphine in the management of moderate to severe cancer pain and also as first-line treatment [21]. Patient Controlled Analgesia is an alternative method which is gaining popularity amongst cancer patients as the patient has the freedom to self-assess the need of a tailored analgesic dose.

The analgesic effect of anesthesia is often achieved using opioids. Commonly, synthetic and semisynthetic opioids such as fentanyl, oxymorphone, hydromorphone or natural opioids such as morphine are used in anesthesia [22].

Morphine intravenously has been used for several years for the early stabilization of patients with acute left ventricular failure patients based on its hemodynamic and sedative properties. Morphine has been reported to reduce preload, heart rate, and possibly afterload, the net effect of which is a reduction in myocardial oxygen demand [23]. But, a recent observational analysis from the ADHERE registry suggested that the use of morphine is associated with worse outcomes in acute heart failure, including the need for mechanical ventilation, increased the duration of hospital stay, a higher ICU admission rate, and a higher overall risk-adjusted mortality [24]. The AHA guidelines do not address morphine use for acute heart failure [25].

Semisynthetic opioid analgesics like codeine, dihydrocodeine, ethylmorphine, hydrocodone, and hydromorphone have potent cough suppressant actions and are therefore used in a dry cough. However, addiction liability remains a drawback. To mitigate this, a new synthetic opioid derivative, dextromethorphan, which is as potent as codeine but with the least addiction liability was developed. But, a meta-analysis of five studies with dextromethorphan and codeine in adults concluded that these central antitussives are marginally superior to placebo [26]. These are very much used even today and are available in combination with other agents like anti histaminics and bronchodilators.

A side effect of opioid use is constipation due to the activity on the peripheral μ2 receptors, and some opioids may, therefore, be used to control diarrhea. However, opioids are not usually used to control infective diarrheas due to the risk of serious, life-threatening consequences. Drugs such as diphenoxylate and loperamide, which are structurally related to pethidine, are useful in treating irritable bowel syndrome and some other organic causes of diarrhea [27].

Some opioids such as methadone and buprenorphine are used to help wean patients off some of the most potent opioids such as heroin. Methadone is given in low doses after stopping heroin to reduce dependency on the opioid but without causing severe withdrawal symptoms [28]. Opioids are found to suppress anxiety [29] and thus targeting the opioid network by opioid agonists may help treat anxiety.

Amongst all the agents of abuse, the most widely used as a therapeutic agent are no doubt the opioids. The adverse effects and limitations to their use have now been overcome by developing the more efficacious and safer synthetic and semisynthetic opioids.

Cannabinoids

Cannabis sativa, the hemp plant, has been used for its psychoactive properties for thousands of years. Tetrahydrocannabinol (THC), the main psychoactive component was isolated in 1964. Apart from THC, the other abundant cannabinoids are its precursor *cannabidiol*, and *cannabinol*, a breakdown product formed spontaneously from THC. Cannabidiol and cannabinol lack the psychoactive properties of THC, but can exhibit anticonvulsant activity and induce hepatic drug metabolism [30]. Most of the effects of cannabis preparations are based on the agonistic action of THC on the various cannabinoid receptors [31].

Cannabis preparations exert numerous therapeutic effects. They have antispastic, analgesic, antiemetic, neuroprotective, and anti-inflammatory actions, and are effective against certain psychiatric diseases. Currently, however, only one cannabis extract is approved for use. It contains THC and CBD in a 1:1 ratio and was licensed in 2011 for the treatment of moderate to severe refractory spasticity in multiple sclerosis (MS). The cannabis extract, which goes by the generic name nabiximols, has been approved by regulatory bodies in Germany and elsewhere for use as a sublingual spray [32].

Cannabinoid receptor agonists were developed in the 1970s in the hope that they would prove useful non-opioid/non-NSAID analgesics, but there had several side effects that outweighed its benefit. Nabilone is used clinically for nausea and vomiting caused by cytotoxic chemotherapy if this is unresponsive to conventional antiemetics. The antiemetic activity exhibited is due to activity on the cannabinoid Cannabinoid 1 and 2 receptors [33]. Another cannabinoid receptor agonist, dronabinol has been found to be as effective as ondansetron in delayed onset nausea [34]. In the USA, dronabinol has been licensed since 1985 for the treatment of nausea and vomiting caused by cytostatic therapy and since 1992 for loss of appetite in HIV/AIDS-related cachexia. The cloning of cannabinoid 2 receptors and their absence from healthy brain led to the synthesis of CB2-selective agonists in the hope that these would lack the CNS-related adverse effects of plant cannabinoids. Several such drugs are being investigated for possible use in inflammatory and neuropathic pain [35].

Cocaine

Cocaine is one of the thirteen alkaloids obtained from the leaves of the *Erythroxylon coca* plant nd brings about its activity by inhibiting the reuptake of serotonin, norephinephrine, and dopamine [40].

Coca leaves have been reported to exhibit antibacterial and antiparasitic effects in the treatment of stomach pain, infections and diarrhea. It also reduces fever, has anaesthetic effects during childbirth, body pain, toothache and irritations to skin and eye. Likewise, use of coca leaves is also found to have a regulatory effect on the blood circulation and heart; protect against lung diseases such as asthma, altitude sickness and embolism; have a stimulating effect in case of impotence and other forms of fatigue, and a calming and analgesic effect in case of central nervous disorders [41].

The therapeutic use of cocaine is however, limited to that of a local anaesthetic for surgery [40]. It was the use of cocaine that influenced the development of nerve and regional blocking techniques [42]. It also stimulated the development of local anaesthetics like lignocaine. Nowadays, due to the adverse effects of cocaine and the risk of addiction, the indications for the use of cocaine as an anaesthetic are strictly limited [42].

Hallucinogens

Research into the pharmacology and effects of psychedelics surged in the mid-2000s. Magic mushrooms, Lysergic Acid Diethylamide, ecstasy and ketamine, are being studied for legitimate therapeutic uses [43]. Scientists believe these agents have the potential to help patients with post-traumatic stress disorder, drug or alcohol addiction, unremitting pain or depression and the existential anxiety of terminal illness [43].

As of July 2014 most clinical research had been conducted with psilocybin, but other studies had investigated the mechanisms and effects of ecstasy, ketamine, and LSD. These studies included studies to mitigate anxiety in people with terminal cancer, in obsessive compulsive disorder and as an adjunct to psychotherapy for anxiety in people with serious illness [44, 45].

In general, presently these drugs remain poorly understood. Their effects are strongly dependent on the environment in which they are given and on the recipient's state of mind [44].

Sedative, hypnotic, or anxiolytics

Barbiturates and benzodiazepines belong to this class of drugs [1]. Barbiturates have been used as a preanaesthetic medication to relieve anxiety during surgery and in anaesthesia as fast inducing agents especially, the ultra-short acting thiopental [1]. It is also used as an anticonvulsant particularly for prophylaxis of febrile seizures in children. The intranasal route of midazolam, a short-acting benzodiazepine for febrile seizures in children is being developed and looked upon as a step forward in treating this common condition [45]. Pentobarbitone and thiopental have been used to control refractory intracranial hypertension in patients with severe traumatic brain injury, with thiopental appearing more effective than the former [46]. However, these drugs are seldom used these days because of their potential to cause cardiovascular and respiratory depression [47].

Benzodiazepines are commonly used sedative hypnotics to treat anxiety neuroses, insomnia, as anaesthetic medication, as skeletal muscle relaxants, as anticonvulsants and for the treatment of alcohol withdrawal [48].

Methaqualone is another recreational drug which is a central nervous system depressant and has sedative and hypnotic properties [49]. Its use peaked in the 1970s when it was used as a hypnotic for insomnia, as a sedative and a muscle relaxant [49]. The mechanism of action of this drug is increased activity at the GABA receptors in the brain, similar to that of benzodiazepines and barbiturates [49].

Amphetamine

Amphetamine brings about its psychomotor stimulating effects by displacing dopamine and norepinephrine from the storage vesicles and inhibiting the metabolism of dopamine by inhibiting the monoamine enzyme oxidase-B. [1] The amphetamines are used in Attention Deficit Hyperactivity Disorder [50], narcolepsy and as appetite suppressants [1]. It is often prescribed off-label for its past medical indications, such as depression, obesity, and nasal congestion [51]. Oehen P *et al.* [52] reported that methylenedioxy methamphetamine assisted psychotherapy was more effective than non-assisted psychotherapy in Post Traumatic Stress Disorder in 12 patients which were in accordance with earlier studies. Schuster C *et al.* [53] reported that dexamphetamine augmented physiotherapy for upper arm during rehabilitation after stroke in a pilot study of 16 patients. Many studies have also explored the usefulness of one analogue to treat addiction to another amphetamine analogue. Galloway GP *et al.* [54] reported that dextroamphetamine 60 mg sustained release tablet for 8 w along with 50-minute sessions of individual psychotherapy led to significant reductions in withdrawal and craving scores compared to placebo. Greenwald MK *et al.* [55] showed the ability of sustained release amphetamine to attenuate cocaine self-administration, as well as its selectivity, in cocaine/ heroin polydrug abusers in buprenorphine stabilized patients in a pilot population.

Amphetamine and its analogues have been used extensively for their psychostimulant and neuroprotective properties [1]. But as suggested from the above-mentioned studies performed in a small number of patients, they may also prove to be useful in neurological disorders and drug addiction. Larger studies are warranted to prove these observations with certainty [52-55].

CONCLUSION

The restricted availability of these compounds and stringent rules and regulations governing them makes research with these agents very difficult. But with the resurgence of interest in these agents as research tools, we can expect many more therapeutic benefits to be discovered particularly with respect to cerebrovascular and cardiovascular disorders.

CONFLICTS OF INTERESTS

The authors hereby declare no conflicts of interest

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