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History of Pharmacological Treatment for Substance Use Disorders

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The pharmacological treatment of substance use disorders developed in tandem with the medicalization of these problems in the late eighteenth and early nineteenth centuries (Levine, 1978). Dr. Benjamin Rush (1784) described one of the earliest pharmacological treatments for chronic drunkenness—the use of an emetic to create a conditioned aversion to alcohol. During the nineteenth century, pharmacological adjuncts were used within the inebriate asylums and private addiction cure institutes in the United States and Europe. Agents used to aid detoxification included alcohol, chloral hydrate, strychnine, mercury, arsenic, atropine, belladonna, hyoscyamus, coca, cannabis indica, opium, atropine, hyoscyamus, belladonna, sulphur, quinine, and paraldehyde. Many of the addiction cure institutes (e.g., the Keeley Institutes) centered their treatments on medicinal specifics (usually combinations of strychnine, atropine, cocaine, codeine, and apomorphine) that promised to destroy the morbid craving for alcohol and opiates. These specifics were also sold as bottled home cures. The success of the Keeley products spawned many patent medicine cures for addiction. Repeated exposés of addiction cures that secretly contained alcohol, opium, morphine and cocaine led to prescription and product labeling laws (White, 1998).

The use of cocaine as a treatment for alcoholism and morphine addiction achieved brief popularity. Medical reports as early as 1880 described successfully treating morphine addicted patients with pounds of prescribed cocaine (Bently, 1880). The most famous of such claims was Sigmund Freud's 1884 laudatory essay on cocaine was retracted in 1887 with an acknowledgement of cocaine's addiction potential. Another unusual treatment for alcoholism in the 1880s involved the substitution of opiates for alcohol. This substitution was recommended on the grounds that morphine was cheaper and less physically (Black, 1889).

Pharmacological adjuncts in the treatment of alcoholism during the early twentieth century included a surge in interest in apomorphine, ipecac, and other emetics as aversive agents (Crothers, 1902). These treatments became particularly popular in Europe following experiments by Russian researcher N.V. Kantorovich in the 1920s and the development of clinical protocol for the use of apomorphine by English physician, Dr. John Dent. The treatment of alcoholism using aversion therapy was later re-popularized in North America by Dr. Walter

Voegtlin and Dr. Frederick Lemere at the Schick's Shadel Hospitals (Shadel, 1944). Early twentieth century treatments for alcoholism also included experiments with an alcoholism vaccine; use of a mixture of belladonna, hyoscyamus and xanthoxylum; glucose and insulin injections; and experiments with metrazol- or cardiazol-induced convulsions (Sournia, 1990; Corwin and Cunningham, 1944).

There were three approaches to narcotic withdrawal in the late nineteenth and early twentieth centuries: 1) rapid and complete withdrawal, 2) gradual withdrawal utilizing a step-down of drug dosage over a short period of time, and 3) prolonged withdrawal over an extended period of time. Pharmacological adjuncts used to facilitate these processes included narcotic substitutes (e.g., codeine); non-narcotic substitutes (cannabis indica, strychnine, belladonna, atropine, cocaine, quinine, whiskey, and coffee); purgatives to speed the elimination of toxins; sedatives to provide comfort and sleep (e.g., chloral hydrate, bromides, sulphonal, trional, and veronal); aversive agents (e.g., tartar emetic); drugs whose resulting disorientation reduced flight from treatment (e.g., hyoscine or atropine); and plant specifics thought to destroy narcotic craving (e.g., Avena sativa or Viola sagittata) (Kolb & Himmelsbach, 1938).

Formal narcotic addiction withdrawal protocols of the early twentieth century included the Lambert-Towns treatment (a combination of belladonna, xanthoxlyun, hyoscyamus, strychnine, and digitalis), the Petty method (atropine, scopolamine, sparteine sulphate, and sodium thiosulfate), the Sceleth method (scopolamine, pilocarpine, ethyl-morphin, strychnine, and various cathartics), the Nellens and Massee method (mercurous chloride, magnesium sulphate, and chloral) and Narcosan treatment (a mixture of lipoids, proteins, and vitamins). There was also a brief (1919-1925) American experiment with morphine maintenance clinics as a method of treating intractable addiction, but these clinics closed when physicians were threatened with federal indictment (White, 1998). Some therapies of this period defy explanation: "serum therapies" in which blisters were raised on the addict's abdomen and thighs and then the fluid from the blisters was withdrawn and re-injected into the addict during narcotic withdrawal; "blood therapies" in which blood was withdrawn and then re-injected during withdrawal; and "bromide sleep treatments" that had mortality rates of 20 percent (Kolb & Himmelsbach, 1938; Kleber & Riordan, 1982).

Several pharmacological advancements occurred in the treatment of alcoholism in the mid-twentieth century, including the introduction of vitamin B-3 (Niacin) and related nutritional therapies, brief experiments in the use of a variety of adrenal steroids and adrenocorticotropic hormones, and the use of tranquilizers, sedatives and amphetamines (Corwin and Cunningham, 1944). Sedatives and amphetamines (Bloomberg, 1939) were prescribed to treat the depression thought to be the etiological source of alcoholism. These substances fell out of favor in the treatment of alcoholism following discovery of their abuse addictive potential. However, benzodiazepines (particularly chlordiazepoxide (Librium®) and diazepam (Valium®) continued to be used in alcohol detoxification and presently are the medications of choice for that purpose. Other drugs used in the treatment of alcoholism during the mid-twentieth century include Lithium and various anti-depressant medications.

Disulfiram, was introduced in 1947 by two Danish researchers, Jens Hald and Erik Jacobsen, following discovery that disulfiram interfered with the breakdown of alcohol, resulting in flushing, sweating, nausea and other unpleasant side effects (Hald & Jacobsen, 1948). As an adjunct in the treatment of alcoholism, it was hoped disulfiram would provide a chemical shield protecting the alcoholic from a return to drinking. Although disulfiram and drugs with similar effects were widely marketed under such trade names as Antabuse, Abstinyl, Antiethyl, Aversan, Contralin, Esperal, Stopetyl, Refusal, Temposil, and Abstem and continue to be used in many parts of the world, their utility has been limited by medical contraindications for some patients, unpleasant side-effects, the requirement for continued voluntary or monitored administration,

and research findings suggesting a substantial placebo effect and only modest (at best) specific effect (Miller, & Hester, 1986).

LSD was introduced into the treatment of alcoholism by two Canadian psychiatrists, Dr. Abram Hoffer and Dr. Humphry Osmond. Between 1949 and 1966, LSD was employed by many researchers and psychotherapists to treat of alcoholism. The use of LSD in the treatment of alcoholism faded with its emergence as a drug of abuse and controlled studies that challenged claims of its effectiveness (Miller & Hester, 1986).

Mid-twentieth century treatments for narcotic addiction paralleled treatments for alcoholism, e.g., insulin-coma therapy, "hibernation therapy" (withdrawal aided by sodium pentothal narcosis), apomorphine and socinyl choline to induce aversion to narcotics, phenothiazines as an aid in withdrawal, LSD as an adjunct in psychotherapy, and the use of methamphetamine as a medically prescribed substitute for heroin (Kleber and Riordan, 1982).

Nalline (nalorphine), a semi-synthetic derivative of morphine with narcotic antagonist properties, was synthesized in 1941 and was followed by other antagonists, e.g., naloxone, cyclazocine, pentazocine, naltrexone and buprenorphine. In the early 1960s, William Martin and Abram Winkler began using daily doses of a narcotic antagonist to block the euphorogenic effects of narcotics. An early review of these procedures by Senay and Renault (1971) found problems related to unpleasant side effects, effectiveness contingent upon high patient motivation, and severe withdrawal following regular use. Later reviews noted particular populations (e.g., opiate-addicted physicians) for whom antagonist therapy was highly effective (Washton, Gold, and Pottash, 1984).

Dolophine (methadone), a long-acting synthetic narcotic that was developed in Germany in 1943, has played a unique role in the modern treatment of narcotic addiction. It first entered addiction treatment in the late 1940s as a detoxification agent. In 1964, two American physicians, Dr. Marie Nyswander and Dr. Vincent Dole (1968), announced a new protocol for the treatment of heroin addiction that used orally administered "blockade" doses of methadone as a maintenance agent for chronic opiate addicts. Early evaluations of methadone maintenance treatment revealed substantial effects in reduced drug use, criminal activity and health-related problems and increased rates of employment and psychological and social health (Senay & Renault, 1971).

Although Methadone continues to be the dominant medication used in the treatment of opiate addiction, LAAM (levomethadyl acetate hydrochloride) was tested in the latter 1970s as a pharmacologic alternative. Originally synthesized in 1948 as an analgesic, LAAM was found by Fraser and Isabel (1952) to suppress opiate withdrawal symptoms for more than 72 hours. Studies conducted during the 1970s found that orally administered LAAM has the same ability as methadone to block the actions of other opiates (e.g., heroin) while alleviating narcotic withdrawal symptoms, and to have no adverse effects (National Institute on Drug Abuse, 1993). Methadone clients who were given LAAM indicated that they preferred the latter because it made them feel "more stabilized" (Goldstein, 2001). However the drug languished until the HIV/AIDS epidemic began to spread to intravenous injection drug users in the 1980s. LAAM was approved by the FDA as a pharmacological treatment for opiate dependence in 1993, but never achieved widespread use.

A major shift in the science of opiate detoxification occurred when research was published showing that Catapres® (clonidine), an alpha 2-adrenergic agonist primarily used to treat hypertension, was capable of suppressing a wide range of opiate withdrawal symptoms (Gold, Pottash, Sweeney & Kleber, 1980). Unlike all previous medications used for this purpose, clonidine does not produce sedation or intoxication nor occupy brain opiate receptor sites, but rather acts on the locus ceruleus to suppress adrenergic activity and reduce the intensity of withdrawal symptoms. Clonidine does produce light-headedness, faintness or postural

hypotension in some patients, even at relatively low doses. However, in patients who can tolerate clonidine, these same side effects as well as the drug's lack of sedating and intoxicating effects discourage drug-seeking behavior and requests for higher doses that can occur in methadone-maintained clients. Clonidine has also been used as a final detoxification agent following decreasing doses of methadone (Kleber, Gold & Riodan, 1980). A related substance, lofexidine, a structural analogue of clonidine, was found to be equal to and in some cases superior to the latter in the detoxification of opiate addicts. It has been used in the United Kingdom since 1991 under the brand name BritLofex to withdraw patients from opiates.

Buprenorphine is an atypical narcotic with both agonist and antagonist properties, i.e., it produces typical opiate effects and will prevent withdrawal symptoms in dependent drug abusers at lower doses but can block the effects of "full agonists" such as heroin and precipitate withdrawal symptoms at higher doses. In October 2002, the FDA gave approval to market a sublingual buprenorphine monotherapy product, Subutex®, and a buprenorphine/naloxone combination product, Suboxone®, for use in opioid addiction treatment. The combination product is designed to decrease the potential for abuse by injection, since naloxone produces antagonist effects when administered intravenously, but does not do so when taken sublingually. The approval of buprenorphine ushered in a new era in the treatment of opiate dependency in the United States since licensed physicians trained in the use of the drug were allowed to dispense it from their offices.

The precipitous increase in the use of cocaine in the 1970s and 1980s led to increased research into pharmacological methods of treatment. The goal of pharmacological treatment is to prevent or minimize the potential for cocaine relapse by reducing depression, anxiety and drug hunger. The neurochemical mechanism that underlies these withdrawal problems (depletion of adrenergic neurotransmitters- particularly dopamine) was understood by the 1970s, and most approaches to the pharmacological treatment of cocaine dependency centered on normalizing brain chemistry. Drugs tested for their potential use in the treatment of cocaine dependency included the tricyclic antidepressants (Gawin & Kleber, 1984), MAO-A/B-inhibitors (e.g., phenelzine) (Maletzhy, 1997), bromocriptine (Parlodel®) (Dackis and Gold, 1985), fluoxetine (Prozac®)) and sertraline (Zoloft®) (Kosten, et, al., 1992; Covi, et. al., 1994), methylphenidate (Ritalin®) (Khantzian, Gawin & Riordan, 1984), and amantadine (Symmetrel®). While initial reports were positive, further studies revealed mixed or harmful results (Gawin, Riordan, and Kleber, 1985; Weiss, 1988; Handelsman, Rosenblum, et. al., 1997).

In the early 1990s, the National Institute on Drug Abuse commissioned a meta-analysis of the existing literature on the pharmacological treatment of cocaine dependency. The resulting report indicated that Antabuse was the only medication that consistently reduced the incidence of cocaine relapse (Rawson, 1993). Initially, it was hypothesized that disulfiram simply reduced cocaine relapse by discouraging alcohol consumption and thus the impairment of judgment and impulse control that often results from drinking. Later, however, it was found that disulfiram reduces the presence or intensity cocaine craving and/or reduce the intensity of cocaine reward (Petrakis, Carroll, Nich, et. al., 2000) due to its effect on dopamine and norepinepherine.

Recent animal research (Woolverton, et. al., 2002) has held out the hope the cocaine analog, (+)-CPCA ("norcaine") might be useful in mitigating the aversive effects associated with cocaine abstinence. A final medication that appears to hold promise for the treatment of cocaine dependence is gamma vinyl-GABA (GVG), an anti-epilepsy drug marketed as Vigabatrin®. GVG is known to inhibit dopamine increases in the nucleus acumens, a vital part of the human "reward pathway", and a site of action for most abused drugs (Gerasimov, Ashby, Gardner, et, al., 1999). Investigators conducted a study in which daily administration of GVG over a period of 2-3 weeks reduced and eventually eliminated craving for cocaine (Brodie, Figueroa & Dewey, 2003).

On-going research has also led to the realization that medications previously thought to be helpful in treating only limited types of dependency might have a much broader applicability. The finding that administration of naltrexone to animals could decrease consumption of alcohol led to the initiation of studies using human subjects, and subsequently, two studies demonstrated that naltrexone could have the same dampening effect on drinking in human subjects (Volpicelli et al., 1992; O'Malley, Jaffe, et. al., 1992). In 1994, the FDA officially approved the use of naltrexone for the treatment of alcoholism. A naltrexone metabolite, 6-beta naltrexol, has shown promise for drinkers whose pre-existing liver damage precludes their use of naltrexone. Animal studies involving 6-beta naltrexol have produced hopeful results, and it has been found that this drug has a longer duration of action than its parent compound (Rukstalis, et. al., 2000). Recent research has also focused on Acamprosate (calcium acetylhomotaurine). Although this drug is not yet approved for use in the United States, studies in Europe have shown that acamprosate appears to reduce relapse rates following a period of abstinence, perhaps by blunting the euphorigenic effects of alcohol. Acamprosate is commonly thought to work by simultaneously inhibiting the receptors of the inhibitory neurotransmitter, GABA and while enhancing those of N-methyl-D-aspartate (Berton, et. al., 1998). One major advantage of using this drug is that it is not significantly metabolized in the liver, making it safer for those with liver disease.

In the early years of the 21st century, interest in the use of ibogaine has increased virtually worldwide. Ibogaine is an indole hallucinogen derived from the root of the African shrub Tabernanthe iboga, which has traditionally been used as a medicinal and ceremonial agent in West Central Africa. Although no controlled scientific studies have been done with humans, anecdotal reports, some published in major journals, have indicated that single dosages of this substance appears to reduce or eliminate craving for abused substances in addicted individuals as well as alleviate withdrawal symptoms associated with cessation of heroin, cocaine and alcohol dependence (Sheppard, 1994). The hypothesized mechanism for such effects is a yet-unspecified "resetting" or adaptation of neurotransmitter levels. Although such reports seem incredulous, they come from credible sources, and cause one to wonder what the future of pharmacological treatment of addictive disorders may bring.

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