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History of Opioid Addiction and Steps Taken for De-addiction

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ABSTRACT

Opioids are one of the world's oldest known drugs. The medical, recreational, and religious use of the opium poppy is going on since centuries. In the 19th century morphine was isolated and marketed. Synthetic opioids were invented in the 20th century.

Non-clinical use of opioid was criminalized in the United States by Harrison Narcotics Tax Act of 1914, and by other regulations and ruling worldwide. Since then, nearly all non-clinical use of opioids has been barred from approval of nearly every social institution. However, in United Kingdom the 1926 report of the Departmental Committee on Morphine and Heroin Addiction under the Chairmanship of the President of the Royal College of Physicians reestablished medical control and introduced the "British system" of control, which lasted till the 1960s. In the U.S. the Controlled Substances Act of 1970 markedly relaxed the harshness of the Harrison Act.

Before the 20th century, institutional approval was mostly higher, including in Europe and America. In some cultures, opioid approval was significantly higher than approval of alcohol. This lead to large scale problem of opioid addiction. Subsequently various treatment options for opioid withdrawal and opioid addiction have been introduced.

Key words: Morphine addiction, Opioid withdrawal, History of Opioid abuse, Drug dependence.

For thousands of years, humans have used drugs of one sort or another. The use and misuse of narcotics had been known since 4000 B.C., however, it was in the 19th century A.D. that active substances of poppy, a well-known narcotic, were extracted. Then followed a time when some of these newly discovered compounds like, morphine, laudanum, cocaine were totally unregulated and freely prescribed by the physicians for a large variety of ailments. They were available in patent medicines and sold by travelling tinkers, in medical stores, or they arrived through the mail. During the American Civil War opium dens flourished[1], there was free distribution of morphine, and wounded veterans returned home with their kits of morphine and hypodermic needles.

As long as 3400 B.C., the poppy plant was grown in the lower Mesopotamia region. The most ancient testimony related to the opium poppy till date was carved in cuneiform

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script on a small white clay tablet during the end of the third millennium BC. This tablet was found in 1954 at the time of excavations at Nippur, and is presently placed at the University of Pennsylvania, Museum of Archaeology and Anthropology. It was deciphered by Samuel Noah Kramer and Martin Leve. It is thought to be the most ancient pharmacopoeia in existence[2].The Sumerians named it as *Hul Gil* or the 'joy plant.' The Sumerians passed the knowledge of poppy cultivation to the Assyrians, the Babylonians, and later on to the Egyptians[3].

By 1300 B.C. the Egyptians were farming *Opium thebaicum*, named after their capital city of Thebes. From Thebes, the Egyptians traded opium in all over the Middle East and into the Europe. The effects of opium were considered to be magical or mystical throughout this period. As mentioned by a Roman writer, Prosper Alpinus, Egyptians used to prepare and drank opium in the form of 'Cretic Wine', which they flavoured by adding pepper and other aromatics. Interpretations of certain sections of the Old Testament suggest that Opium was known to the ancient Hebrews. Their word *merosh*, meant to the juice of the Poppy and the word rosh, is believed to refer to the head of the Poppy[4].

Papyrus Ebers, which happens to be the earliest record in medicine dated about 1550 BC, also mentions opium in its record. This document was found with a mummy in a tomb near Luxor, a town on the east banks of the river Nile. It describes a mixture of opium and another material, which was found effective in quietening crying children[4].

The Greek physician, Hippocrates, some eight hundred years later, dismissed the notion that opium was "magical." Instead, he found out that it is effective as a painkiller and a styptic (a drug used to stop bleeding.)

Around 330 B.C. Alexander the Great carried opium to the people of Persia and India, where the poppies later came to be grown in vast quantities. By 400 A.D., *opium thebaicum* was introduced to China by Arab traders.

Homer (The Greek poet, ninth century BC) mentions opium in his epics Iliad and Odyssey. In his time, the use of a peculiar drug, Nepenthes, also known as the 'drug of forgetfulness' was fairly common in Greece. Opium was a major constituent of Nepenthes. Likewise, when Telemachus, one of the Trojan War heroes visited Menelaus in Sparta, he was extremely nervous about the fate of his father, Odysseus. At this time, wife of Menelaus, Helen, gave Nepenthes to him so that he could not remember his worries[4, 5].

Asia minor or modern-day Turkey is possibly the original home of opium poppy. It was from here that opium spread to other places. Hebrews called it ophion and Arabs, af-yunboth. The Chinese o-fuyung was in turn derived from the Arabic word[4].

The Greek physician, Hippocrates (460-377 BC), known as the 'father of medicine' was possibly aware with poppy juice and referred to it as substance called mecon with both antipurgative and narcotic action. However, Greek botanist, Theophratus (327-287 BC), applied term meconium, which is the first authentic reference to the juice of the poppy[4].

Galen was the leading practitioner of medicine in Roman Empire from about 169 - 192 AD. It was Galen who so devotedly acclaimed the qualities of opium that its popularity grew to new heights by the end of the second century. Roman emperor, Severus released opium for common use following which the drug was even distributed by roman shopkeepers and quack.

Approximately 220-264 A.D., the noted Chinese surgeon Hua To used opium preparations and *Cannabis indica* for the patients to swallow before undergoing major surgeries[6].

Arab physicians used opium extensively, the most eminent of whom was IbnSina (980-1037 AD). IbnSina recommended opium especially for diarrhoea and eye problems[7] and it is said that he himself succumbed to an overdose of the drug[8].Opium was introduced to the East by Arab traders around 980-1037 AD. Alcohol prohibition by the Holy Quran made Muslims very vulnerable to the use of opium. The mughal emperors, Babur, Humayun and Akbar, were habitual opium-eaters[4, 7].

In the ninth century, the Arab traders brought opium to China and other parts of the eastern world. In his description of the Malabar Coast, Barbosa quoted opium as an Indian product on his travels to India in 1511. In 1546, the French naturalist, Belon, travelled through Asia and Egypt and found Turks to be the greatest addicts of opium who used to prepare and purchase it with their last penny.

Doctors sang its praises during the early days as an effective medicine while literatures cited it, as a 'thought-provoker'. Along with its very strong suppressive action on pain, it suppresses cough and causes constipation, thus it was found very useful in cough and diarrhoea. 'Laudanum' (from the Latin word Laudare, meaning 'to praise') which is a solution of opium became one of the most commonly used drug in the seventeenth century for treating dysentery. Laudanum was nothing but a solution of opium in alcohol known as 'tincture of opium' (10 percent Opium or 1 g of morphine to 100 cc of alcohol). The British physician, Thomas Sydenham (1624 - 1689) known as 'the English Hippocrates', flavoured the tincture with saffron, cinnamon and clover. An official stamp of approval by encouraging its use in dysentery and other such conditions was also put by Sydenham. The famous 'Dover's powder' was developed by Dr. Thomas Dover (1660-1742) which contains 10% of opium. Dover's powder became a popular remedy for alleviation of pain and cough. Paracelsus (1493-1541) Swiss physician, mentioned opium as the 'stone of immortality'. Three centuries later Oliver Wendell Homes (1809-1894) the famous US writer and physician, also admired its uses. The famous Anglo-Canadian physician, Sir William Osier (1849-1919), referred Opium as 'God's own medicine' [4].

Alkaloids of Opium

One fourth of the weight of raw opium comprises of about twenty five different alkaloids. Morphine is the major alkaloid and constitutes about 10 to 20 per cent of raw opium. In 1805 a German pharmacologist Friedrich Wilhelm Adam Sertürner (1783-1841) isolated morphine from raw opium.

Morphine dissolves readily in boiling water, about one part dissolving in 500 parts of boiling water; however it is very sparingly soluble in cold water. Because of this property, these days morphine is extracted by placing raw opium in boiling water and removing the undissolved opium gum and then processing the solution to obtain morphine. It is officially prepared in about 3" x 4" x 1" size blocks, measuring about 300 to 350 gms and often marked with the trade marks '999' or 'AAA'. Approximately 10 kg of raw opium is required to extract 1 kg of morphine. As the poppy capsule ripens the morphine percentage in it quite paradoxically starts decreasing. Only traces of morphine can be found in ripe and dry poppy capsules (about 0.1 per cent) [4].

The French chemist, Pierre Jean Robiquet (1780-1840), in 1817, isolated noscapine and he also isolated alkaloid codeine in 1832 from opium. French chemist, Pierre Joseph Pelletier (1788-1842), isolated thebaine from opium in 1835. George Merck (1815-1888), is a German chemist, who isolated papaverine from raw Opium in 1848. Heroin, which is a diacetyl-morphine, was prepared by Heinrich Dreser in the year 1898[4].

Drug dependence

The Tenth Revision of the International Classification of Diseases and Health Problems (ICD-10) defines the dependence syndrome as being a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value[9]. Dependence on drugs comprises of three distinct and independent features: tolerance, physical dependence, and drug-seeking behaviour resulting in compulsive abuse or psychic craving as pointed out by Goldstein and colleagues[10]. Also, these features are noticed in different intensity and degrees with different drug dependence. In some cases of drug dependence, only one or two of these components are present. "An example of tolerance and physical dependence without compulsive abuse is provided by the morphine congener and antagonist nalorphine"[10].

Psychic dependence

Psychological or psychic dependence refers to the experience of impaired control over drinking or drug use (WHO, 2014)[11]. Psychic dependence is characterized by compulsive drug-seeking behaviour in which the individual consumes the drug repetitively for personal satisfaction, even after its known risks to health[12].Tolerance may or may not be present and if present its usually either of pharmacokinetic type or tachyphylaxis but rarely pharmacodynamic. Withdrawal effects are less frequent and mild in psychic dependence which can be tolerated as these are never life threatening[13].

Physical dependence

Physiological or physical dependence is characterized by intense craving for the drug, tolerance (mainly pharmacodynamic) is invariably present and withdrawal effects are severe. In biologically-oriented discussion, dependence is often used to refer only to physical dependence[11]. Physical dependence is present when withdrawal of the drug produces symptoms and signs that are frequently the opposite of those sought by the user. It has been postulated that the body adjusts to a new level of homeostasis during the period of drug use and reacts in an opposite manner when this newly set equilibrium is disturbed. Physical dependence is almost always preceded by psychic dependence but does not inevitably lead to it[12].

Drug Tolerance

Tolerance is defined as a decrease in pharmacologic response following repeated or prolonged drug administration. Tolerance signifies a decreased response to the effects of the drug, necessitating ever-larger doses to achieve the same effect. Physical dependence and tolerance are closely associated. There are two main classifications of tolerance: innate or acquired. Innate tolerance is due to pharmacogenetic makeup of individual which predisposes to drug sensitivity or insensitivity. Innate tolerance, in most situations is exhibited upon administration of the initial dose. However, acquired tolerance is a manifestation of repeated exposure to the drug. It can be subdivided into three basic types based on the prevailing mechanism: pharmacokinetic, pharmacodynamic, or learned. Pharmacokinetic tolerance occurs when drug disposition or metabolism is altered as a function of time, often a consequence of the drug being an inducer or inhibitor of a specific metabolic enzyme or transporter system, resulting in a time-dependent decrease in presentation of the active moiety to the receptor bio phase. Reduction of intrinsic response of the receptor system over time occurs in case of pharmacodynamic tolerance[14]. The drug's pharmacodynamic action is mitigated largely due to the compensatory responses. Behaviour tolerance, which is an ability to compensate for the drug's effects, can be another possible mechanism of tolerance. Behavioural tolerance is said to occur when a person learns to function in spite of repeated exposure to a drug. For example, chronic alcohol abusers may not show an outward appearance of motor impairment as a consequence of intoxication because of awareness of their impairment and learned motor function adaptations.

Conditioned tolerance is based on Pavlovian principles in which situational or circumstantial cues are associated with drug administration. Removal of these environmental cues will result in an enhancement in pharmacologic effect. Functional tolerance, which is thought to be the most common type, is due to compensatory changes in receptors, effecter enzymes, or membrane actions of the drug[12].

Acute tolerance is predominantly mediated by pharmacodynamic mechanisms, presents as a decreased sensitivity after a single administration of the agent or during repeat-dosing but develops in a short time frame. This phenomenon is exemplified by nasally-administered cocaine. In contrast to acute tolerance, chronic tolerance can be mediated through either pharmacokinetic or pharmacodynamic mechanisms, with an end result of a long-term decrease in drug response in the face of constant systemic exposure. In cases in which chronic tolerance develops, cross-tolerance within the pharmacologic class also may occur. Replacement of the initial drug with a similar agent results in a diminished pharmacologic effect in comparison to that experienced by a drug-naive person. Cross-tolerance is the principle underlying basis for methadone substitution in the treatment of heroin addicts.

Opioid Withdrawal Syndrome:

Abrupt termination of opioids in a physically dependent person leads to the development of withdrawal signs and symptoms. The only actual evidence of physical dependence is the appearance of a withdrawal syndrome when the administration of drug of abuse is terminated. The withdrawal syndrome is very unpleasant but not life-threatening. The withdrawal symptoms are apparent within 6 to 12 hours after the last dose of a short-acting opioid and can stay for as long as 72 to 84 hours in case of a very long acting opioid medication[15].

SYMPTOMS	SIGNS
Regular withdrawal	Pupillary dilation
Craving for opioids	Sweating
Restlessness, irritability	Piloerection (gooseflesh)
Increased sensitivity to pain	Tachycardia
Nausea, cramps	Vomiting, Diarrhea
Muscle aches	Increased BP
Dysphoric mood	Yawning
Insomnia, Anxiety	Fever
Protracted withdrawal	Cyclic changes in weight & pupil size
Anxiety	Respiratory center sensitivity
Insomnia	
Drug craving	

DSM-5 Criteria for Opioid Withdrawal

Description:

DSM-5 Criteria for Opioid Withdrawal (APA, 2013)[16]

A. **Any** of the following:

1. cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer)
2. administration of an opioid antagonist after a period of opioid use

B. **Three (or more)** of following, developing within minutes to several days after Criterion A

1. dysphoric mood
2. nausea or vomiting
3. muscle aches
4. lacrimation or rhinorrhea
5. pupillary dilation, piloerection, or sweating
6. diarrhoea
7. yawning
8. fever
9. insomnia

C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The signs or symptoms are not due to another medical condition and are not better accounted for by another mental disorder, including intoxication or withdrawal from another substance.

Opioid Use Disorders (Amerian Psychiatric Association, 2013)

The American Psychiatric Association (APA) uses the terms Opioid Use Disorders and Opioid Induced Disorders under opioid-related disorders. Opioid use disorders include 'opioid dependence' and 'opioid abuse' instead of addiction for the overall behaviour syndrome (DSM 5). According to APA, substance dependence (addiction) is defined as a cluster of symptoms indicating that the individual continues use of the substance despite significant substance related problems. Evidence of tolerance and withdrawal symptoms are included in the list of symptoms, but for the diagnosis of substance dependence neither tolerance nor withdrawal is necessary or sufficient.[16]

Prevalence

In 2014, an estimated 1.9 million people had an opioid use disorder related to prescription pain relievers and an estimated 586,000 had an opioid use disorder related to heroin use. Overdoses with opioid pharmaceuticals led to almost 17,000 deaths in 2011. Since 1999, opiate overdose deaths have increased by 265% among men and 400% among women[17].In India, it is estimated that 75 million people are alcohol users and nearly 3 million are opioid users[18]. The prevalence of opium use in India has also been increasing and it is now considered to be a 'party drug' or 'relaxation drug'. Several studies have described the prevalence of opium abuse to be 1.51-2 %[19], although in another study it was noted to be around 0.4%[20].The 12-month prevalence of opioid use disorder is approximately 0.37% among adults age 18 years and older in the community population[21]. Though, it can be an underestimation of the real problem because of the large number of incarcerated individuals with opioid use disorders[22]. Males are affected more than females (0.49% vs. 0.26%), with the ratio of male-to-female being 1.5:1 for opioids other than heroin (i.e. prescription drugs) and for heroin it is 3:1. There is a higher likelihood of opioid use disorders, to develop in adolescent females[23]. There is decrease in prevalence with age, with the prevalence being highest (0.82%) among adults who are 29 years or younger in age, and it is reduced to 0.09% in adults age 65 years and older. The prevalence of opioid use disorder is lower among African Americans adult at 0.18% and overrepresented among Native Americans at 1.25%. It is almost similar among whites (0.38%), Asian or Pacific Islanders (0.35%), and Hispanics (0.39%)[23].

Development and course

Substance abuse disorders including opioids can involve any age group, but problems of opioid abuse are most often first noticed in the late teens or early 20s. Once developed, the opioid use disorder usually remains over a large period of many years, even though brief periods of abstinence are also seen sometimes. Relapse following abstinence is commonly seen in population which has been treated. Even though relapses do occur, long term abstinence is achieved in 20%-30% of the opioid dependent population, while some long-term mortality rates may be as high as 2% per year[24]. As a result of early mortality, increasing age is associated with a decrease in prevalence; also there is remission of symptoms and signs after 40 years of age (i.e., "maturing out"). Although, many opioid abusers continue to have presentations that meet opioid use disorder criteria for decades[25].

Management Principles and Alternatives

The development of desired therapy for opioid abuse is of much importance given the devastating consequences of the disease. Pharmacotherapies for opioid addiction include opioid agonists, partial agonists, opioid antagonists, and alpha-2-adrenergic agonists, which are targeted toward either detoxification or long-term agonist maintenance. Management of opioid use disorders is made complex by the intoxication and withdrawal episodes.

Diagnostic Criteria: (DSM-5, APA 2013)

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Strong desire, urge or craving to use opioids.
5. Inability to fulfil the main obligations at work, school or home because of the recurrent opioid use.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Because of the use of opioid all the important social, occupational, or recreational activities are reduced or completely given up.
8. Recurrent opioid use inspite of the situation being physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.

b. A markedly diminished effect with continued use of the same amount of an opioid. Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.

11. Manifestation of withdrawal by presence of features as mentioned below:

a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal).

b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms

Score the severity as "mild" if 2 or 3 criteria are met, "moderate" when 4 or 5 features are met, and "severe" if 6 or more criteria are present.

Opioid use disorder are associated with drug-related crimes (e.g., possession or distribution of drugs, forgery, burglary, robbery, larceny, receiving stolen goods), which are supportive of the diagnosis. Among health care professionals and individuals who have ready access to controlled substances, there is often a different pattern of illegal activities involving problems with state licensing boards, professional staffs of hospitals, or other administrative agencies. Unemployment, irregular employment and marital difficulties (including divorce), are linked with opioid use disorder often at almost all socioeconomic levels.

Diagnostic markers: (DSM-5, APA 2013)

Toxicology test results on urine are often found positive for opioid drugs in persons with opioid abuse disorder. Test results of urine continue to be positive for most of the opioids (e.g., heroin, morphine, codeine, oxycodone, propoxyphene) after administration for 12–36 hours. Standard urine tests does not detect fentanyl, however it can be identified by other specialized methods for several days. Drugs which have to be specifically tested and that will not have a positive result on routine screening tests for opiates are buprenorphine (or buprenorphine / naloxone combination), methadone and LAAM (L-alpha-acetylmethadol). They can be detected by specific tests for up to or more than 1 week. The lab evidence of the presence of other substances is common (like, cocaine, alcohol, amphetamines, marijuana, benzodiazepines). Results of screening test for hepatitis antigen (signifying active infection) and hepatitis antibody (signifying past infection)- for hepatitis A, B, and C virus are also positive in approximately 80%–90% of parenteral opioid users,. HIV is also very prevalent in i.v. opioid users. Mildly elevated liver function test results are common, either as a result of resolving hepatitis or from toxic injury to the liver due to contaminants that have been mixed with the injected opioid. Subtle changes in cortisol secretion patterns and body temperature regulation have been observed for up to 6 months following opioid detoxification.

Treatment (APA Practice Guidelines, 2010)

Early treatment efforts

Until the 1919 Supreme Court decision upholding Treasury's interpretation of the Harrison Act, numerous municipalities with large numbers of residents who were opioid addicted were operating treatment clinics in which morphine was prescribed or dispensed. Some clinics prescribed heroin and cocaine[26]. These early OTPs varied in how they

functioned; some provided detoxification treatment and others adopted a maintenance policy[27]. Perhaps the best known of these early OTPs were the Department of Health program in New York City, where those with addictions were detoxified with decreasing doses of heroin and morphine, and the program established by Dr. Willis Butler in Shreveport, Louisiana, which not only detoxified patients but also maintained some of them on morphine[26].

Courtwright and others state that Treasury regarded these clinics as a threat to its anti maintenance philosophy. By the early 1920s, it had succeeded in closing them through legal pressure, critical inspections, and threats. The last program to be closed was Dr. Butler's in Shreveport[26, 27].

In the 1920s, an increase in crime related to the acquisition of illicit opioids was reported in cities throughout the country. In 1929, Congress appropriated funds to establish two new treatment facilities, initially called "narcotics farms"[28], in Fort Worth, Texas, and Lexington, Kentucky. The Lexington facility, which opened to patients in 1935, was renamed the U.S. Public Health Service Narcotics Hospital in 1936. These institutions detoxified patients with opioid addiction who entered voluntarily, and they also served as hospitals for prison inmates who had opioid addictions and were legally committed through a Federal court. The prescribed stay was about 6 months, although some patients stayed longer. Prisoners could stay for up to 10 years. These hospitals offered social, medical, psychological, and psychiatric services in addition to detoxification and had a low patient-to-staff ratio (about 2 to 1), but the atmosphere was described as prisonlike, especially at the Lexington facility. Two major followup studies showed the program to be a failure. One reported a relapse rate of 93 percent in 1,881 former patients over a 1.0- to 4.5-year follow up period[29]. The second found a relapse rate of 97 percent in 453 former patients over follow up periods of 6 months to 5 years[30]. The Lexington hospital facility was turned over to the Bureau of Prisons in 1974. Despite the failure of these programs, White credits the research conducted there with providing "much of the foundation upon which modern treatment advances were built"[28].

The increase in heroin addiction in New York City after World War II led, in 1952, to the establishment of Riverside Hospital for adolescents with addiction disorders. This program also proved to be a failure. A follow up study in 1956 showed a high post treatment relapse rate (e.g., at least 86 percent of patients admitted in 1955), and the Riverside facility was closed in 1961[31].

Five settings or modalities under which most of the treatment of opioid-associated disorders takes place are: opioid treatment programs, inpatient hospital settings, outpatient clinics and offices, self-help programs, and therapeutic communities. The setting of treatment depends on the preferences of the patient and clinical characteristics, the perceived treatment requirements of the patient, and alternatives which are available. For the treatment of opoid dependent patients, the least restrictive setting that is most likely to help in the safe and effective therapy must be preferred. There are some general guidelines and recommendations for treatment settings for opioid related disorders. A life-threatening emergency is opioid overdose, which should be initially evaluated and managed in a medical setting under supervision for example an emergency department or inpatient service. Typically treatment includes opioid effects reversal by an opioid antagonist (for e.g., naloxone). Withdrawal from opioid can also be dealt with in an inpatient setting and may be managed effectively with pharmacological agents which are agonist at opioid receptor(e.g., methadone, buprenorphine) or nonopioid medications (e.g., clonidine). Although symptomatic management of opioid withdrawal can be achieved relatively rapidly in an

inpatient setting (within 7 days), long-term results is generally poor for such withdrawal, with larger frequency of relapse after discharge from the inpatient setting.

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