

The Schedule of Controlled Substances and Modern Psychopharmacology

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ABSTRACT

The controlled substances act of 1970 established a system by which substances with abuse potential are classified into 5 different schedules which greatly impact the lives of a significant percentage approximately 40% of Americans who suffer from chronic pain, addictions and psychiatric disorders. This article explains the psychopharmacological bases of the schedule of controlled substances. The schedule seems to be dismissive of the psychobiological properties- latency, addictive potency, half-life illumination time and the mode of administration of various substances. The exclusion of tobacco and alcohol and the dismissal of “potential harm versus benefit” represent major flaws of the current schedule. The basic architecture of the schedule of controlled substances does not seem to correspond to the modern principles of psychopharmacology; rather it appears as if it’s rooted in subjective and less than scientific criteria. A new hypothetical system is proposed and may serve as a rough platform to develop a scientifically sound classification for addictive substances.

Keywords: Addiction, Substance abuse, Opiates, THC, Alcohol

HIGHLIGHTS

- The schedule seems to be dismissive of the psychobiological properties-latency, addictive potency, half-life illumination time and the mode of administration of various substances.
- The exclusion of tobacco and alcohol and the dismissal of “potential harm versus benefit” represent major flaws of the current schedule.
- The schedule of control substances has possibly had serious adverse influence on the quality of life of a significant percentage of the US population who suffer from chronic pain and psychiatric disorders.
- There is an urgent need to develop an evidence-based schedule for controlled substances.

INTRODUCTION

The controlled substances act of 1970 established a system by which substances with abuse potential are classified into 5 different schedules [1]. Schedule one substances are considered to have no medicinal value. Substances listed under schedule two to five are available for medical use with a prescription from a medical professional registered with the Drug Enforcement Agency (DEA) and has a valid license to prescribe controlled substances [1].

Approximately 40% of the American population - Americans with chronic pain addictions and psychiatric disorders - depend on treatments regulated by “the schedule of controlled substances” [1,2]. Hence, the quality of medical care and lives of millions of Americans depend on the schedule of controlled substances.

This correspondence tries to address several questions about “the schedule of controlled substances”:

- A. What is the psychopharmacological basis of the schedule?
- B. Does the schedule have objective criteria to measure and classify addictive potency?
- C. Does the schedule have any adverse effects?

PSYCHOBIOLOGY

In general, a psycho active substance would elicit biological responses both at the time of entry into the brain and upon

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its departure corresponding to psychotropic and withdrawal effects, respectively [1] (Table 1).

Table 1. Psychobiology of addictive substances.

Substance	Effect	Toxic effect	Neurotransmitter
Alcohol	Euphoria Calmness	Mental dysfunction	Dopamine GABA
Tobacco	Euphoria	Cancer, Cardiovascular disease	Dopamine
THC	Euphoria Pain Relief Calmness	Memory loss, Psychosis	Dopamine
Methylphenidate	Euphoria + Attention	Agitation Psychosis	Dopamine
Amphetamine salts	Euphoria + Attention	Agitation Psychosis	Dopamine
Benzodiazepines	Calmness	Cognitive dysfunction	GABA
Barbiturates	Calmness	Cognitive dysfunction	GABA
Opiates	Euphoria Pain Relief Calmness	Cognitive dysfunction	Dopamine Endorphins
Cocaine	Euphoria	Psychosis	Dopamine
LSD	Euphoria	Psychosis	Serotonin
PCP	Euphoria	Psychosis	Serotonin
Modafinil	Alertness	Agitation	Histamine

Addictive substances and their psychobiological properties including latency, euphoric potency, half elimination life, therapeutic and toxic blood levels and route of administration are of essence to determine their addiction potency and harm [2]. Thus, it is of essence that “The schedule for controlled substances” be sensitive to the psychobiological properties of the very substances it classifies and has a scientific inclusion and exclusion criteria.

Addictions are complications of brain dysfunctions, addictive substances with long half-life; fentanyl (duragesic), Opana ER (oxymorphone), methadone concerta have low risk of misuse potential [3] and opiates are neuroprotective [4] in contrast to cocaine tobacco LSD PCP which are neurotoxic [1].

Consistent with the narrow focus of this correspondence and because opiates seem to induce the predominant psychotropic influences of addiction, withdrawal and

potential harm, I will selectively review the psychobiology of opiates. Noteworthy of emphasis is the observation that diverse substances have distinct psychobiological influences that made me different than opiates.

PSYCHOTROPIC PROPERTIES OF OPIATES FOR PAIN, DEPRESSION AND ADDICTION

Opiates and endorphin agonists activate nucleus accumbens resulting in dopamine release yet at the same time they dampen the limbic cortical activity consistent with their calming influence [1]. Endorphins mediate heat and heat induced changes in the brain. Endorphin antagonists counteract, acute hyperthermia induced changes in rat brain such as reduction in the cerebral blood flow, increased blood brain barrier permeability, vasogenic edema and cellular changes [5].

Opiates and their receptors are crucial in pain control, pleasure and addictive behavior [1]. The opiate receptors (mu, delta, kappa) have a high affinity for opiates [6].

Endorphins, enkephalines and dynorphines (morphine like substances) are produced by brain. By opening potassium and calcium channels, opiates enjoy an inhibitory influence in the central nervous system [6]. Opiates induce acute analgesia and euphoria. Analgesia is due to opiates acting as agonists at opiate receptor subtypes primarily in the sub cortical and limbic regions. Prefrontal cortex dopaminergic activation is associated with euphoric effects [6].

Evidence of abnormal endogenous opioid neurotransmission are seen in people with impulsiveness [7], dysregulation of endogenous endorphins in major depression and women [8]. Various opiates, methadone, buprenorphine and diacetylmorphine (heroin) intramuscular have been effective to treat addiction to opiates [6]. Ten patients with refractory depression who had previously failed to respond to traditional treatments had a positive response to buprenorphine [9].

Three depressed patients unresponsive to electroconvulsive treatment had a robust response to buprenorphine and oxycodone [10]. Antidepressant effects of buprenorphine (11) and methadone have been shown. Also, historically, opiates have shown antidepressant and therapeutic benefits [11].

Discontinuation of stable opiate treatment following practice closures have been associated with strikingly high suicide rates [4,12]. High mortality among patients with heroin addiction who discontinued buprenorphine treatment has been reported [13]. The largest US epidemiological study of mood, anxiety and substance use disorders had a special warning by the authors: Suicides may occur discontinuation of opiates in stable patient populations [14]. These observations suggest endorphin specific neuroprotection for some vulnerable subgroups.

In summary, converging evidence are consistent with the observation that opiates offer remarkable psychotherapeutic benefits to treat pain, addictive disorders and treatment resistant depressions.

ADDICTION TO OPIATES

Animal studies have shown marked differences in chronic consumption of heroin versus cocaine [15]. The attainment of prevention of or relief from withdrawal symptoms seems to be the predominant influence for chronic heroin use in mice versus seeking reward and euphoria for chronic cocaine use [15].

Animals learn to regulate with some accuracy the amount of morphine they require [16]. The observation is that the increase in self-administration is not infinite and correspondence to a specific pattern. The animal self-administers morphine just the amount to prevent discomfort associated with withdrawal symptoms [16]. Bioengineered mice that had become dependent on morphine like substance would still benefit from the analgesic effect without any

withdrawal symptoms upon discontinuation of opiates [17]. Also there is a big difference between heroin and cocaine self-administration. Rats self-administering cocaine lose up to 47% of the pretesting body weight and showed profound deterioration in general health. Animals self-administering heroin maintained grooming behavior pre-testing body weight and a good state of general health [15].

After stopping regular intake of opiates, opiate abstinence syndrome develops [1,2]. Symptoms emerge in the first 24 hours gradually resolving in 7 to 10 days. Increased anxiety, restlessness, irritability, dilated pupils, goose flesh, hot flashes, vomiting, diarrhea, fever, elevated blood pressure, increased heart rate and abdominal and generalized muscle cramps are common [1].

Increased noradrenergic parasympathetic and glutamatergic activity and the emergence of withdrawal symptoms correlate with plasma concentration half-life and the final clearance of opiates [1]. The onset of withdrawal from an opiate does not always coincide with the onset of its terminal effects. A patient may be pain-free yet show withdrawal symptoms. Withdrawal is triggered by the downward shift of the plasma concentration of the endorphin agonist whereas the analgesic effect is determined by CNS effect. Animal studies and clinical observations suggest addiction to opiates is primarily driven by behavior to prevent withdrawal discomfort rather than personal pleasure and reward [1].

Various endorphin agonists with long elimination half-lives or slow release preparations (long-acting IM heroin, methadone and buprenorphine) are the most effective therapeutic agents for addiction to opiates [6].

REVIEW OF THE SCHEDULE OF CONTROLLED SUBSTANCES

Absence of inclusion and exclusion criteria

Alcohol and tobacco are not included in the schedule of controlled substances although there is overwhelming evidence to suggest that they are not only addictive but they also contribute to serious health hazards [1]. This omission represents a major scientific flaw for the schedule.

The scientific flaws of schedule 1

Substances in schedule 1 (heroin, mescaline, LSD, marijuana, MDMA) are described as substances that have no medical benefit and are highly addictive.

Evidence suggests marijuana and heroin have proven therapeutic benefits in the treatment of various medical disorders. For instance, intramuscular long-acting heroin has been effective in treating opiate dependence [18]. There is also a large literature consistent with the therapeutic benefits of marijuana to combat nausea and pain of diverse origin [19].

The scientific flaws of schedule 2

Substances in schedule 2 (opium, meperidine, PCP, cocaine, amphetamine, methylphenidate, ritalin and pentobarbital) have a high abuse potential with severe psychic and physical dependence liability.

There is considerable medical literature consistent with the observation that long acting slow release forms of opiates, methylphenidate and amphetamines have very low overuse potential and do not increase risk of psychiatric disorders [4,12].

In essence the inclusion of all forms of opiates methylphenidate and amphetamines in schedule 2 is not based upon evidence based medicine for it fails to differentiate crucial psychobiological properties and in particular latency and absence of euphoric effects of the long acting slow release preparations of diverse addictive substances.

Insensitivity to addictive potency

There is considerable evidence to suggest that the addictive potency of a substance correspondence to its biological properties (latency, euphoric potency and half-life elimination) [2]. In general, substances with shorter latency and half-life elimination seem to have greater addictive potency than substances with longer latency and half-life elimination.

The route of administration (by mouth, skin, air, intramuscular or intravenous injection) is also of significance for addictive potency. For instance, methylphenidate oral tablets are fundamentally different than methylphenidate slow release tablets which have potentially no overuse or addictive potency [2].

THE SCHEDULE AND POSSIBLE ADVERSE EVENTS

It has been suggested that because a large percentage of Americans suffer from chronic pain, addictions and psychiatric disorders, the imperfections of the schedule of controlled substances have had adverse psychosocial influences. For instance, there has been a statistically significant association between the recent dual epidemics of deaths from heroin overdose and suicide and the criminalization of medicine partly built upon the schedule of controlled substances [20-22]. These observations are consistent with the butterfly effect-theory (the sensitive dependence of complex systems upon initial errors) and the flaws of the schedule of controlled substances.

Of significance, it is true that, the United States seems to be the only country experiencing dual epidemics at a time the rest of the world have recorded statistically significant improvements in reducing deaths from suicides and heroin addiction [23] (Table 2).

Table 2. US deaths (2000 vs. 2014) per 100,00 population.

	2000	2014
Overdose (OD)	6.2	14.7
Suicide	10.1	12.9
Prescription opiates (PO)	2.3	4.3
Medications (non-opiates)	3.2	5.7
Heroin	0.7	3.4
PO/OD%	↓↓↓ 38.1	28
Heroin/OD%	↑↑↑ 11	28

CDC vital statistics reported 9 deaths per 100,000 populations for opioid overdose deaths in 2014; of those 3.4 were from heroin and 1.8 from synthetic opioids (fentanyl and tramadol) which nearly doubled in one year consistent with the police reports of dramatically increased illicit fentanyl manufacturing. Thus the actual overdose deaths from prescription opioids were 4.3 per 100,000 population in 2014 (4.3 may be an overestimation because 19% of drug

overdose deaths did not include any information on the death certificate about the specific types of drugs involved) [24-26].

A NEW HYPOTHETICAL CLASSIFICATION OF CONTROLLED SUBSTANCES

A new classification system of diverse addictive substances is proposed. The architecture of the proposal system would

be sensitive to the psychobiological properties of addictive substances including potential benefits versus harm, addictive potency, latency, half-life elimination time and the mode of administration.

Class 1

No medicinal benefits, high addictive potency and some potential harm (cocaine, PCP, LSD, DMT, heroin iv, MDMA, mescaline).

Class 2

Medicinal or euphoric benefits, high addictive potency and potential harm. Alcohol, tobacco, THC, methylphenidates, amphetamine salts, opiates, benzodiazepines, barbiturates, buprenorphine.

Class 3

Medicinal benefits, low addictive potency and some potential harm. Methylphenidate (long acting), amphetamine salts (long acting), opiates (long acting). Further studies to investigate the scientific validity of the proposed schedule are necessary.

CONCLUSION

The basic architecture of the schedule of controlled substances does not seem to correspond to the modern principles of psychopharmacology; rather it appears as if it is rooted in subjective and less than scientific criteria [27]. Furthermore, because a large percentage of people who suffer from chronic pain, addictions and psychiatric disorders have possibly and adversely been effected by the imperfections of the schedule of controlled substances, there is some urgency to upgrade the current schedule. A new hypothetical system presented in this article may serve as a rough platform to develop a scientifically sound classification for addictive substances.

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