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Addictive potential: $A = E/T_{max} \times t_{1/2}$

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SUMMARY

This hypothesis named Salerian Addictive Potential (SAP) suggests that the addictive potency of any substance may be calculated with an algebraic equation of $A = E/T_{max} \times t_{1/2}$, where A is the addictive potency, E represents the euphoric potency, T_{max} is the time to reach peak plasma concentration, and $t_{1/2}$ is the plasma elimination half-life.

This review offers medical evidence to suggest there is a negative association between the addictive potency of a substance and T_{max} and $t_{1/2}$, whereas the euphoric potency of a substance increases its addictive potency.

SAP seems incompatible with the current FDA and government sponsored schedule for classification of addictive substances.

Introduction

Psychoactive drugs have been a part of human existence since antiquity and have mood-altering and addictive properties [1]. Many psychoactive substances such as nicotine, caffeine, cocaine, etc., are made by plants and naturally accessible to people. According to the 2002 survey by the Substance Abuse and Mental Health Services Administration, approximately 9-1/2 million Americans were current users of at least one illicit drug at that time [2].

The Diagnostic and Statistical Manual of Mental Disorders (DSM) specifies a group of substance-related disorders where substance refers to typical drugs of abuse as well as some psychoactive medications that have abuse potential [3]. Within the category of substance-related disorders are two general disorders called substance dependence and substance abuse [3].

The Controlled Substances Act of 1970 established a system to classify substances for their abuse potential [1]. Heroin, mescaline and marijuana, for instance, are Schedule I drugs with very high addictive potential, whereas cocaine, opium, morphine and amphetamines are classified as Schedule II (Table 1). Since 1970, a number of studies have shown a serious disparity between the official classification of addictive substances and the scientific data [2] (Table 2).

Review of medical evidence

Clinical evidence and animal studies suggest several psychobiological mechanisms influence substance abuse and addiction [1,2]. Evidence suggests the positive reinforcement mechanism is mediated by pleasure and reward pathways of dopaminergic activation [1,2]. There is also solid research to observe the validity of a positive correlation between the euphoric and addictive potency of a substance. It is also true that there is a linear relationship between C_{max} (maximum concentration of a substance) and T_{max} (time to reach C_{max}) and the euphoric effect [1,2].

Various studies reveal withdrawal responses also mediate addictive behavior [1,2,4].

Soon after the discontinuation of morphine-like substances, a constellation of symptoms defined as morphine abstinence syndrome develops. Most of the symptoms slowly emerge in the first 24 h, gradually resolving within 7–10 days from the onset of withdrawal [1]. The symptoms include 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 [1]. Morphine abstinence syndrome seems to represent: Increased noradrenergic, parasympathetic and glutamatergic activity [1,2]. The emergence of withdrawal symptoms coincide with plasma concentration half-life and total clearance of a morphine-like substance [1,2].

The study from Basile and colleagues [4] compared genetically normal mice to mutant mice in which the M5 receptor gene had been inactivated. Loss of M5 receptor function reduced withdrawal symptoms in mice that were made dependent on morphine, but it had no effect on morphine-induced analgesia. These findings suggest that M5 muscarinic receptors selectively influence the addictive properties of opiate drugs [4]. Further, this also suggests the critical influence of withdrawal symptoms in the genesis of addiction.

The conceptual psychobiological framework to guess the euphoric potency of a substance is consistent with the observations

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Table 1
Controlled substances act schedule.

Schedule	Description	Representative substances
I	Substances that have no accepted medical use in the US and have a high abuse potential	Heroin, LSD, mescaline, marijuana, THC, MDMA
II	Substances that have a high abuse potential with severe psychic or physical dependence liability	Opium, morphine, codeine, meperidine (Demerol), cocaine, amphetamine, methylphenidate (Ritalin), pentobarbital, phencyclidine (PCP)
III	Substances that have an abuse potential less than those in Schedule II, II, including compounds containing limited quantities of certain narcotics and nonnarcotic drugs	Paregoric, barbiturates other than those listed in another schedule
IV	Substances that have an abuse potential less than those in Schedule III	Phenobarbital, chloral hydrate, diazepam (Valium), alprozolam (Xanax)
V	Substances that have an abuse potential less than those in Schedule IV, consisting of preparations containing limited amounts of certain narcotic drugs generally for antitussive (cough suppressant) and antidiarrheal purposes	–

Table 2
Addictive potential of various substances based upon SAP.

Substance	Route of intake	Euphoric potency	T_{max}	$t_{1/2}$	Equation	Score
1. Cocaine	Inhale	5	0.16	1	$5/0.16 \times 1$	31
2. OxyContin chewed	p.o.	4	0.11	4.5	$4/0.11 \times 4.5$	11.4
3. Alcohol	p.o.	4	0.25	1.5	$4/0.25 \times 1.5$	10.6
4. Morphine	IV	4	0.16	3	$4/0.16 \times 3$	8.3
5. Nicotine	Inhale	2	0.16	2	$2/0.16 \times 2$	6.25
6. Morphine	p.o.	4	0.5	3	$4/0.5 \times 3$	2.6
7. Oxycodone tablet	p.o.	4	0.5	3.5	$4/.5 \times 3.5$	2.28
8. OxyContin	p.o.	4	0.5	4.5	$4/0.5 \times 4.5$	1.7
9. Amphetamine salts	p.o.	4	0.5	10	$4/0.5 \times 10$	0.8
10. Diazepam	p.o.	4	1	50	$4/1 \times 50$	0.8
11. Methadone	p.o.	5	1.5	55	$5/1.5 \times 55$	0.6
12. Methylphenidate	p.o.	4	1.5	4	$4/1.5 \times 4$	0.6
13. Alprazolam	p.o.	4	1	11	$4/1 \times 11$	0.3
14. THC	Inhale	4	0.16	72	$4/0.16 \times 72$	0.3
15. Lisdexamfetamine	p.o.	4	3.5	12	$4/3.5 \times 12$	0.09
16. Concerta	p.o.	4	7	10	$4/7 \times 10$	0.05
17. Dronabinol	p.o.	4	1	72	$4/1 \times 72$	0.05

[1] Meyer JS, Quenzer LF. Psychopharmacology. Sinauer Associates; 2005.
[2] Lacy CF, Armstrong LL, Goldman MP, Lance LL. Drug information handbook. Lexi-Comp., Inc.; 2009.
[3] Physician's desk reference. New Jersey: Thompson PDR; 2009

that prefrontal cortex dopamine function is the predominant determinant of joy and euphoria [2].

Thus, the euphoric potency of a substance may reflect its influence on prefrontal cortex dopaminergic function. And this is why it is reasonable to rate the euphoric potency by the direct or indirect dopaminergic influence correlated with C_{max} of a euphoric substance.

The euphoric potency scale used in SAB is subjective. It is based upon the rating system proposed by two leading addiction experts Drs. Henningfield and Benowitz and the study authors' clinical observations consistent with the relative prefrontal cortex dopaminergic activation of a substance.

Discussion

Neuroscientific research can be summarized the following way: Three properties including the euphoric potency, euphoric latency and the severity of withdrawal symptoms may predict the addictive potential of a substance. Or we can algebraically express that $A = E/T_{max} \times t_{1/2}$, where A is the addictive potency, E represents the euphoric potency on a scale of 0–5 with 5 representing the strongest euphoric potency and 0 none, T_{max} is the time to reach peak plasma concentration in hours, and $t_{1/2}$ is the plasma elimination half-life in hours. This equation is the Salerian Addictive Potential or SAP.

An algebraic equation of biology does not preclude crucial psychosocial influences that mediate addictive patterns in a society. For, addiction is a complex human disorder rooted in diverse psychosocial and biological factors. This is precisely why this algebraic formula can only measure the relative addictive biological potency of a substance, and complex negative or positive societal and environmental influences will dampen or promote the biological addictive potency of any substance.

SAP has several implications specifically for some behavioral treatments of substance abuse that advocate abrupt withdrawal as a precondition for recovery. An abrupt switch is often a biological prelude to serious physiologically induced discomfort, hence an adverse influence. Thus, psychotherapeutic strategies that advocate abrupt and total abstinence of all addictive substances may unnecessarily hinder therapeutic success.

SAP also clashes with the classification of Schedule of Controlled Substances (Table 1). The disparity between what science dictates and what the laws demand may be harmful for it coerces healthcare professionals to choose between unscientific medicine or face punishment by irrational laws. The simplest example of the scientific paucity of the controlled substances act is its classification of marijuana as Schedule I when alcohol and tobacco are 0.

Several limitations of SAP are inherent in its hypothetical nature. A major shortcoming is the general assumption of T_{max} as a clinical correlate of euphoric effect and $t_{1/2}$ as the onset of withdrawal. Another potential weakness is the subjective nature of

the euphoric scale and the association between the euphoric effect and T_{max}.

For sure, SAP needs further clinical evidence and validation. Yet, in view of our possibly infinite coexistence with addictive substances, an urgent reevaluation of the current classification of controlled substances seems appropriate.

Conflicts of interest statement

None declared.

References

[1] Salerian AJ. Thermodynamic laws apply to brain function. Medical Hypotheses 2009.
[2] Mayer JS, Quenzer LF. Psychopharmacology. Sunderland, MA: Sinauer Association, Inc.; 2005.
[3] Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 2005.
[4] Basile AS, Fedorova I, Zapata A, Liu, X, Shippenberg T, et al., 2002. Deletion of the M5 muscarinic acetylcholine receptor attenuates morphine reinforcement and withdrawal but not morphine analgesia. In: Proceedings of the national academy of science USA. p. 11457.