The Linares Addictive Potential Model

Oscar A. Linares*

Wayne State University, Detroit, MI 48202, USA and PRS Wound Management, P.C., 20927 Kelley Road, Eastpointe, MI 48021, USA

Abstract: The Salerian Addictive Potential (SAP) hypothesis indicates that addictive potential may be calculated as $A = E / T_{max} \times t_{1/2}$, where A is addictive potency, E euphoric potency, T_{max} (hr) is the time to reach peak plasma concentration, and $t_{½}$ (hr) is the plasma elimination half-life. However, this approach is inconsistent with first-order linear pharmacokinetics. The units of the denominator of the equation are units of acceleration (hr^2), not speed (the first derivative). Therefore, the present contribution presents a minimal-model hypothesis for quantifying a drug's addictive potential. This model is superior to the SAP model because it is the simplest model, with the minimum number of parameters and assumptions, and it decreases variance through less loss of information.

Keywords: Addiction, modeling, pharmacokinetics, opioids, euphoria, drugs of abuse.

INTRODUCTION

The ability to numerically quantify addictive potential has far reaching public health implications, but, addictive potential has defied precise numerical quantification. Although, attempts to understand the nature of illicit drug abuse and addiction can be traced back for centuries, one of the earliest accounts of addiction research in America is that of a young physician, who on or about June 9, 1883, while treating a case of opium addiction, began a search for an antidote by experimenting on himself with hypodermic morphia. His patient recovered but the incautious experimenter fell victim to his ill-starred zeal [1]. But, medical and scientific interest in opiate addiction first began in the two decades following the Civil War—hypodermic injection of morphine was first used on a widespread basis during the war, and many soldiers ended up becoming addicted to it as a result. At roughly the same time, increased Chinese immigration led to a concern about opium smoking, especially as it moved into the white population. By the first decade of the 20th century there was a widespread concern about opium smoking, injected morphine, and heroin (introduced in 1898). However, the historical origins of modern addiction research lie in the Addiction Research Center (ARC), a laboratory that was once part of a federal prison-hospital in Lexington, Kentucky [2, 3], and in the "monkey colony" at the University of Michigan in Ann Arbor [4]. The ARC is important because it is the beginning of a pharmacological approach to addiction research. Acker [5] has chronicled the formative generation of addiction researchers up through World War II. Beginning in the 1980s NIH then started to push the neurobiological model which is largely dominant today [6-9].

Thus, from a neurobiological perspective, the goal of addiction research is to determine the actions of abusable drugs on the brain which result in dependence, and to determine the neural substrates that make one individual inherently vulnerable to it and others relatively resistant [10, 11]. Initially, all drugs of misuse interact with receptors or neuronal reuptake proteins. For example, opiates activate opioid receptors, and cocaine inhibits the neuronal reuptake proteins for the monoamine neurotransmitters which include dopamine, norepinephrine, and serotonin. These initial effects lead to alterations in the levels of specific neurotransmitters, or to different activation states of specific neurotransmitter receptors in the brain. Opiate activation of opioid receptors, for example, leads to recruitment of inhibitory and related G proteins. This, in turn, leads to activation of K^+ channels and inhibition of Ca^{2+} channels. Both are inhibitory actions, because more K^+ flows out of the cell and less Ca^{2+} flows into the cell. Thus, the electrical properties of the target neurons are rapidly affected by opiates. Recruitment of the inhibitory G protein also inhibits adenylyl cyclase [12], and associated reductions in intracellular Ca^{2+} levels decrease Ca^{2+}-dependent protein phosphorylation cascades, altering the activity of additional ion channels. These effects, along with changes in many other neural processes within target neurons, further contribute to the acute effects of opioids. The sum of these changes may be involved in triggering the long-term effects of drugs of misuse that eventually lead to abuse, dependence, tolerance, and withdrawal.

The acute-dose effect comparison study in volunteers with histories of drug abuse is the current

*Address corresponding to this author at the PRS Wound Management, P.C., 20927 Kelley Road, Eastpointe, MI 48021, USA; Tel: (734) 735-4022; Fax: (734) 453-7019; E-mail: oscar.linares@wayne.edu

ISSN: 2223-3806 / E-ISSN: 1927-5951/12

"gold standard" for initial abuse liability testing [13]. However, systematic methods for measuring subjective effects of drugs have been refined through the use of standardized questionnaires. Volunteers who are experienced drug users complete the questionnaires after they have taken a drug; their answers to the subjective-effects questions—how they feel, their likes and dislikes—readily distinguish between the various drugs and doses, as well as between drug presence or absence [14, 15]. The measure that has proven most useful in assessing human drug-abuse-liability is the assessment of the ability of a drug to reinforce and maintain self-administration behaviors much like the behaviors used to obtain food and water. Not surprisingly, however, it has also been shown that the preference for one drug over another or one drug dose over another agrees well with independent ratings of "drug liking." The addiction potential of such commonly used drugs of misuse as cocaine [16], opiates [17], alcohol [18], sedative-hypnotics [19], nicotine [20], anxiolytics [21], cannabis [22], inhalants and anesthetics [23], and PCP and hallucinogens [24] have been the subject of extensive review, and a selective literature reference list has been provided [25]. The history of the use and misuse of inhalants and anesthetics has been chronicled by Gabriel [26].

Despite those comprehensive assessments of addictive potential, the postulate of a mathematical or pharmacokinetics-based model as a means to launch an assault on quantifying addictive potential has been previously made only by Salerian [27], even though pharmacokinetics are known to influence addictive potential [28].

Little doubt now exists that the development of addiction to drugs of misuse, in part, is due to predisposing individual-based genomic determinants as well as determinants associated with early psychological development [6, 10, 11]. But much of what is "known" is correlative rather than mechanistic, historical rather than predictive, and qualitative rather than quantitative. Development of a mathematical model of addictive potential could provide a quantitative understanding of addictive potential and allow predictions about addictive potential to be made. A mathematical model is a hypothesis defined by a set of parameters in a mathematical framework [29]. In a mathematical model, parameters or their functions may be used without regard to mechanistic aspects of the system under investigation. By contrast, in a physical model, parameters reflect physiological, pharmacological, or biochemical mechanisms. A model's parameters are the quantifiable constants, equations or functions of the model.

Recently, Salerian [27] developed a mathematical model for measuring the addictive potency of several drugs based on the Salerian Addictive Potential (SAP) score. The Salerian model improved methodology for drug addiction classification by structuring classification in a mathematical pharmacokinetics-based framework, accounting for the rate at which a drug can be absorbed and excreted from the body. Despite its benefits, use of the SAP model as an index of addictive potential is associated with several problems: (i) the SAP model takes into account both drug absorption and elimination as reflected in the T_{max} parameter, which confounds the computed value of addictive potential; (ii) in the SAP model, E, the euphoric potency of the drug, is subjectively assigned; (iii) the SAP model provides no insight into the relative contributions that absorption and elimination make to the addictive potency of a drug since absorption and elimination are important determinants of the "high" produced by drugs of misuse [15]; and (iv) the SAP model is inconsistent with first-order linear pharmacokinetics.

In the study of the metabolism of drugs of misuse, confounded parameters vary together so that one cannot tease apart the relative contribution of each parameter to the observed effects. It is important to assess the relative contribution of each parameter because the direction of the effect of a confounder can lead to either an over or under estimate of the primary outcome measure. This misestimate may cause misclassification of the primary outcome measure.

Using modeling [30], the present work was undertaken to address the effect of confounding on the SAP model and to quantify more precisely the addictive potential of drugs of misuse. The present contribution presents a minimal-model hypothesis for quantifying a drug's addictive potential. This model is superior to the SAP model because it is the simplest model, with the minimum number of parameters and assumptions, and it decreases variance through less loss of information.

METHODS

Theory

The SAP model [27] is described by Eq. (1):

$$A = \frac{E}{(T_{\max} \times t_{1/2})} . \quad (1)$$

In this model, A represents addictive potential in units of hr^{-2}, E represents euphoric potency on a scale from 1 to 5 with 5 being the most potent, $t_{½}$ (hr) is the elimination half-life and T_{max} (hr) is the time to peak absorption (rate of exposure) or time to peak concentration (extent of exposure) in plasma, blood or serum [31]. T_{max} is thus a hybrid pharmacokinetic parameter dependent on the fractional rate of drug absorption, [k_a hr^{-1}], into the body, as well as the fractional rate of drug elimination, [k_e hr^{-1}], from the body:

$$T_{max} = \frac{\ln(k_a / k_e)}{(k_a - k_e)}. \quad (2)$$

The peak concentration, C_{max} is also a function of k_a and k_e [32]:

$$C_{max} = \frac{k_a FD}{V_d (k_a - k_e)} (e^{-k_e T_{max}} - e^{-k_a T_{max}}), \quad (3)$$

where F (%) represents the bioavailability of the drug, D (mg) represents the oral dose administered, and V_d (L) represents its apparent volume of distribution.

The half-life for the absorption process, defined as the time required for half the absorbed dose to be absorbed, is expressed as

$$t_{1/2a} = \frac{\ln(2)}{k_a}, \quad (4)$$

where ln(2) ≅ 0.693. The $t_{½a}$ units are hours. Multiplying $t_{½a}$ by 5 to mark five half-lives to steady state gives the elapsed time equal to 96.875% of the absorbed dose (FD) which, for clinical purposes, represents complete absorption. Similarly, the half-life for the elimination process, expressed as

$$t_{1/2} = \frac{\ln(2)}{k_e}, \quad (5)$$

multiplied by 5, represents complete elimination. Thus, as shown by Eqs. (4) and (5), k_a and k_e are "unconfounded" independent predictors of drug absorption and elimination, unlike the T_{max} in Eq. (2).

Model Development

The SAP model given by Eq. (1) may be decoupled by decomposition of T_{max} into its independent parts:

$$A = \frac{E}{(k_a / k_e) \times t_{1/2}}. \quad (6)$$

In this version of the model, A depends on both k_a and k_e. Both k_a and k_e are independent processes driven by different kinetics which cannot be ignored [32] because they quantify drug absorption and elimination. The units of Eq. (6) are inconsistent with those of Eq. (1). Although the units of Eq. (1) are hr^{-2} which is a unit of acceleration, the units of Eq. (6) are hr^{-1} which is a unit of speed.

Because a dimensionless quantity in the denominator of Eq. (6) is needed, the $t_{½}$ term is dropped from the denominator in Eq. (6) giving,

$$A_L = \frac{E}{(k_a / k_e)}, \quad (7)$$

where A_L represents the Linares addictive potential index. Although T_{max} is a non-compartmental model parameter, its calculation is based on a linear dynamic compartmental model that follows linear first-order kinetics [33], i.e., dC/dt, not dC^2/dt^2, which is implied by the units of Eq. (1). Dropping the $t_{½}$ term from Eq. (6) is allowable because $t_{½}$ measures drug elimination, which is accounted for by k_e. In addition to being both theoretically and dimensionally correct, Eq. (7) now proposes the simplest model hypothesis or the minimal-model for the Linares addictive potential index.

Model Testing

No "gold standard" exists for estimating the classification accuracy of addictive potential. Pepe [34] and Hagdu [35] suggest approaches to studying comparisons without a gold standard. One approach is to use values adjudicated by a committee of experts as the gold standard. Using this approach, Table **3** tabulates the drugs in reference [36] that are also used in Tables **1** and **2**. The nine drugs that were common to both studies were ranked from one to nine on the basis of their addictive score settled by the expert committee [36]. The drug's A scores and A_L indices were then used to match-rank the drugs relative to their scores based on fact, scientific knowledge, and expert opinion (FSKEO) as shown in Table **3**.

Computational Methods

To determine the accuracy of the models while controlling for model complexity, the Akaike Information Criterion (AIC) [37] was used as a measure of information content. The lower the value of the AIC, the more statistically accurate the model because less information is lost when the model is used to describe data. The AIC was calculated as

Table 1: Drugs Ranked by the Salerian Addictive Potential Score *A*. This Table Presents the SAP Score for Drugs Calculated Using Eq. (1). Table 1 Parallels Table 2 in Salerian [42] but Adds Clonazepam, Lorazepam and Heroin

Rank	Drug	Intake Route	*E*	T_{max}	$t_{½}$	*A*
1	Heroin	intravenous	5	0.078	1.6	39.89
2	Cocaine	inhalation	5	0.16	1.0	31.25
3	Alcohol	oral	4	0.25	1.5	10.67
4	Morphine	intravenous	4	0.16	3.0	8.33
5	Oxycontin	chewed	4	0.11	4.5	8.08
6	Nicotine	inhalation	2	0.16	2.0	6.25
7	Morphine	oral	4	0.50	3.0	2.67
8	Oxycodone IR	oral	4	0.50	3.5	2.29
9	Lorazepam	oral	4	2.00	1.0	2.00
10	Oxycodone CR	oral	4	0.50	4.5	1.78
11	Clonazepam	oral	4	2.50	1.3	1.28
12	Amphetamine Salts	oral	4	0.50	10.0	0.80
13	Methylphenidate HCl	oral	4	1.50	4.0	0.67
14	THC	inhalation	4	0.16	72.0	0.35
15	Alprazolam	oral	4	1.50	11.2	0.24
16	Lisdexamphetamine	oral	4	3.50	12.0	0.10
17	Diazepam	oral	4	1.00	50.0	0.08
18	Buprenorphine	oral	4	2.00	26.0	0.08
19	Methadone	oral	5	1.50	55.0	0.06
20	Methylphenidate ER	oral	4	7.00	10.0	0.06
21	Dronabinol	oral	4	1.00	72.0	0.06

Table 2: Drugs Ranked by Addictive Potential Using the Linares Addictive Potential Index A_L. Table 2 Presents the Drugs Tabulated in Table 1 Ranked According to A_L

Rank	Drug	Intake Route	*E*	T_{max}	$t_{1/2a}$	$t_{1/2}$	k_a	k_e	k_a/k_e	A_L
1	Heroin	intravenous	5	0.1	0.17	1.6	4.16	1.386	3.00	1.67
2	Methylphenidate ER	oral	4	7	3.500	10.0	0.20	0.069	2.86	1.40
3	Methylphenidate HCl	oral	4	1.5	0.750	4.0	0.92	0.173	5.33	0.75
4	Lisdexamphetamine	oral	4	3.5	1.750	12.0	0.40	0.058	6.86	0.58
5	Cocaine	inhalation	5	0.16	0.080	1.0	8.66	0.693	12.50	0.40
6	Alcohol	oral	4	0.25	0.125	1.5	5.54	0.462	12.00	0.33
7	Morphine	oral	4	0.5	0.250	3.0	2.77	0.231	12.00	0.33
8	Lorazepam	oral	4	2.0	1.000	1.0	0.69	0.058	12.0	0.33
9	Oxycodone IR	oral	4	0.5	0.250	3.5	2.77	0.198	14.00	0.29
10	Oxycodone CR	oral	4	0.5	0.250	4.5	2.77	0.154	18.00	0.22
11	Alprazolam	oral	4	1.5	0.750	11.2	0.92	0.062	14.93	0.27
12	Buprenorphine	oral	4	2.0	1.000	26.0	0.69	0.027	26.00	0.154
13	Clonazepam	oral	4	2.5	1.250	1.30	0.55	0.020	27.20	0.15
14	Morphine	intravenous	4	0.16	0.080	3.0	8.66	0.231	37.50	0.11
15	Amphetamine Salts	oral	4	0.5	0.250	10.0	2.77	0.069	40.00	0.10
16	Nicotine	inhalation	2	0.16	0.080	2.0	8.66	0.347	25.00	0.08
17	Methadone	oral	5	1.5	0.750	55.0	0.92	0.013	73.33	0.07
18	Diazepam	oral	4	1.0	0.750	50.0	0.92	0.014	66.67	0.06
19	Oxycontin	chewed	4	0.11	0.055	4.5	12.60	0.154	81.82	0.05
20	Dronabinol	oral	4	1	0.500	72.0	1.39	0.010	144.00	0.03
21	THC	inhalation	4	0.16	0.080	72.0	8.66	0.010	900.00	0.004

Table 3: "Gold Standard" Ranking of Selected Drugs Using Values for Addictive Potential by Adjudication by Expert Committee Based on Fact and Scientific Knowledge [Column FSKEO] in Nutt and Coworkers [36] and Match-Ranked by *A* and A_L*

Gold Standard	FSKEO Rank	FSKEO	*A* Rank	Residual	A	A_L Rank	Residual	A_L
Heroin	1	3.00	1	0	39.89	1	0	1.67
Cocaine	2	2.39	2	0	31.25	2	0	0.08
Tobacco	3	2.21	4	-1	6.25	8	-5	0.04
Methadone	4	2.08	9	-5	0.06	7	-3	0.07
Alcohol	5	1.93	3	3	10.67	3	2	0.33
Benzodiazepines	6	1.83	7	-1	0.24	4	2	0.27
Amphetamine	7	1.67	8	-1	0.10	6	-1	0.58
Cannabis	8	1.51	6	2	0.35	9	-1	0.004
Methylphenidate HCl	9	1.25	5	4	0.67	5	4	0.19
Sum-of-Squared Residuals†				*57*			*60*	
AIC‡				*52*			*49*	

**A*=Salerian Addictive Potential score.
A_L=Linares addictive potential index.
†Calculated as the row-wise difference between the FSKEO Rank and the *A* and A_L Ranks squared, respectively.
‡Akaike information criterion calculated as $AIC = N \times \ln(SS_R) + 2 \times P$, where *N* is the number of drugs studied, SS_R is the sum of squared residuals and *P* is the number of parameters in the model.

$AIC = N \times \ln(SS_R) + 2 \times P$ [38], where *N* is the number of drugs studied, SS_R is the sum of squared residuals calculated from the difference between the model rankings of addictive potential using *A* and A_L relative to the FSKEO (see Results, Table **3**), and *P* is the number of parameters in the model. While the SAP model has four parameters, the Linares minimal-model (LMM) has only three parameters, which is superior given the principle of parsimony [39].

RESULTS

As shown in Table **1**, *A* identified heroin, cocaine, and alcohol as the highest addictive potential. By contrast, A_L ranked heroin, methylphenidate ER, and methylphenidate HCl as the drugs with the highest addictive potential, followed by cocaine and alcohol.

Although the SS_R was lower for the SAP model compared to the LMM (57 vs. 60, respectively), the AIC was lower for the LMM compared to the SAP model (49 vs. 52, respectively). While the lower SS_R with the SAP model would indicate that it is a better model if SSR were being used as the criterion for model selection, it is the AIC that provides the better model selection criterion because it considers both accuracy and parsimony.

Thus, the LMM more accurately describes the observations and postulates the simplest model hypothesis for quantifying addictive potential.

DISCUSSION

What is offered here is not an ironclad rule for computing a drug's addictive potential, but rather a parsimonious hypothesis for its computation that must be judiciously applied.

The study of mathematical modeling has three objectives: prediction, description, and prescription [33]. Predictive mathematical modeling consists in identifying both the parameters that are relevant to the prediction of kinetic properties of phenomena (drugs, disease, etc.), and identifying methods for their determination. Descriptive mathematical modeling consists of measuring the relevant parameters of the phenomena. Prescriptive mathematical modeling consists of using known concepts and previously determined parameters for achieving an appropriate clinical goal. The LMM, as well as the Salerian model, are meant to provide quantitative measures of addictive potential and are meant to be used under a variety of conditions, e.g., they may be used to predict the addictive potential of new chemical entities, and also, to compare the addictive potential of drugs. Most importantly, they provide a means to objectively begin to address the problem of heterogeneity of addictive potential among and within individuals. But we have shown that only the LMM is unconfounded.

Since modeling is rarely used in the absence of prior information, a special measure of addictive

potential was derived by tailoring the SAP model [27]. The LMM dissociates the independent k_a and k_e components from T_{max} and drops the $t_{½}$ term from the denominator of the SAP model, giving rise to the simpler LMM represented by Eq. (7). Because no gold-standard exists to compare the models, Eqs. (1) and (7), values for addictive potential adjudicated by a committee of experts [36] were used to compare the models as shown in Table **3**.

Using the AIC as an objective model selection criterion [40], compared to the SAP model, the LMM, Eq. (7), emerged as the simplest model with the smallest number of parameters that captures the important pharmacokinetic determinants of addictive potential, k_a and k_e, reflected in A_L. Because it only depends on independent parameters, A_L, is a clean, unconfounded index of addictive potential.

As shown by Eqs (2) and (3), both T_{max} and C_{max} are confounded parameters because both depend on k_a and k_e. Basson and coworkers [41] found that C_{max}, but not T_{max} was confounded. However, Basson and coworkers did not dissociate T_{max} into its independent components, as was done in the present contribution in order to create a simpler model.

Salerian [42] suggests that the euphoric potency of a drug may be related to its extent of exposure (C_{max}) to the neuronal milieu of the prefrontal cortex through mediation of dopaminergic system function. Positron emission tomographic (PET) imaging of the human brain in drug misuse individuals [43], reveals that although drugs of misuse are associated with rapid increases in central extracellular dopamine levels, these individuals experience a marked decrease in central dopamine release and D2 dopamine receptor number. These effects have been found to persist months after detoxification [43]. The reduction in dopamine release may represent the central inhibition of dopamine outflow in the setting of higher intrasynaptic dopamine concentration. In addition to local feedback mechanisms, the decreased dopamine outflow may be mediated by central actions such as pathways involving α_2-adrenergic receptors [44].

Because central dopamine outflow is reduced, a concomitant compensatory decrease in central dopamine clearance would be needed to maintain dopamine levels elevated in the synaptic axoplasm. This decrease in central dopamine clearance may explain the observed decrease in dopamine D2 receptor number, which may in turn determine a drug's euphoric potency. Volkow and associates [45, 46] have observed a reduced clearance of methylphenidate HCl from the brain. This is an important finding because it suggests addictive potential may be related more to how slowly a drug is cleared from the synaptic axoplasm, where as the "euphoric high," may be related more to how fast the drug reaches peak concentration (C_{max}) in the synaptic axoplasm. LMM's prediction that a drug's C_{max} may be a reasonable biomarker of euphorigenic potency is consistent with Salerian's reasoning and illustrates how LMM can be used in a predictive capacity. However, the neuronal dopaminergic mechanisms involved in the euphoric response to drugs of misuse is a complex process [47] requiring further study.

CONCLUSION

The LMM is superior to the SAP model because: (i) LMM is the simplest model with the minimum number of parameters and assumptions; (ii) LMM is associated with lower AIC; and (iii) unlike the SAP model, LMM is dimensionally and theoretically correct.

The LMM represents a working hypothesis. Validation through alternate independent approaches including the design of experiments to test the model is needed. For example, carrying out a human abuse liability study to determine the degree to which the drug under investigation is chosen based on its liking or engendering of euphoria. Furthermore, by the use of qualitatively different experimental techniques, new types of data may be derived which are beyond the predictive domain of the model. Under these circumstances, a new more extensive model would have to be proposed that could provide more precise information and a more complete description of addictive potential. But, regarding assessing addictive potential, LMM appears to be useful for practical applications because it provides reasonably accurate indices of addictive potential compared to adjudicated values from a panel of experts. The LMM thus provides an improved approach for the quantitative study of addiction potential in humans.

ACKNOWLEDGEMENTS

The author appreciates the assistance of cultural medical historian Joseph M. Gabriel. The author is also grateful to Craig Loehle, PhD for helpful discussions and encouragement. Some of the ideas presented here were explored while the author was a Visiting Scholar at the Horace H. Rackham School of Graduate Studies and The Geriatrics Center, University of Michigan, Ann Arbor.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST DISCLOSURE

No conflicts of interest.

REFERENCES

[1] Connor L. The Detroit Lancet. Detroit: George S. Davis, Medical Publisher 1884.

[2] Walsh J. The Lexigton Narcotics Hospital: A special sort of Alma Mater. Science 1973; 182(7): 1004. http://dx.doi.org/10.1126/science.182.4116.1004

[3] Walsh J. Addiction Research Center: Pioneers still on the frontier. Science 1973; 182: 1229-31. http://dx.doi.org/10.1126/science.182.4118.1229

[4] Domino E. Sixty-One Years of University of Michigan Pharmacology, 1942-2003. University of Michigan Medical School Center for the History of Medicine Monograph Series No. 8. Ann Arbor: NPP Books 2007.

[5] Acker C. Addiction and the laboratory: The work of the National Research Council's Committee on Drug Addiction, 1928-1939. Isis 1995; 86: 167-93. http://dx.doi.org/10.1086/357152

[6] Koob G, Sanna P. Neuroscience of addiction. Neuron 1998; 21: 467-76. http://dx.doi.org/10.1016/S0896-6273(00)80557-7

[7] Nestler E. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci 2001; 2: 119-28. http://dx.doi.org/10.1038/35053570

[8] Volkow N, Li T. The neuroscience of addiction. Nat Neurosci 2005; 8(11): 1429-30. http://dx.doi.org/10.1038/nn1105-1429

[9] Campbell N. Discovering Addiction: The Science and Politics of Substance Abuse Research. Ann Arbor: The University of Michigan Press 2010.

[10] Koob G, Moal M. Neurobiology of Addiction. San Diego, CA: Academic Press 2005.

[11] Kuhn C, Koob G. Advances in Neuroscience of Addiction. Boca Raton, FL: CRC Press Taylor & Francis Group 2010. http://dx.doi.org/10.1201/9781420007350

[12] Supiano M, Linares O, Halter J, Reno K, Rosen S. Functional uncoupling of the platelet alpha 2-adrenergic receptor-adenylate cyclase complex in the elderly receptor. J Clin Endocrinol Metab 1987; 64(6): 1160-4. http://dx.doi.org/10.1210/jcem-64-6-1160

[13] Balster R, Bigelow G. Guidelines and methodological reviews concerning drug abuse liability assessment. Drug Alcohol Depend 2003; 70: S13-S40. http://dx.doi.org/10.1016/S0376-8716(03)00097-8

[14] Brady J, Lukas S. Testing drugs for physical dependence potential and abuse liability. NIDA Research Monograph 52. Washington, DC: U.S. Government Printing Office 1984.

[15] Fischman M, Mello N. Testing for abuse liability of drugs in humans. NIDA Research Monograph, 92, No 89-1613. Washington, DC: U.S.Government Printing Office 1989.

[16] Dackis C, Gold M. Addictiveness of central stimulants. Adv Alcohol Subst Abuse 1990; 9: 9-26. http://dx.doi.org/10.1300/J251v09n01_02

[17] Ternes J, O'Brien C. The opioids: Abuse liability and treatments for dependence. Adv Alcohol Subst Abuse 1990; 9: 27-45. http://dx.doi.org/10.1300/J251v09n01_03

[18] Lewis M. Alcohol: Mechanisms of addiction and reinforcement. Adv Alcohol Subst Abuse 1990; 9: 47-66. http://dx.doi.org/10.1300/J251v09n01_04

[19] Morgan W. Abuse liability of barbiturates and other sedative hypnotics. Adv Alcohol Subst Abuse 1990; 9: 67-82. http://dx.doi.org/10.1300/J251v09n01_05

[20] Collins A. An analysis of the addiction liability of nicotine. Adv Alcohol Subst Abuse 1990; 1990: 83-101.

[21] Roache J. Addiction potential of benzodiazepines and non-benzodiazepine anxiolytics. Adv Alcohol Subst Abuse 1990; 9: 103-28. http://dx.doi.org/10.1300/J251v09n01_07

[22] Compton D, Dewey W, Martin B. Canabis dependence and tolerance production. Adv Alcohol Subst Abuse 1990; 9: 129-47. http://dx.doi.org/10.1300/J251v09n01_08

[23] Pollard T. Relative addiction potential of major centrally-active drugs and drug classes - inhalants and anesthetics. Adv Alcohol Subst Abuse 1990; 1990: 149-65.

[24] Carroll M. PCP and hallucinogens. Adv Alcohol Subst Abuse 1990; 9: 167-85. http://dx.doi.org/10.1300/J251v09n01_10

[25] Raper J, Kasner-Morgan L. Addiction potential of abused drugs. Adv Alcohol Subst Abuse 1990; 9: 191-201. http://dx.doi.org/10.1300/J251v09n01_11

[26] Gabriel J. Anesthetics and the Chemical Sublime. Raritan 2010; 30(1): 68-93.

[27] Salerian A. $A = E/T_{max} \times t_{1/2}$. Med Hypotheses 2010; 74: 1081-83. http://dx.doi.org/10.1016/j.mehy.2010.01.008

[28] Kalivas P. Predisposition to addiction: Pharmacokinetics, pharmacodynamics, and brain circuitry. Am J Psychiatry 2003; 160(1): 1-2. http://dx.doi.org/10.1176/appi.ajp.160.1.1

[29] Linares O, Jacquez J, Zech L, *et al*. Norepinephrine metabolism in humans: kinetic analysis and model. J Clin Investig 1987; 80: 1332-41. http://dx.doi.org/10.1172/JCI113210

[30] Wastney M, Patterson B, Linares O, Grief P, Boston R. Investigating Biological Systems Using Modeling. New York: Academic Press 1999.

[31] Khoo K, Gibaldi M, Brazzell R. Comparison of statistical moment parameters to C_{max} and T_{max} for detecting differences in *in vivo* dissolution rates. J Pharm Sci 1985; 74: 1340-42. http://dx.doi.org/10.1002/jps.2600741219

[32] Gibaldi M, Perrier D. Pharmacokinetics. New York: Marcel Decker 1975.

[33] Wastney M, Patterson B, Linares O, Grief P, Boston R. Investigating Biological Systems Using Modeling. New York: Academic Press 1999.

[34] Pepe M, Longton G. Standardizing markers to evaluate and compare their performances. Epidemiology 2005; 16: 598-603. http://dx.doi.org/10.1097/01.ede.0000173041.03470.8b

[35] Hagdu A, Dendukuri N, Hilden J. Evaluation of nucleic acid amplification tests in the absence of a perfect gold-standard test: a review of the statistical and epidemiologic issues. Epidemiology 2005; 16: 604-12. http://dx.doi.org/10.1097/01.ede.0000173042.07579.17

[36] Nutt D, King L, Saulsbury W, Blakemore C. Development of a rational scale to assess the harm of drugs of potential misuse. Lancet 2007; 369: 1047-53. http://dx.doi.org/10.1016/S0140-6736(07)60464-4

[37] Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974; 19: 716-23. http://dx.doi.org/10.1109/TAC.1974.1100705

[38] Daly A, Linares O, Smith M, Starling M, Supiano M. Dobutamine pharmacokinetics during dobutamine stress echocardiography. Am J Cardiol 1997; 79: 1381-86. http://dx.doi.org/10.1016/S0002-9149(97)00144-6

[39] Dieter G. Ockham's razor and its improper use. J Sci Explor 2007; 21: 135-40.

[40] Landlaw E, DiStefano J. Multiexponential, multicompartmental, and non-compartmental modeling. II. Data analysis and statistical considerations. Am J Physiol (Regulatory Integrative Comp Physiol) 1984; 246: R665-R677.

[41] Basson R, Cerimele B, DeSante K, Howey D. T_{max}: An unconfounded metric for rate of absorption in single dose bioequivalence studies. Pharmaceut Res 1996; 13(2): 324-28. http://dx.doi.org/10.1023/A:1016019904520

[42] Salerian A. Addictive potential: $A = E/T_{max}$ x $t_{1/2}$. Med Hypotheses 2010; 74: 1081-83. http://dx.doi.org/10.1016/j.mehy.2010.01.008

[43] Volkow N, Fowler J, Wang G, Baler R, Telang F. Imaging dopamines role in drug abuse and addiction. Neuropharmacology 2009; 56(Suppl 1): 3-8. http://dx.doi.org/10.1016/j.neuropharm.2008.05.022

[44] Devoto P, Flore G, Pira L, Longu G, Gessa G. Alpha2-adrenoceptor mediated co-release of dopamine and noradrenaline from noradrenergic neurons in the cerebral cortex. J Neurochem 2004; 88: 1003-1009. http://dx.doi.org/10.1046/j.1471-4159.2003.02239.x

[45] Volkow N, Ding Y, Fowler J, *et al*. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. Gen Psychiatry 1995; 52: 456-63. http://dx.doi.org/10.1001/archpsyc.1995.03950180042006

[46] Volkow N, Wang G, Fowler J, *et al*. Cocaine uptake is decreased in the brain of detoxified cocaine abusers. Neuropsychopharmacology 1996; 14: 159-68. http://dx.doi.org/10.1016/0893-133X(95)00073-M

[47] Volkow N, Wang G, Fowler J, *et al*. Relationship between psychostimulant-induced "high" and dopamine transporter occupancy. Natl Acad Sci 1996; 93: 10388-92. http://dx.doi.org/10.1073/pnas.93.19.10388

Received on 15-09-2012 Accepted on 20-10-2012 Published on 05-11-2012

DOI: http://dx.doi.org/10.6000/1927-5951.2012.02.02.3