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New Theory on Addictions

Larry D Reid*
Department of Psychology, Neuroscience and Cognitive Science, University of Utah, USA

Abstract

This review questions the value of the extant, 60-year-old dopamine theory of addictions (and hence, theory on pleasure) and provides a different way of explaining how addictions are developed. There is a section of the review particularly associated with addictions involving ingesting fluids (e.g., alcoholic beverages) and food (binge eating disorders and obesity). That section also provides a way of controlling the addictions involved with ingestion similar to what others have promoted via the use of naltrexone as a drug with value in managing ingestive disorders. There are also comments associated with the commerce effective on addictions of alcoholism and eating disorders.

Keywords: Addiction; Addiction Therapy; Addiction Research; Dopamine; Ethanol; Opioids; Ingestive disorders; Pleasure; Relief

Introduction

The dopamine theory is the predominant theory of addictions, i.e., accordingly all addictive drugs, and certain behavioral practices, can produce a surge of dopamine in circuitry whose functionality induces the same pleasurable effects (rewarding effects) such as the reward of food to a hungry rat, or the gift of a large amount of money to a poor person, or a win at gambling, or any other well recognized sources of pleasure (e.g., ingesting Ice cream). The dopamine theory of addictions has been extant for over 60 years. Dopamine has been christened as the "pleasure" neurotransmitter.

Prof. David Nutt and his collaborators [1] reviewed the basis for the dopamine theory of addictions, citing 132 references, and leading to the conclusion that the dopamine theory of addictions was not supported by the extant literature. Despite the extensive research reviewed by Prof. Nutt and colleagues, the dopamine theory of addictions (and its base, the theory of pleasure) continues to be the predominant theory of addictions.

The first observable effects of doses of known addictive drugs vary from mild sedation to hyperactivity. According to prominent versions of the dopamine theory of addictions both sedation and hyperactivity are pleasurable due to the consequences of dopaminergic neurons of the ventral tegmental area inducing a surge of dopamine to the accumbens nucleus and the frontal cortex [2]. Ethanol and cocaine are both addictive but produce observable, different initial effects, different neuronal effects, and induce different toxicities. It is difficult to imagine how one set of neurons whose axons are supposedly innervating one nucleus, and some frontal cortex can produce almost opposite observable effects.

Dictionaries define pleasure with an array of synonyms such as enjoyment and then enjoyment also has synonyms, and each can have a slightly different meaning when used in a sentence. The words pain and painful convey the opposite of pleasure. Pleasure is a rather distinct event, and there is no chronic pleasure (however, there can be continuing health, contentment, or satisfaction). We have different words for states of well-being such as happiness and comfortable (manifest as being healthy). The opposites of pleasurable are such as chronic pain, lethargy, sadness, and depression (which can be manifest as disease).

It is not surprising that one or a few words for complexities are not precise, however, words can convey meaning when in a sentence or a broader context. The dopamine theory of addictions and the dopamine theory of pleasure may convey a single, cohesive, useful conceptualization. On the other hand, the theory may have little worth, despite its popularity in scientific journals and popular media. Also, there are dopamine theories of schizophrenia and Parkinson's disease which do not fit into a grand theory of pleasure.

The perception of a betterment in affect is not the same as having unmitigated pleasure (such as euphoria or even a mild sense of pleasure). For example, a reduction in pain is not the same as pleasure because pain persists. However, the reduction of pain is a "good" and is appreciated but to call the diminution of pain as pleasure does not seem right. A reduction or an end to pain surely yields relief (relief: removal or reduction of something painful, oppressive, distressing, or irritable).

Dopamine is a neurotransmitter and/or neuromodulator extensive throughout both the peripheral and central nervous systems [3]. Given the omnipresence of dopamine throughout the physiology, drugs affecting dopamine can have multiple effects (side-effects) that are dose and duration sensitive. There are 5 slightly different dopamine receptors, so a dopaminergic drug can theoretically be specific for one of the receptors and one disease and might only be associated with one system of the physiology. However, given the complexity of the nervous system and knowing many circuits involve more than one neurotransmitter, the goal of specificity of a dopaminergic drug to a specific affect or disease will be rare.

Jose Yong, Norman Li & Satoshi Kanazana [4] have written an article on being rational or engaging in rationalizing, they say: "Our craving for coherence can also make us construct meaning where none exists". This seems to be the case with the dopamine theory of addiction. Perhaps, the dopamine theory remains the theory of addictions because there are no well-developed alternatives.

The posited anatomy and physiology of the dopamine theory of addictions

Walter Rudolf Hess, a Swiss physiologist, was aware that electrical

***Corresponding author:** Reid LD, Department of Psychology, Neuroscience and Cognitive Science, University of Utah, USA, E-mail: reidl@rpi.edu

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stimulation of features of the cortex could reliably produce specific movements. When he began his research-career, there was knowledge about the differing functions of different parts of the cortex, but little was known about the functions of the midbrain. Hess implanted electrodes (small wires) into the brains of cats so that electrical stimulation might activate a small part of the midbrain, hence providing information about the function of the place of stimulation. His findings indicated that activation of different parts of the midbrain could induce complex behaviors, such as apparent fear, sleeping, etc. Such findings were of such significance as to be recognized via a Nobel Prize.

Donald Hebb, while a professor of psychology at McGill University, literally established, via his theorizing, what is now called behavioral neuroscience. His perspectives attracted a number of talented psychologists to work with him and his associates. Among those attracted was James Olds. Olds working with Peter Milner were implanting electrodes in the fashion of Hess, except using lab-rats. Olds, while observing the effects of the electrical stimulation (often called intracranial stimulation, ICS) noted that one rat always returned to the place where the ICS occurred. Olds surmised that the ICS was rewarding and then set about verifying that by allowing the rat to press a lever to get brief ICS at the place of the tip of an electrode. After the rat was shaped to press a lever for ICS, the rat repeatedly pressed the lever for ICS. Olds then began a series of experiments mapping the places in the brain where rats could be trained to press a lever in a small enclosure (i.e., a Skinner box) which also was equipped to record automated graphs of pressing across time (i.e., cumulative records similar to those used by Skinner). Olds posited: there was circuitry in the brain whose functions induced reward and pleasure and could be artificially induced by ICS to relevant parts of the brain.

As more data were developed, no one disputed the obvious, i.e., rats and subsequently cats and primates would press levers to obtain brief ICS of selected sites within the brain because such were demonstrated in many laboratories [5]. What was disputed was the theory that the ICS was activating the neural substrate of pleasure. A dictionary defines pleasure as a list of synonyms but does not provide such as an anticipation of pleasure as being pleasurable (yes, an incomplete definition of pleasure, hence providing some confusion about "pleasure and pleasurable"). There are affective states opposite to pleasure (e.g., pain, loneliness, sadness, disgust, and unpleasant symptoms of a wide array of diseases). Subsequently, we will address the issue of the affect between the two polar opposites, pleasure, and pain.

The noun *affect,* as used by psychologists, refers to the perception of the ongoing status of emotions, feelings, and perceptions. Affect is a summary of the status of well-being, a summary of the current status of the ongoing physiology, often a summary of deviance from homeostasis. Affect is a running tabulation of the status of health and well-being, hence provides feedback for efficiency of ongoing behaviors. That feedback can induce preferences.

The ventral tegmental area of the brain is a place with a number of different kinds of neurons whose axons are contained within the medial forebrain bundle (MFB) [6]. The MFB is a tract within the lateral hypothalamus and the preoptic area and innervating the accumbens n. and the frontal cortex as well as other places within the brain. When tips of an electrode are within or very close to the MFB and a brief ICS of that electrode is used to shape rats to press a bar for the brief ICS, rats quickly learn to press for the ICS and, once pressing is begun, pressing is sustained for long periods.

Axons of the dopaminergic neurons of the ventral tegmental area are part of the MFB. Many of those axons terminated in the accumbens n, and the frontal cortex. Given the following:

a. Brief ICSs can sustain rapid pressing in Skinner boxes for considerable times.

b. Procedures were developed to verify that dopamine was released in the accumbens n. and areas of the frontal cortex subsequent to activity in the MFB (7).

c. The cumulative records for pressing levers for ICS and water reinforcement by thirsty rats were nearly identical [8]. These early data, and subsequent data, support the dopamine theory of addiction and pleasure.

The MFB's anatomy is very complex with many axons originating in various parts of the brain and terminating in various parts of the brain. Consequently, ICS to the MFB must also innervate wide swathes of brain other than the accumbens n. and parts of the frontal cortex. The circumstance of widespread neural activity from an ICS of the medial forebrain bundle was summarily ignored as the dopamine theory of addictions, involving the accumbens n, became the explanation of addictions (and pleasure).

Complex contingencies

The perception of a betterment in affect is not the same as having unmitigated pleasure (such as euphoria or even a mild sense of pleasure). For example, a reduction in pain is not the same as pleasure because pain persists. However, the reduction of pain is a "good" and is appreciated but to call the diminution of pain as pleasure does not seem right. A reduction or an end to pain surely yields relief (relief: removal or reduction of something painful, oppressive, distressing, or irritable).

Generally, the concept of reward implies that a reward is clearly something of value with few negatives. Generally, punishment is also often viewed as single event (without much consideration of the extent or kind of punishment). This is particularly the case when studying the effects of rewards and aversive circumstances in studies of the kind B.F. Skinner and colleagues used to characterize schedules of reinforcement. However, in the ordinary stream of life, almost all actions have both benefits and costs, hence studies [9,10] began in which a single bar press yielded both a positive and an aversive ICS often separated by 0.25 sec.

When harsh events (aversive ICS or brief foot-shock) immediately followed an ICS ordinarily sustaining rapid bar pressing for the ICS, we learned that rats continued to press for a combination of positive ICS and an event that ordinarily would be painful. It seemed that when there was little time between positive ICS and "pain" that the effect is a meld into a single affective event less than when only positive ICS was programmed. When the positive ICS and the stimulus causing pain were separated for, say, some minutes, then the full force of the pain had the effect of slowing or halting pressing. If an act has consequences that are both immediate and delayed (with intervals beyond a few minutes to years), then it is likely that the two induced consequences will not be associated with one another (i.e., no learning that an act had dual consequences) (generally the greater the intervals the less likely an association) (such is well known).

Casper and Reid [11] arranged a procedure in which a rat in a box could press a lever and get 4 brief ICSs for each lever-press. The pressed lever retracted to outside of the box with a single lever press and then quickly returned to present an opportunity to press the lever again. There were two kinds of brief ICS, one capable of eliciting

rapid, prolonged pressing for ICS of the MFB (a positive experience designated with a +) and one kind eliciting pain as indexed by the subjects running from a place where the ICS was programmed (a negative, aversive experience designated by a -). We programmed each of 16 different contingencies of ICS during 4 min sessions with each possible pattern of contingencies and did those multiple times. All combinations of 4 events were tested. The contingencies are listed in the accompanying table. Each ICS, regardless of a positive one or an aversive one lasted for 0.25 sec. and were separated from one another by 0.25 sec. (there were tests when times between ICSs were as long as 1.0 sec., but such did not significantly change the patten of responses for the differing contingencies).

It is not surprising that the rats pressed many times when the contingency was 4 positive ICSs (nearly achieving the maximum possible presses) and pressed almost none when the contingency was 4 negative ICSs (had to press once to know the contingency). There was more pressing for the contingencies in which the positives were more prevalent than the negatives (not surprising). When a negative ICS was the first stimulation of a contingency, that diminished pressing for the contingency. For example, when the contingency was +++- , rats pressed at nearly the same rate as when the contingency was ++++; however, when the contingency was -+++, there was a marked reduction in pressing (but some pressing for sure) (Table 1).

If one *arbitrarily* assigns 50 to each positive ICS (abbreviated +) and assigns -50 to a negative ICS (abbreviated -): then ++++ would have a value of 200. The contingencies +++- would have a value of 150 and -+++ would also have a value of 150. The number of presses when the contingency is +++- was188 compared to 73.5 presses when the contingency was -+++. Note: 188/73.5 indicates that +++- was about 2.6 times more satisfying than -+++ (as indexed by extent of pressing). So, assigning the "affective value" for each positive and negative ICS does not account for the extent of pressing for different patterns of positives and negatives ICSs that were programmed. It is difficult to discern the value of a singular positive ICS and a singular negative ICS occurring at different locations in the brain. In this experiment, both kinds of ICS were deemed to be among the most intense stimulations as noted by when all positives and all negatives were programmed.

Arbitrarily, ++-- and --++ has a value of zero and hence little or no bar pressing. However, the average number of presses when the contingency ++-- was 104.6 and was 41.1 presses when the contingency was --++. The 104.6 presses divided by 41.1 indicates that ++-- was about 2.5 times more satisfying than --++. You can continue comparing patterns of positive and negative ICSs and such will show that when the pattern has positive effects first followed by negative effects that such sustains more pressing for a complex contingency than when negative ICS is programmed first. This observation has some relevance toward explaining binge-drinking of alcoholic beverages (see below). This observation also helps understand the common observations of persisting behavior when that behavior also has harshness.

Table 1: Rank, Contingencies and Mean Presses.

Rank	Contingencies	Mean Presses
1	+ + + +	192.1
2	+ + + -	188.0
3	+ + - +	184.9
4	+ - + +	126.4
5	+ + - -	104.6
6	+ - - +	82.0
7	+ - + -	76.1
8	- + + +	73.5
9	- + - +	53.5
10	+ - - -	48.4
11	- - + +	41.1
12	- + + -	31.1
13	- + - -	6.9
14	- - + -	6.2
15	- - - +	1.0
16	- - - -	1.0

Complex contingencies yield something different than when acts result in either obvious pleasant or painful contingencies. The slot machines of gambling establishments present some complex contingences with schedules similar to our simple experiment with rats. Consider, if every time you put a quarter in the slot and pushed down on a lever you received four quarters in return; and if that happened regularly such seems similar to the contingencies of all positive ICSs. Further, it is likely that a person engaging in such activity would continue to engage the activity for an extended period. It is not a surprise if the slot machines are programmed such that lever-pushes due to quarters in the slot were programmed so that the net effect from multiple lever-pushes was a loss of money (e.g., when an ultimate contingency was similar to +--- in our simple experiment).

Complex contingencies are guiding much of our daily behaviors. For example, chores and jobs involve complex contingencies (jobs demand work and work often is difficult, and even harsh, but also can be satisfying). Consider this extrapolation: Perhaps, if, as an employer you paid workers a week's pay on Monday rather than on Friday, maybe the workers would be more satisfied (see contents of the table).

An adaptive feature of normal activities is anticipation of reward which maybe experienced as pleasant affect and, adaptively, sustains actions toward receiving a reward or a goal, hence sustains actions with a chance of accomplishing the specified goal (e.g., foraging for a meal and when a meal found there is the satisfaction of eating). When there is no motivation to forage (probably due to previous failures in attaining multiple goals and frustration) then, of course, chances of attaining satisfaction are slim and hence manifest as lethargy and, if extended, depression.

The text-book-explanations of how programmed contingencies can be used to modify behavior involve such as a programmed reward (e.g., a small pellet of food for a hungry rat). And pain is usually administered via electrical shock to the feet and tail of a rat. However, outside of the laboratory, pleasure and pain are usually not happening as discrete events but a mixture melding into something like a single affect. Given, complex circumstances are prevailing and there is little research assessing the affect induced by combinations of positive and negative feelings following a given act, it does seem that there is some value in inspecting combinations of contingences. The research reviewed here may be germane to a consideration of new theory of addictions, which involves complex affective issues, such as when a contingence is ++-- which sustained lever pressing for ICSs for over a hundred times during a 4-minute period (below is further explanation of the comment).

When an act induces both an immediate consequence as well a delayed consequence (or consequences), but the delayed consequence is separated in time from the act, then the act seems to be perceived as a separate event and the delayed consequence is likely to be associated with what happened just before the delayed effect (this circumstance can lead to some false conclusions concerning causality). Also germane

to issues of delayed consequences of an act inducing both an immediate positive affect and when the delayed effect is of only small toxicity, there is little effect on whether or not the act will be repeated or not, depending on the value of the initial consequence of the act. At issue: regularly drinking many servings of an alcoholic beverage can have, eventually, severe consequences, e.g., repeated intakes of large amounts of ethanol can incrementally and somewhat slowly lead to sufficient liver-damage to be a very serious, or even a lethal, consequence of drinking alcoholic beverages. Without research linking ethanol-intake with early stages of liver-disease is made available to the drinker, the drinker has no awareness that the liver-disease is a consequence of a history of repeatedly drinking alcoholic beverages. And, of course, advertisements encouraging buying alcoholic beverages never warn the drinker that repeated drinking of the beverages can cause severe disease.

My laboratory developed a means of measuring affect (preferences) among lab-rats [12]; the apparatus and procedures are titled "procedures for assessing Conditioned Place Preferences (CPP)." Also, the procedures can index Conditioned Place Aversions (CPA). Since nearly 7000 articles indexed by PubMed use CPP and/or CPA procedures to index affect among rats, mice, or humans, I presume most readers will be familiar with the procedures, and if not, there is a rather long description in Reid [13], available free. Also, an apparatus was developed allowing acts for rewards in a place of putative CPPs, an extension of testing for preferences [14].

Research throughout the decades following the development of CPP procedures, led to the conclusion that addictive drugs (mimicking doses used among addicts) each established a CPP compared to placebos. Initial effects of a dose of an addictive drug does produce an affective state more satisfactory than the affect prior to taking an addictive drug [15]. Note: I did not say pleasure was the consequence, but rather a betterment of the state experienced prior to drug-use.

My laboratory [16], using the procedures of CPP, assessed the effects of doses of ethanol using the procedures of CPP. Unlike the assessments with some other addictive drugs, ethanol did not induce a CPP. A puzzling outcome because there is plenty of "information" indicating ethanol can induce betterment in affect. Tests for place preferences were done at different times after injections of ethanol. A CPP was established when the rats spent a brief time in the side of the alley (say 5 min) shortly after an injection of ethanol. However, a CPA was established when other rats were put in the same place after the same injections but after 8 or 14 min after the injection. Extrapolating to what a person might experience: a serving of an alcoholic beverage may induce a betterment compared with what was happening just before drinking the beverage but, as ethanol was being metabolized, the affect changed to something similar to dislike (similar to a CPA). Another serving of an alcoholic beverage blunts the dislike emerging after the first serving of an alcoholic beverage. A repetition of like, then dislike, then like, etc. can lead to binge drinking. Stated differently: a usual serving of ethanol induces a CPP, however with the passage of a rather short time, the affect is similar to a CPA which can be diminished by another serving of ethanol.

If a surge in dopamine to limited portions of the brain is not the common factor of addictions that opens the question of what other characteristics, if any, are common to both ethanol and cocaine other than both being addictive. Or, maybe, the initial effects and diseases induced by ethanol and cocaine are sufficiently different that differing theories are necessary.

I suspect that those who are selling addictive drugs (both legal and not legally) appreciate the help they receive by the widespread statements that addictive drugs induce pleasure.

Given that addictive agents probably do not uniformly induce "pleasure" via a dopamine surge or a surge of any other major neurotransmitter, it seems wrong that addictive agents are advertised as agents producing pleasure. Yes, addictive agents might provide some relief from troubling circumstances but also unpleasant after-effects (i.e., the functional equivalent of CPA).

Drug-addictions are a trap. A dose of addictive drugs' first effects produce relief or distractions from troubling circumstances and that relief is appreciated. However, as the dose of the addictive drug is distributed and metabolized, there can be a return of the initiating feelings bolstered by some toxicity associated with disturbances to homeostasis due to side-effects of the drug. With respect to intake of alcoholic beverages, the metabolism of ethanol yields acetaldehyde, which has known toxic effects. Both a return of troubling feelings and minor withdrawal effects are a setting condition for taking another dose of the addictive agent or maybe trying another addictive drug to induce some sense of satisfaction which will, in turn, inevitably not address what might be troubling (e.g., financial problems or loneliness or living in harsh circumstances or not being appreciated). Stated differently, addictive drugs induce feelings (affect) better than what was being experienced before the decision to take a drug. However, as the drug-effects wax and wane such becomes a setting condition for taking another dose of the addicting drug which may induce something better than before the intake of the drug.

With respect to alcoholism, the idea: Doses of ethanol (servings) provide some distraction, calming, and/or relief from troubling circumstances such as being anxious, troubled, fearful, disturbed, lonely and general unpleasantness and being unhappy. Ethanol can provide a somewhat better affective state than that immediately before a serving of ethanol [17]. However, as a serving of ethanol is metabolized and the distraction and relief are no longer being felt, the easy solution is to have another serving of an alcoholic beverage [18]. Such can lead to binge-drinking.

When the affective state is one of lethargy, being tired, listless, fatigued, or depressed, a serving of coffee or a dose of cocaine can provide a change for the better than the listed affective states. That is, stimulants can produce a better affective state than the one immediately preceding doses of the stimulants. However, when the effects of the stimulants wane there is a return of the prevailing lethargy and that is a setting condition for taking another dose of a stimulant. Repeating dosing can lead to excessive stimulation which, in turn, sets the stage for taking a drug to "calm down" or to induce needed sleep (e.g., ethanol, a barbiturate or a benzodiazepine). However, ethanol, barbiturates or benzodiazepines can induce a state of unconsciousness that resembles sleep, but is not healthy sleep, so upon arousing to begin a new day, there is a return to being tired and the urge to take a stimulant. Such can lead to a vicious cycle. Such can and does induce sufficient chaos of the physiology to be inducing disease.

Maybe, there are two kinds of agitating circumstances associated with two kinds of drugs:

a. Such as anxiety that can be muted by relief, calming or distraction, or

b. Stimulating drugs inducing arousal from such as lethargy.

An optimal state of health is manifest as enduring satisfaction,

comfort and generally a happy state interspersed with incidents of pleasure and rapid recovery from events experienced as pain and threat. Being healthy is usually a state of homeostasis of the physiology and smooth transitions from *such as* being hungry to being satisfied by a meal or thirsty to being satisfied by a drink or being cold or hot and a return to pleasant temperatures. Generally, the physiology of a healthy person can easily manage many extreme circumstances. However, the taking of drugs (including ethanol and nicotine) can have some similarity to known poisons; that is, they produce changes in the physiology greater than normal hunger and thirst and other ordinary deviations from a stable physiology (e.g., being tried after exertion, being sleepy after an extended period without sleep) which can be managed by the usual functionalities of the physiology. And, of course, there are beneficial drugs and vaccines correcting threats to health (such as bacterial, fungal, and viral infections).

The intake of addictive drugs sets a trap. The effects of the addictive drug provide relief from unpleasant affective states manifest by a wide array of events eventually named anxiety, fear, obsessiveness, agitation, and the other extremes of depression, enduring sadness, and lethargy. However, the drug-induced betterment of affect (most likely being a temporary relief from troubling circumstances) wanes with the ongoing metabolism of the addictive agent, hence, is a setting condition for further dosing. Addictive agents induce betterment in affective status which seemingly, inevitably is followed by a return to the initiating affect and withdrawal effects (an opponent process useful in sustaining homeostasis).

There can be affective states concurrent with the intake of a potentially addictive drug that does not result in the establishment of a habit, because habits are not established quickly. Habits rarely, if ever, are established with one act and its consequences [19]. But when drug-taking habits are established, they resemble other habits, that is, they are automatic and often not under the control of rationality.

Given alcoholic beverages are advertised as pleasure-producing products and young citizens presume that the ads have some validity; they do sample the available alcoholic beverages and do find that they are mildly O.K. and then conform to using them at parties or with meals. However, when troubling circumstances are prevailing that sets a trap leading to binge-drinking, i.e., an attempt to sustain a betterment of affect that is slipping away. Binge-drinking can induce troubling circumstances prevailing on another day and hence elicits drinking to calm troubling affect and such is another day in the history of a potential alcoholic.

Perhaps, there can be a theory of alcoholism more in line with the facts rather than the prevailing beliefs that ethanol is a pleasure-producing-drug having small or no negative consequences if used in moderation. Ethanol, drunk in lesser amounts, *might produce* some small benefits to health, hence making drinking alcoholic beverages acceptable ingesta (any benefits to health are not extensive). The marketing of alcoholic beverages is highly sophisticated and, of course, never mentions the harm done. Oh, they say "drink responsibly," knowing full well that the phrase has no practical effect on buying an alcoholic beverage. Further, drinking "in moderation" is not the goal of the alcohol beverage industries and drinking "in moderation" can be, and often is, a step toward becoming an alcoholic (an enduring customer for the alcohol beverage industries).

A new appreciation of the development of alcoholism does not demand every drink of alcoholic beverages is calming or a distraction from harsh circumstances. However, when circumstances are troubling, then ethanol can produce distraction or calming, but that is only temporary. Also, regular drinking of alcoholic beverages does induce disease (e.g., progressive loss of the liver's functionality), a troubling circumstance, and can be a setting condition for another bout of drinking an alcoholic beverage or maybe taking another mildly addictive drug such as one of the barbiturates or one of the benzodiazepines. As Professor Kripke has demonstrated the use of hypnotics is a setting condition for diseases resulting in a shortened life-span [20].

A step toward being rational is to stop retelling, in both the scientific literature and what is provided to the public, the message: addictive drugs are pleasure-producing. Generally, addictive drugs do not produce unmitigated pleasure and surely do not promote happiness. Relief from troubling circumstances can motivate the use of an addictive drug, however, that is not the same as inducing pleasure.

The side-effects of medicines designed to cure a disease can induce troubling circumstances (e.g., interference with cholinergic systems, or an accumulation of drug-induced problematic side-effects particularly if there is excess polypharmacy) can be a setting condition to use a drug providing some relief (adding to polypharmacy). There is good research indexing the anticholinergic effects of drugs and those findings allow a careful consideration of what drugs to be prescribed or sold without prescriptions. Unfortunately, the knowledge of which drugs have severe anticholinergic effects is not being used sufficiently.

There is a consensus among pharmacologists that regular consumption of as many as 5 or 6 drugs is apt to be harmful due to the desired and undesired side-effects of that many drugs which can induce considerable disturbance of the physiology, i.e., inducing disease. Unfortunately, often citizens' intakes of drugs exceed what is thought to be a safe limit. Among the drugs that should be counted is ethanol.

The examples of the problems presented in the previous two paragraphs (i.e., intake of excessive anticholinergic drugs and excessive polypharmacy) are the kind of problems that can induce troubling affect which are setting conditions for taking doses of ethanol (or other addictive drugs). A step toward preventing drug-addictions is to better regulate the sale of legally available drugs (e.g., put something like labels on containers indicating a *severe anticholinergic burden*) as well as better control of illegal drugs, hence reducing troubling circumstances.

Prescribers of drugs should conform to advice given by the periodic Beer's reports' list of potentially harmful drugs and there should be more adherences to limiting drugs with anticholinergic burdens.

Increasing the taxes on alcoholic beverages will reduce consumption of the beverages [21] If part of the income from higher taxes could be used to subsidize housing for those in need and provide for best treatments, such will produce a profit for the culture.

The dopamine theory of addictions specifying that addictive drugs induce pleasure is not only an incomplete, unproven theory, it is also a reason individuals experiment with drug-effects as a remedy for their troubling circumstances, a trap leading to addictions.

Will Power to Pill power to Sustaining Health

The ingestive disorders, alcoholism, binge-eating-disorders, and obesity, are diseases causing diseases; consequently, eventually leading to shortened lifespans compared to those who do not suffer from the listed diseases. Persons who have the listed diseases are usually aware of the negative consequences of their gluttony, but nevertheless continue to drink and/or eat too much to sustain optimal health.

There are huge commercial enterprises selling alcoholic beverages and they skillfully promote their products. Also, there are huge enterprises developing foods tending to being addictive, i.e., foods laden with sugar, salt and animal fats and are generally very palatable (but often with little nutritional value).

Concurrent with the enterprises providing the potentially addictive ingesta, there are huge commercial enterprises specializing in marketing designed to increase the sales of the potentially addictive ingesta. Further, the marketing is developed using scientific methods and has become very sophisticated, and the marketing professionals make use of the science of academic psychology to guide their marketing. Yes, one can earn a PhD in marketing that relies heavily on available science. Alcoholic beverages are advertised as pleasure-producing, safe, accepted by role models and often glorified.

Given the large prevalence of ingestive disorders, many enterprises were developed to treat the disorders, e.g., there are alcohol-treatment-centers fostering 28 days of treatment while living in a resort and often costing large amounts of money; a large array of programs for bodyweight control (i.e., for preventing or reducing obesity); and group or private psychotherapy (common for younger persons who have developed binge-eating-disorders and anorexia).

Briefly, there are substantial, successful commercial enterprises both inducing and treating the ingestive disorders and profit by doing so. The net effect of all of that commerce is a lot of misery and disease.

Opioid agonists, including morphine (at small or moderate doses) enhance ingestion of presented food and drink. The effects of naloxone or naltrexone (opioid antagonists) reduce ingestion of presented food and drink [22-24]. *The conclusion: there is an endogenous, opioidergic circuit of the brain whose functionality is to sustain ingestion to satiation, hence insuring adequate nutrition.* Exogenous opioid agonists can enhance that functionality and overwhelm ordinary inputs from the gut whose continuance usually induces satiation [25], thereby leading to ingestion of excess food and/or drink. Naloxone and naltrexone reduce ordinary intakes of food and drink including highly palatable ingesta and alcoholic beverages (probably modifying influences from the gut given opioidergic circuitry sustaining functions of the gut).

With the knowledge that naloxone and naltrexone can suppress intakes of alcoholic beverages among laboratory animals, clinical trials [6,26] were arranged to test the notion that naltrexone might be helpful in improving treatments for alcoholism. The initial studies did indicate that opioid antagonists might be useful tools to enhance the psychotherapy that was extant. In addition to naltrexone as a medicine to control drinking of alcoholic beverages, there are nalmefene, buprenorphine/naloxone, extended-release naltrexone, and acamprosate each showing signs of reducing drinking of alcoholic beverages while under the influence of the listed drugs. The total reliance on one of the listed drugs to instill the habits of abstinence may not be sufficient, because the drugs do not fully block drinking of alcoholic beverages hence sustains the habits associated with extensive drinking. Naltrexone does reliably reduce binge-drinking, days of drinking, and some craving. The antagonists will reduce binge-drinking and that is good but features of the habit of drinking are sustained. To get better results, there is a tendency to prescribe the extended-release-naltrexone for a number of months, hence allowing a lifestyle free from excessive drinking with the hope that such is rewarding enough to encourage steps toward total abstinence. There is research to indicate that a cessation of naltrexone and like drugs is a setting condition for engaging further consumption which can escalate to problematic levels of intake of ethanol [27,28].

An optimal treatment for alcoholism would be a regime of activities beginning with stopping all drinking of alcoholic beverages, often an unpleasant process, best managed by a licensed health-care provider and in a place adequate for the task. The process usually spans 4 to 7 days. As part of the preliminaries of the therapy, there should be a full assessment of the patient's health including a survey of drugs usually taken. When excess polypharmacy is noted there should be steps to reduce the number of drugs being taken. Also, drugs with a severe anticholinergic burden should be limited because they can induce the troubling circumstances, a condition sustaining drinking. If the patient has a history of taking other addictive drugs that should be noted and those habits also need attention. If the survey of all drugs taken is beyond the safe limit, there should surely be attempts to limit any excessive polypharmacy and reduce use of drugs with severe anticholinergic burdens. If the patient is taking an antidepressant, it would be prudent to systematically reduce the use of the antidepressant while suggesting that treating alcoholism is apt to also prevent depression [29].

Post the most severe withdrawal discomforts, there should also be some rest and relaxation involving healthy diets; particularly a diet involving a pill providing all of the B-vitamins [30]. A program of comfortable physical exercise is useful. During recovery, cognitive behavioral therapy with a focus on how to manage not relapsing back into regularly drinking alcoholic beverages seems almost imperative. Therapy should deal with problematic circumstances which seem to trigger the desire for relief from the troubling circumstances which were likely instrumental in the establishment of an addiction. The techniques of mindfulness training can be useful in dealing with situations difficult or impossible to modify for the better.

Provided that the person who has recently stopped drinking alcoholic beverage (probably due to best extant therapy) and who is not taking opioid agonists for pain (and other issues associated with other drug-interactions and existing diseases), there is the option of being prescribed the extended-release-injectable naltrexone providing circulating naltrexone for at least 28 days or daily an oral dose of naltrexone for at least 28 days. Naltrexone does reduce intake of alcoholic beverages hence preventing binge-drinking when it is circulating and reduces days of drinking. However, the habit of drinking will likely persist (manifest as craving but not as intense as when there were previously daily or near daily intakes of ethanol). After the full regimen of optimal therapy designed to achieve abstinence and no opioid antagonist circulating, there is still a likelihood of excessive drinking on a day and then on more days and eventually full relapse to problematic levels [30]. Given the temporary effects of current therapies and the limited effects of current naltrexone-therapy to sustain total abstinence is further evidence that drug-induce benefits are merely a setting condition for further psychotherapy directed toward developing the ability (will-power) to sustain abstinence.

Naltrexone, as long as it is circulating, reduces bouts of drinking alcoholic beverages and may reduce excessive intake of palatable food and other calorie-laden drinks. However, prolonged antagonism of circuits blocking the functionalities of the extensive endogenous opioidergic systems may not be optimal (too much disturbance of homeostasis). The side-effects of sustained-release-naltrexone is not as intense as seen with many drugs, but includes sore throat, nausea, insomnia, hypertension, influenza-like symptoms, toothache, headache, dizziness, fatigue, back pain, upper abdominal pain, and decreased appetite for food (which may be useful for those with obesity).

It would be good for there to be an expensive tax on alcoholic beverages, according to the amount of ethanol in a container, because

such will reduce consumption of the beverages [21]. It would also be good if a large proportion of those taxes were used to pay bills for those who cannot afford best therapy and free housing for those needing it. A reduction in the prevalence of binge-drinking will yield more benefits and less costs than what is spent on incomplete or no treatment [31].

Prof. Parsons investigated neurocognitive deficits in sober alcoholics for several decades [32]. His research showed that both male and female adults with a previous diagnosis of alcoholism, but at the time of testing were sober, had "deficits on tests of learning, memory, abstracting, problem-solving, perceptual analysis and synthesis, speed of information processing and efficiency". His data indicated that some of the deficits can be overcome to some extent during a period of abstinence or near abstinence of 4 to 5 years. We now recognize that the brain has considerable plasticity and practicing computer-assisted game-like programs have a good chance improving cognitive skills [33], hence reducing the time to overcome some of the lost cognitive skill. The programs of the company, Posit Science, have been tested and the results indicate that, with sustained practice on their programs that might lead to a faster recovery of lost cognitive skill. Also, computer-assisted game-like programs can be developed to improve impulsiveness. For former alcoholics being housed at government expense, the patients might have a job of improving cognitive skills and impulsiveness (useful in many situations, hence becoming more adaptive citizens).

Taking pills of naltrexone daily or getting injections of sustained-release-naltrexone monthly to sustain abstinence is sort of relying on the naltrexone to do the work of extinguishing the habit of drinking. Naltrexone limits the intake of alcoholic beverages, and such is an improvement for sure, but does not train for abstinence.

As mentioned, post the miseries of withdrawal symptoms, there is ideally cognitive behavioral treatment focused on preparing patients for managing a quest for total abstinence. The poem by William Ernest Henley ends with this phrase: "I am the master of my fate; I am the captain of my soul." Therapies for post withdrawal should focus on the value of the idea that one should take charge of their craving and drinking of alcoholic beverages (as a virtual pilgrimage, a new and expanded meaning of self or a better good) because ethanol is toxic, and patients need to fully understand they are being manipulated by the alcohol beverage companies. Modern Alcohol Anonymous meetings can be helpful, and they vary and focus on being "sober support meetings."

Given that continuous naltrexone may disrupt homeostasis because there are multiple circuits of the nervous system involving endogenous opioids, including the one sustaining ingestion. There is an alternative to sustained naltrexone (and like drugs) that maybe more efficacious. Post withdrawal from intake of alcoholic beverages and some days of abstinence, the patient ending formal treatment might be prescribed a large supply of pills of naltrexone to be used to prevent the compulsion to drink large amounts of alcoholic beverages when opportunities to drink alcoholic beverages are perceived or presented. There is some evidence [34] that it is best to have the patient, when approaching a usual opportunity to drink alcoholic beverages, to take a single dose of naltrexone as early as an hour before an opportunity and/or strong urges to consume alcoholic beverages. If an hour before is missed, taking a dose of naltrexone just before an opportunity to drink will be helpful in preventing binge-drinking. Recall that opioid antagonists reduce ingestion, hence tend to reduce instances of binge-drinking. This targeted use of naltrexone has advantages in that the patient is an active player in an attempt to gain lasting abstinence. The naltrexone dose before the opportunity to drink may reduce craving [26] and if a serving of ethanol is consumed, the naltrexone will likely reduce further ingestion. There is value in the act of a patient to have a sense of control over potential binge-drinking. The patient recalls the psychotherapy focusing on "I am the master of my fate, I am the captain of my soul." The patient should carry throughout every day a small box of pills of naltrexone and take one when the urge or opportunity to drink is presented [35]. That small act provides a sense of control over drinking alcoholic beverages and that sense is strengthened with every intake of naltrexone preventing consumption of the toxic beverage (that previously led to drunk driving, family problems, etc.). Periodic, single doses of naltrexone will not, I guess, accrue the same troubling side-effects characteristic of continuous naltrexone.

A reiteration

The dopamine theory of addiction is based on the following: any addictive drug, when taken, is a gift of pleasure to a consumer. To get that supposed gift, merely buy a dose (or doses) of a known addictive drug. However, any pleasure is temporary (the dose is metabolized) hence to get pleasure again, merely buy more of the drug and then consume it. If the drug is consumed often, the physiology sustaining homeostasis develops tolerance to the drug hence less pleasure than previously which can be rectified by taking a larger dose or enhancing the frequency of dosing so there is some cumulative effect leading to a larger dose of the drug. Larger doses or more frequent dosing costs more. Repeating the act of buying the drug establishes the habit of frequently buying the drug (hence entailing a high price). If a consumer assesses the benefit-cost ratio of regularly consuming a drug and decides the cost outweighs the benefits and then decides to stop consuming the drug such induces adverse withdrawal effects which can be overcome with further dosing of the addictive drug. Hence the road to an addiction. Hence, there is no unmitigated pleasure from consuming known addictive drugs. The known addictive drugs are a trap, good effects followed by bad effects, particularly if taken often (e.g., extensive use of opioids are manifest by itching and constipation, neither of which is pleasure).

An alternative: Any one of the addictive drugs, when taken, *might provide* a betterment of the affective state extant just before using the drug (if not a betterment of affect, the drug is not likely to be taken again and no addiction is established). Given that premise, the extant affect prior to taking the drug may be critical. When the extant affect is something similar to anxiety, then a drug having effects of calming or distraction may provide a better affect. However, if anxiety is the issue and cocaine is the potential addictive drug, then cocaine's exciting effects and waning of stimulation are apt to elicit more anxiety. When, the extant affect is lethargy or depression, and then a stimulating drug, e.g., cocaine, can counter lethargy. The cocaine's better affective state will likely be enhanced activity and something similar to foraging for desired outcomes (as always, dose-sensitive). As the cocaine is metabolized, there is a return to the affect extant upon taking the drug and possibly some minor to major withdrawal effects, hence inducing the urge to take another dose of the drug. However, when the extant affective state is lethargy, a drug inducing less activity (e.g., a barbiturate) is apt to be harmful.

Addictive drugs when consumed often actually induce troubling circumstances. For example, anxiety is not pleasant, but a dose of ethanol can initially provide some calming, mild sedation (if it might, because it inhibits neural activity), but as ethanol is metabolized the anxiety is returning, acetaldehyde is circulating, and an easy way to muting the adversity is to take another serving of ethanol, the setting

condition for binge-drinking. The extant affective state may be one of stress due to circumstances like poverty, difficult working conditions, poor family relations, and if a drug provides a somewhat better affective state, then that provides some relief from the less-than-optimal affective state. Again, the metabolism of the drug is apt to be felt as something akin to the less-than-optimal affective state that was relieved initially, but a setting condition for further dosing.

The premise of an alternative theory of addictions is that addictive drugs are not a gift of pleasure; and if there is some initial pleasure (again, dose and duration-sensitive), it will almost inevitably be followed by something akin to a condition place aversion. The short summary: *Drug addictions are due to attempts to get relief from troubling circumstances.* Regularly taking doses of known addictive drugs does not have subtle effects (dose-sensitive). Continued use of addictive drugs often leads to disease and asocial behavior, hence setting conditions for an attempt to mute the induced effects of disease and asocial behaviors via an addictive drug, a vicious cycle. If the initial effects of addictive drugs induce some betterment of affect (again dose-sensitive), it is inevitable that there will be something like a condition place aversion will soon become apparent, an opponent process of the physiology sustaining homeostasis. If somewhat after an addictive drug is taken and the consumer is asked "would you like more of the drug you took?" the answer will likely be yes. Probably, the second or third dose of the drug is done to overcome an emerging adversity, i.e., more likely to be an attempt to postpone adversity rather than heightened pleasure and eventually only postponing harsh adversity.

If a citizen is experiencing troublesome affect, and the additive drug only induces a somewhat better affect that is a setting condition for doing another dose of the addictive drug and if done repeatedly, the citizen may have never experienced drug-induced pleasure, only some relief and a bad habit.

Conflict of Interest Statement

None

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None

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