International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Activities Accelerating Aging, Hence likely Inducing Alzheimer's Disease

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Abstract: ***Alcoholism and the widespread use of drugs with an anticholinergic burden are salient risk factors sustaining the development of Alzheimer's disease (Alz). Both risk factors are within our grasp to reduce the risk of developing Alz as well as an array of other diseases. Here is an extensive review of what sustains binge drinking of alcoholic beverages and binge eating and comments on how to treat the diseases. There is a brief review on the status of managing the use of drugs interfering with cholinergic systems of the nervous system. The conclusion: attending to reducing alcoholism and the widespread use of drugs with an anticholinergic burden, that such will reduce the acceleration of aging sufficiently to extend the life spans of many citizens.***

Keywords: Alcohol Use Disorder, Alzheimer's disease, Drugs' Anticholinergic burdens, Naltrexone

1. Introduction

In a recent article (Reid, 2021), I posited late-onset Alzheimer's disease (Alz) develops due to processes accelerating aging (not a novel concept). That global assertion is worthless unless one can specify, with some assurance, that there are activities and circumstances accelerating aging, and those activities and circumstances are within our grasp to modify for the better. The issue: Can lifestyles be managed in a way to not accelerate aging? No one wishes to have the last years of their life characterized by Alz and eventual dementia.

Epidemiologists have identified a number of correlates, named risk-factors, related to the development of Alz and dementia. Chronological aging is inevitable and *the ultimate* risk-factor, the issue is what other events accelerate aging.

This article does not focus on all circumstances accelerating aging; it does focus on two particularly pertinent risks: alcoholism and drugs with anticholinergic burdens (often a feature of harmful polypharmacy). A larger list of salient risks is given in Reid (2021).

Why do people drink too much ethanol when it is known to be detrimental?

In any recent year, over 44 million adults (USA data) suffer from alcoholism (alcohol use disorder, AUD) and over 93millionsuffer such during segments of a lifetime. The economic burden is estimated to be about $250 billion annually. AUD can aid and abet diseases, e. g., induces liver-disease, enhances the risk of breast cancer, and can interfere with adequate nutrition (e. g., inducing Wernicke-Korsakoff syndrome manifesting as chronic loss of memory). AUD enhances all kinds of accidents due to ethanol's deleterious effects on motor skills and coordination. Those suffering from AUD often engage in a social behavior while drunk and regret such when sober. AUD is a risk-factor associated with the development of Alz-related dementia. Given all of the misery, it seems prudent to try to answer the question of the above subtitle.

There seems to be little understanding of how the first alcoholic drink of a day often leads to binge drinking. Stated differently, what sustains multiple servings of ethanol when such leads to drunkenness, and in some cases to feeling sickly, vomiting, having black outs, and even inducing coma? Rationally, one should surely stop drinking alcoholic beverages before there are undesirable consequences. Generally, citizens usually limit their intake of alcoholic beverages. However, for some and for some during episodes of troublesome times, the day's first drink of ethanol often leads to more drinking and eventually to sufficient poisoning of ordinary physiology to be detrimental; often first manifest by cognitive inefficiency (an embedded additional risk). The issue: What sustains regular drinking of large amounts of alcoholic beverages?

When an alcoholic beverage is drunk, ethanol is quickly distributed throughout the body and brain. Ethanol is as an agonist at GABA receptors (gamma-aminobutyric acid receptors), i.e., the receptors whose actions inhibit the generation of a neuron's action potentials. GABA-induced inhibition modulates input from excitatory influences, hence gating the production of a neuron's action potentials, hence contributing to optimal functioning of a nervous system's circuit (or multiple circuits).

There are GABA receptors on a large proportion of the brain's neurons. Consequently, exceedingly large doses of ethanol can inhibit neural activity of so many neurons that consciousness is not sustained. When moderate doses (servings) are taken one after another, the consequences can manifest as slurred speech, staggered walking, reduced impulse control, verbosity, and eventually reduced activity.

If an individual is overly excited, feeling uncomfortable, dissatisfied, tense, anxious, bored, or lonely, a dose of ethanol may reduce the experience of being troubled via increases in neuronal inhibition, hence providing some satisfaction via distraction from worrisome situations (i.e., some relief or mild sedation). However, as detailed below the relief is only temporary, and when unpleasant affect is again experienced, another drink of an alcoholic beverage is likely to again provide some relief followed by, again, dissatisfaction. A reiteration of the cycle can lead to binge drinking. Regular use of alcoholic beverages and frequent binge drinking establishes a severe habit of drinking

alcoholic beverages (known as alcoholism). If regular ethanol-intake is suspended, mild to severe withdrawal symptoms are induced. Such is a setting condition for taking a dose of ethanol, hence sustaining the habit of drinking.

The above description of why ethanol is taken regularly is different than what has been posited. A usual explanation: ethanol induces some sense of pleasure via activation of dopamine neurons in the ventral tegmental area. I posit that ethanol temporarily reduces unpleasantry and such is likely to be what sustains a bout of drinking. Careful study (Dcuma & de Kloet, 2020) of the various actions taking place in the ventral tegmental area indicates stress dampens excitatory influences and slows the release of dopamine. If that is true, then the dopamine theory of addictions cannot be an all-inclusive theory of addictions. The alternative idea: ethanol induces a change in affect from unpleasant to a reduction of unpleasantness, hence can sustain a bout of drinking alcoholic beverages.

B. F. Skinner, a leader of the behaviorist model of psychology, stated behavioral acts (e. g., bar-presses and such) were measurable in a concrete way, but concepts such as affect could not be measured well, hence would be futile in building a comprehensive, useful technology (wasted effort that could be better directed toward studying measurable activity).

A way of measuring affect (preferences) was developed.
My laboratory developed a novel, easy way to assess affect induced by various drugs (Rossi & Reid, 1976). Basically, on any given day, male rats were given a choice of where they might be in a long alley. The two ends of the alley were made distinctive, by such as the floor's texture and the decoration of the walls (e. g., black & white strips on the walls running vertically on one end of the alley and the strips running horizontally in the other end). Between the two ends of the alley was a middle space (with grey walls) that could be separated from the two ends by guillotine doors serving as a starting place.

A rat was placed in middle space in the alley, then the guillotine doors opened allowing a rat to explore the alley for some minutes, say 30 min. The apparatus had a means of measuring the times spent in either side of the alley. Rats tend to explore the alley when given the opportunity to do so, hence entering each end of the alley upon initial and subsequent exposures to the alley. Post initial exploration, a rat will reduce exploration and spend time in one end of the alley. Initially, we wished for no preference for one side of the alley. When a group of rats were tested without any injections, the average time on one side of the alley was roughly the same as on the other side.

We gave a small dose of morphine just before a rat was trapped in one part of the alley. On another occasion, a rat previously given morphine was given a placebo before being confined to the other end. We did this for a few times (number of times experiencing the two procedures, i.e., drug-dose vs. placebo, did not change the outcome much if any; given placebos first or morphine first also seemed irrelevant).

The question: would the subjects prefer or not prefer the side of the alley in which they experienced morphine's effects (or any drug's effects)? The results: small to medium sized doses of morphine (all smaller than those inducing analgesia) induced the subjects to spend more time on the side where morphine's effects were experienced. The publication of the procedure did not elicit much attention and what commentary was evoked indicated that the procedure was too simple and easy to use to be useful (something I have never understood) and needed considerably more research before being adopted as a valid test of affect.

Ron Mucha stopped by a poster at a Society of Neuroscience meeting describing the procedure and its early results. He indicated he was looking for a way to measure affect in lab-animals and thought the procedure might be useful. Ron, sometime afterwards, became first author of two extensive articles whose results independently verified the utility of the procedure (Mucha+3 coathors, 1982; Mucha & Iversen, 1984).

A meeting was held among the first users of the procedure and a name for it was adopted: "testing for a putative *Conditioned Place Preference (CPP)."* When a procedure, often a dose of a drug, induced harshness, the name became *Conditioned Place Aversion (CPA)*, i.e., rats preferred a place of no or reduced harshness (obviously). After initial findings, the procedure began to be widely adopted. Using the search-item *Conditioned Place Preference* on PubMed yields over 5, 225 articles from the initial experiment to late 2021 (i.e., some 54 years after the first demonstration of a CPP and seemingly increasing yearly). When the search-term was Conditioned Place Aversion, PubMed indexed 1, 634 experiments using the procedure.

There were tests using the CPP-procedure of various drugs known for developing addictions among people. Seemly, all commonly taken addictive drugs at doses comparable to what people might take, induced a CPP (McKendrick & Graziane, 2020). However, when we gave injections of ethanol, ethanol did not establish a reliable CPP. We were perplexed knowing that ethanol was an addictive drug and people often experienced a positive affective experience when drinking alcoholic beverages (there were a considerable number of direct tests among me and my colleagues to verify that).

To explore why ethanol did not establish a CPP using our standard procedures, we limited the time in a side of the alley to merely 5 minutes shortly after receiving an injection of ethanol. We also put injected rats into a side of the apparatus at various times after the injections, e. g., 8 or 14 minutes afterwards. The results were clear, a CPP was established during the first effects of ethanol but surprisingly a CPA was established when the effects of a dose of ethanol was waning (Reid+3 coauthors, 1985). This pattern of changing affective states seems to be characteristic of many addictive drugs, i.e., their initial effects produce positive effect, but as the dose is being metabolized to nearly no circulating drug, unpleasing affect is induced, i.e., a CPA (McKendrick & Graziane, 2020). These results are germane to theories of addictions, particularly bouts of intakes of

known addictive drugs. A drug inducing an initial change from unpleasantness to one of less unpleasantness is sufficient to be a setting condition for taking another dose of a drug, including ethanol. This pattern of affective states with known addictive agents, i.e., a dose of the drug in question induces an initial sense of satisfaction but a sense of dissatisfaction emerges as the addictive drug's dose is nearly completely metabolized. The dissatisfaction can be muted by another dose of the addictive agent. This pattern of affective states can explain why drinking alcoholic beverages sustains intake of multiple doses of an alcoholic beverage in a single setting (binge drinking),

There are drugs which are, seemingly, *stimulating* and *initially* pleasurable, e. g., doses of cocaine. With respect to ethanol, I posit something different, i.e., relief from troubling circumstances, via ethanol's inhibitory and sedative effects, is reinforcing the habit of drinking (particularly with drinking multiple servings of an alcoholic beverage in a session of drinking). Relief from troubling circumstances can combine with some available circumstances (e. g., a party atmosphere, a celebration, or watching a sporting event in which your favorite team is seemingly winning) can *temporarily* induce something akin to brief happiness and even brief jubilation.

The effects of GABA agonists and effects of small doses of an exogenous opioid agonist both induce, initially, a more pleasant affective state then experienced previously. The induced better affect fades as the amounts of circulating opioids are reduced. Ethanol, barbiturates, and benzodiazepines are all agonists at GABA receptors, hence have similar consequences. That is, neural inhibition provides some initial relief from an unpleasant state; however, with the waning effects of the drug there can be a return of the initiating unpleasantness which might be enhanced by minor to intense withdrawal effects. This pattern of changes in affect is a setting condition sustaining a bout of drinking alcoholic beverages, i.e., binge drinking. Habitual binge drinking leads to alcoholism. Alcoholism is manifest by variety of diseases. Among the diseases is an erosion of cognitive skill and, relatedly, little control of impulsiveness. The same processes are associated with barbiturates and benzodiazepines but on a daily schedule since the initial doses are generally large and long-lasting.

An experiment (Childs & de Wet, 2016) with humans measuring a potential CPP following administered drinks of alcoholic beverages found that humans indeed preferred the place where they experienced the effects of ethanol. When asked about their preference they expressed the idea that some sedation (being calmer) was the desired effect from drinking an alcoholic beverage. Those results align with the idea that ethanol's inhibition of a troubling circumstance or some troublesome circumstances (whose solution, or solutions, are probably not readily available) is causative in sustaining binge drinking.

Given that morphine and other opioid agonists induce positive affect (i.e., establish CPPs) upon initial circulation and concurrently induce some relief (as indexed by general relaxation, pain-reduction and including the "pain" of social rejection or loneliness experienced by people) seem to be causal consequences with respect to opioid agonists' addiction liability.

The eventual withdrawal effects associated with intake of opioid agonists are also setting conditions motivating taking another dose of an opioid agonist. This pattern of initial satisfaction due to the initial effects of addictive agents (as indexed by a CPP) plus the nearly *inevitable negativity* associated with the termination of dosing (as indexed by a CPA) is a pattern explaining, at least, some addictions. As noted by McKendrick & Graziane (2020), the addictive process involves an opponent process germane to sustaining homeostasis.

The development of a way of measuring affect or preferences using rats (i.e., CPP procedures) and experiments modelling similar CPP procedures among people with similar outcomes allows new perspectives (McKendrick & Graziane, 2020). McKendrick & Graziane make the case that a CPP is an index of complex processes involving such as memory and perceived benefits of a drug-induced change in physiology. It is that complex of events yielding a perception of enhanced satisfaction, compared to what was perceived previously, that drives future behavior. A CPP or a CPA signaling preferred or not preferred situations guide's behavior toward what was preferred and not providing motivation for what is not preferred. *Note*, what is not preferred is not necessarily punishing or harsh but just not the preferred choice derived from past experiences.

Preferences are a more sensitive index than the bipolar characterizations of either positive or negative reinforcement. The term *negative reinforcement* seems to be contradictory in itself and needs explaining (relief is a positive affective experience). The term negative reinforce often seems to indicate something like an electric shock which is not a reinforcer (rather a punisher) but is a setting condition for relief. The common language term relief is just a better characterization of an event providing some measure of relief, and a setting condition for learning to avoid unpleasantness. And the common language terms reward and rewarding, satisfying, and pleasant seem more descriptive than positive reinforcement (which dictates an increment in learning).

The extensive work carried forward from the original CPP experiment (Rossi & Reid, 1976) and its extensions verifying the results of the initial CPP-experiments (e. g., Reid+3 coauthors, 1989); and the research by Thomas M. Tzschentke and colleagues; and the research & the comprehensive reviews by Nicholas Graziane and colleagues; and the research of Christopher Cunningham and colleagues; and the research by Michael Bardo and colleagues, and the research of Harriet de Wit and colleagues; as well as many others who have authored the more than 6, 800 articles studying or using the CPP and CPA procedures provide a sound scientific base for translating the findings to practical applications. For a very simple example, when practicing cognitive behavioral therapy, the clinician can feel comfortable asking about what is preferred and not preferred and then address issues of

whether what is stated to be a preferred choice may not be a good choice and then suggest ways to make better choices.

Research using the procedures and outcomes of CPP and CPA challenge the *dopamine theory of addictions* by indicating that some addictions are due to eliciting mild sedation (see Childs & de Wit, 2016) rather than enhancing stimulation as induced by some drugs such as cocaine or amphetamine which block reuptake of dopamine at the dopaminergicsynapses (hence stimulating). Drinking alcoholic beverages can temporarily provide some relief from troubling circumstances but, yes, only temporarily. Also, regularly taking sedative or hypnotic drugs, including ethanol (mostly GABA agonists), is generally not healthy. To verify the ultimate toxicity of hypnotics such as benzodiazepines and Z-drugs, see Krispe (2016) which provides data confirming *use of hypnotics increases all causes of mortality* even those induced by infections and cancers. Yet, the choice is often made to drink an alcoholic beverage or take a prescribed hypnotic (i.e., trusting the prescriber to act in a patient's best interest) or select an OTC hypnotic (sleeping pills) to provide a purported calmer state which is a prerequisite for, purported, better sleep.

The choice to buy alcoholic beverages or the choice to prescribe for a patient a hypnotic or a citizen to buy OTC hypnotic drugs are aided and abetted via sophisticated advertisements and public relations by those selling the drugs even though the sellers fully know the extensive harm likely to emerge (greed beyond reason and morality). Along those same lines is the harm that can happen when opioids are prescribed for pain-relief while the patient may also be drinking alcoholic beverages regularly or taking other sedatives-hypnotics. Such is a toxic concoction. The circumstances are made worse by the fact that modern cognitive behavioral therapies for such as chronic insomnia and some forms of anxiety have been proven effective and are available and now even available via the internet. Cognitive behavioral therapies will not always correct presented problems (of course), but overall, they are vastly safer than using ethanol and other drugs to abate troubling circumstances. Multiple drugs induce mixtures of side-effects, and such can manifest as a disease which may lead to prescription of another drug. Further, cognitive behavioral therapies can provide the patient with useful skills.

An endogenous opioid is involved in controlling amount of intake of ingest a by events in the oral end of the gut.
Rockwood, Siviy & Reid (1981) fixed rats with gastric fistulas. When the fistulas were open, fluids drained from the middle of the stomach to outside of the body; when closed no fluid leaked from stomach to outside of the body. Naloxone specifically blocks the effects of endogenous and exogenous opioids. Rats with open fistulas drank much more water than when the fistulas were closed. Naloxone reduced intakes of water when rats were drinking with both open and closed fistulas. Rockwood & Reid (1982) demonstrated that naloxone reduced drinking of sweeten water among rats fixed with open gastric fistulas. Under the influence of placebo-injections, and when rats drank with their fistulas open (seemingly drinking as much as they could during a 1-hour opportunity); they drank much more of the sweet fluid than when the fistulas were closed. Under the influence of naloxone and when the fistulas were open, there was a marked reduction in intakes of the sweeten water. The observations of the experiment by Rockwood & Reid (1982) showing that naloxone had a dramatic effect of reducing intakes of sugar-water with open gastric fistulas were verified and extended by Kirkham & Cooper (1988a & 1988b).

The experiments with gastric fistulas and the effect of naloxone complements the observations that naloxone drastically reduces intake of sweetened alcoholic beverages once the appetite for alcoholic beverages has been established and that small doses of morphine increases intakes of alcoholic beverages (sweetened or not).

When rats have a daily opportunity to drink alcoholic beverages, they gradually increase their intakes of ethanol sufficiently to reduce righting reflexes. Post the development of regular intakes of the alcoholic beverage, doses of naloxone reduce intakes. Small doses of morphine and other opioid agonists increase intakes of alcoholic beverages. Also, when rats were fixed with pellets placed under their skins delivering a constant supply of very small doses of morphine for 20 days, the constant supply of small doses of morphine induced very large intakes of sweetened alcoholic beverages that induced very drunken rats (Hubbell & Reid, 1990).

An interesting observation: when rats were presented with a sweetened alcoholic beverage for the first time and daily for 20 days and before each of those presentations was an injection of naloxone; under those conditions, rats never drank the alcoholic beverage (merely sampling the beverage occasionally) but drank only the water available at the same time (Hubbell & Reid, 1990; also see Cunningham et al., 1995).

The outcome of the experiments summarized above reinforce the idea there is an opioidergic system controlling the duration of a bout of ingestion normally sensitive to an accumulation of circulating gut hormones that tends to end a bout of eating and drinking (Livovsky, Pribict & Azpiroz, 2020). When drinking with open gastric fistula, the excess intake of sugar-water was without feedback from intestines and from processes of the liver and kidneys. Therefore, without feedback from the lower endof the gut, satiation is surely delayed, further, given naloxone's influence in controlling intake; it seems that there is an opioidergic physiology involved in sustaining ingestion

The description (Douma & deKloet, 2020) of the circuitry of the ventral tegmental area with circuits involving dopamine and endogenous opioids provides information germane to the physiology of sustaining sufficient nutrients to sustain homeostasis. When hunger mounts (probably a feature of signals from a nearly empty stomach and small intestines) there is likely a dopamine surge motivating foraging for food, water, or both. The surge manifests as a potential for reward (hence, positive affect) and eventually of having the reward of eating or drinking or both. There is strong positive affect when eating or drinking begins. Once consumption of nutrients begins, endogenous opioidergic activity sustains consumption until the hormones and a muscular feedback

from the gut suppresses the opioidergic influence. When foraging for food or water fails, there is frustration which may again be a cause for taking a calming drug such as ethanol. This broad description of the physiology of ingestion is compatible with *a feature* of modern dopamine theory of reward (i.e., both anticipation of reward and the initial experience of reward are motivating and experienced as positive affect).

When rats have had the chance to choose an alcoholic beverage or water for a number of days (say 10 or so), they do develop the habit of drinking alcoholic beverages sufficiently to show signs of drunkenness (slowed righting reflexes). The data indicates that when opioid antagonists are injected among rats that have had days of access to alcoholic beverages, the naloxone-effect is not a total avoidance of ingestion. There is some intake at first, but greatly reduced intake subsequently, i.e., stopping the functionality of the endogenous opioidergic effects in sustaining ingestion.

The theorizing of Berridge & Robinson (2016) indicating that want and liking are different functionalities is compatible with descriptions of the functionalities of ingestion. Hunger is analogous to "want," motivating foraging to find nutrients and probably a function of dopamine-neurons in the ventral tegmental area. "Liking" is analogous to palatability and is likely a function of an endogenous opioidergic sustaining intakes with gradually accumulating feedback from the gut limiting the influence of the endogenous opioid. Hunger (want) and palatability (liking) seemingly are manifestations of somewhat different neural circuits having a role in ingestion.

Regularly ingesting long durations of bouts of food or alcoholic beverages are indicative of eventually developing obesity and/or alcoholism and those durations seem to be a functionality of a circuit involving endogenous opioids. And, both obesity and alcoholism are risk-factors accelerating aging and hence risk-factors for developing Alzheimer's disease.

It is almost too simple, straightforward, and known by common knowledge to verify, via experiments, that one (a human or a rat or a mouse) prefers being in a place in which a sense of betterment was achieved in contrast to a similar place that did not induce satisfaction. What is more novel is the perspective that drugs (including ethanol) initially induce a perception of better circumstances (better feelings, better affect) than what was prevailing previously also induces unsatisfactory affect just after the drug is being nearly or fully metabolized. Given this pattern of shifting affect, it is apt to be useful to warn those who seek some satisfaction from initial effects of addicting drugs to know that shortly there will likely be troubling affective experiences. Taking a dose of ethanol to overcome withdrawal discomfort from a bout of drinking ethanol will merely provide only a small measure of relief and then likely a return to unpleasantness.

Naltrexone can be helpful in curbing alcoholism

Altshuler, Phillips & Feinhandler (1980) demonstrated that naltrexone, an opioid antagonist, reduced the self-administration of ethanol by monkeys with the habit to self-inject ethanol (via an operant). Such effects were and are genuinely interesting but not truly revealing of an effect germane to addictions. Naltrexone could have made the monkeys sickly and that was the reason the monkeys reduced intakes of ethanol under the influence of naltrexone.

Reid & Hunter (1984) arranged a convenient way to assess rats' avidity for an alcoholic beverage. Rats, individually housed in cages, were deprived of water for most of a 24-hour-day but were allowed water for only, say, 1.5 hours a day (the time limited to consume fluids varied slightly among various experiments; food always available). Obviously, the subjects satisfied their needs for water during the limited time to drink and, not so obviously, gained weight at the same rate as those allowed water continuously. We then supplied an alcoholic beverage during the same time as water was available, giving the male, young-adult rats the opportunity to choose to drink either water, the alcoholic beverage, or both. The alcoholic beverage was often 6% pure ethanol plus water sweeten by sucrose. When rats were first presented with both water and the alcoholic beverage, they continued to drink water and they also sampled the alcoholic beverage taking little of the beverage. However, with a continuance of presenting both water and the beverage, intakes of the beverage increased to an intake of about 1 to 2 grams of ethanol per kilogram of bodyweight, an amount producing a slowing of the righting reflex. When the intake of both water and the alcoholic beverage were taken daily there was no discernable change in daily gains of bodyweight characteristic of housing rats having food and water always available. During the limited times rats had fluids available, typically, they spent the early part of the time drinking water and the beverage, i.e., drinking from the two sources of fluids. Once apparently sated, they ate some food, spent some time grooming and then seemed to relax.

Regularly drinking an alcoholic beverage presents a procedure that can be used to test whether a drug might modify ethanol intake (Reid & Hunter, 1984). We found that small doses of morphine (all smaller than a typical anesthetic dose) that could establish a CPP enhanced the intake of alcoholic beverages. Small doses of morphine increased alcoholic-beverage-intake nearly doubling the intake when a placebo was given (the injection of placebo did not modify usual intakes). When the opioid antagonist naloxone was administered, drinking the alcoholic beverage was dramatically reduced. There was some reduction in water-intake, but total fluid intake was not much different than when no opioid was given, except naloxone dosing led to small reductions in total fluid-intake.

After the tests with an opioid agonist and antagonist, we (Beamn+3coauthors, 1984) tested whether benzodiazepines would modify intake of a palatable alcoholic beverage. The agonist, chlordiazepoxide, and the antagonist, Ro 15-1788, were given at doses used in other experiments, to see if they modified intake of an alcoholic beverage. The results indicated that neither the initial effects of a benzodiazepine agonist nor antagonist modified regular intake of a palatable alcoholic beverage indicating some specificity for opioidergic effects.

There were additional studies following the findings of Reid & Hunter (1984). There was also a previous study (Miller, Reid & Porter, 1967; subsequently verified by Bozarth & Reid, 1977) whose results indicated that morphine enhanced the pressing for electrical stimulation (intracranial stimulation or ICS) of the medial forebrain bundle. The medial forebrain bundle is a tract stemming from the ventral tegmental area to the accumbens nucleus and frontal cortex. There are dopaminergic neurons within the ventral tegmental area whose axons are within the medial forebrainbundle. This anatomy plus studies verifying that dopamine was released in the accumbens n. and forebrain (Willuhn+ 3 coauthors, 2010) provides support for the theory that some addictive drugs induce a surge of dopamine manifest as pleasure (an affective experience) and verified by the fact that ICS of the medial forebrain bundle induces persistent bar pressing for brief ICS for each bar press. The enhancing effect of the two experiments, 1967 & 1977, yielded different results from James Olds' original tests of morphine's effects on pressing for ICS. The Olds' studies used large doses of morphine producing lethargy; however, with smaller doses or postponing the test after large doses of morphine (hence smaller doses circulating), morphine clearly enhances pressing for lateral hypothalamic ICS (Bozarth & Reid, 1977). Small doses of exogenous opioids are more apt to mimic endogenous opioid's effects.

Naltrexone, an opioid antagonist, blocks the post-shock increase of ethanol consumption among rats (Volpicelli, Davis & Olgin, 1986). My lab preformed further assessments of the effects of small doses of morphine on rats' intake of palatable alcoholic beverages. Those assessments confirmed that small doses of morphine enhanced intakes of alcoholic beverages and also showed that methadone and fentanyl, both opioid agonists, at small doses, enhanced intakes of alcoholic beverages (Hunter+3 coauthors; Mudar+4 coauthors, 1986; Czirr+4 coauthors, 1987a). Small doses of morphine and fentanyl enhanced *female rats*' intakes of an alcoholic beverage (Czirr+4 coauthors, 1987b). We administered a small dose of morphine to rats who were drinking a 6% solution of pure ethanol and 94% water (no flavoring); morphine enhanced intakes (Wild, Marglin & Reid, 1988). In comparison to other experiments, however, it does seem that sweetened alcoholic beverages are consumed more under the influence of a small dose of morphine than when only ethanol and water are provided (yes, palatability is a factor in ingestion).

Studies done during the 1980s plus the experiences of using the opioid antagonists as treatments among people addicted to opioid agonists led to the conclusion that an opioid antagonist, e. g., naltrexone, would be effective in treating alcoholism. Given that conclusion, a meeting with the staff of DuPont, the holder of the patent for naltrexone, was arranged with the purpose of me presenting my findings to DuPont with the aspiration of having them develop naltrexone as a medicine for treating alcoholism. Subsequently, Charles O'Brien also presented data of his team, including Joseph Volpicelli's research showing naltrexone blocked the post-shock increase of ethanol-consumption among rats (Volpicelli, Davis & Olgin, 1986). O'Brien also mentioned his experiences using naltrexone in the treatment of opioid addictions to the staff of DuPont. Both presentations were seemingly well-received, however, DuPont did not provide the means to do a clinical trial of naltrexone to curb drinking alcoholic beverages.

Charles O'Brien is the hero in the saga of developing a new medicine for the treatment of alcoholism in 50 years. He cobbled together the funds to arrange a clinical trial using naltrexone, as an adjunct to psychological approaches, to test the idea that using naltrexone would improve the treatment of alcoholism (Volpicelli, O'Brien, Alterman & Hayashida, 1990). The trial indicated that the prescription of naltrexone was of benefit in the treatment of alcoholism. The favorable result, plus other confirmations (e. g., O' Malley+5 coauthors, 1992), led DuPont to support further research.

Nalmefene, another opioid antagonist, dose-relatedly decreased intakes of an alcoholic beverage among rats and was effective across days of injections **(**Hubbell+5 coauthors**,** 1991**)**.

Given the extensive research involving opioidergic modulation of intake of alcoholic beverages, the FDA (USA) approved oral naltrexone to treat alcohol dependence in 1994 (brand names: ReVia; Depade). During 2006, the FDA (USA) approved Vivitrol (brand name), an extended-release injectable suspension of naltrexone, for treatment of alcoholism and opioid addictions. The FDA's approvals were 50 plus years after other drugs were approved to be used in controlling AUD and, in practice, the older drugs were not helpful in reducing the habit of drinking alcoholic beverages.

Reviews (Reid, 1990 and again 1996) stated this conclusion: generalizations, from a large number of separate experiments, support the conclusion that alcoholism is a special case of an ingestive disorder involving opioidergic systems. It appears that a function of an opioidergic circuity is to sustain ingestion until gut-hormones signal satiation (Livovsky, Pribict & Azpiroz, 2020). Also, exogenous doses of opioid agonists seem to override the influence of gut hormones inducing satiation.

The effects of a dose of an opioid agonist can induce, initially, positive affect via some relief from pain, plus the potential mild relief from worrisome situations similar to the effects induced by ethanol, hence are setting conditions for taking opioids and ethanol concurrently. If opioid agonists (often morphine) are given for pain-relief, due to such as surgery, kidney stones or broken bones are combined with intake of alcoholic beverages such can lead to intense, difficult to control, addictions often leading to a social activity.

Using opioid agonists to control pain due to disease and injury should be carefully monitored (e. g., limiting dosing to the extent of relief from pain) (again not a novel idea, but one not followed sufficiently). Further, any intake of alcoholic beverages while under the influence of an opioid agonist should be strenuously discouraged to avoid the combined effects of the two kinds of drugs which can induce serious consequences (i.e., intense addictions inducing diseases as well as a social activities) often outlasting the initial medicinal effects of opioid agonists.

Given the results with opioid-involvement on intakes of ethanol, the conclusion is that there is an opioid circuit involving endogenous opioids which ordinarily sustains intakes of ingest a to optimal satiation, hence an adaptive functionality. That circuit can be enhanced with exogenous opioid agonists, hence extending a bout of ethanol intake and other ingesta. That circuit can be blocked by opioid antagonists.

2. Summary

A dose of ethanol can produce neuronal inhibition dampening troubling affect, hence is a positive affective event. Sweetened alcoholic beverages are taken somewhat more than unsweetened beverages. i.e., combining a sweetened beverage with the positive affect that can ensue from neural inhibition is more likely to enhance propensity to drink more of an alcoholic beverage. Such should not be surprising since bar-tenders have for centuries made cocktails of alcoholic beverages to be sweetened, cooled, and made to look nice in the service of selling more ethanol-containing beverages. The recent surge in sales of flavored vodkas is merely an extension of masking the harshness of the taste of ethanol in the service of selling more ethanol. The alcohol-beverage-makers have concentrated on making their beers and wines more palatable because such can induce greater sales of their products, and such is also useful in recruiting young and female patrons to enjoy the purported satisfying affect induced by servings of ethanol. Also, the alcohol beverage industries are very skilled at marketing their products. The problem, of course, is that alcoholic beverages' active ingredient, ethanol, in larger doses is both habit-forming and toxic (germane details of the preceding paragraph are available in a book by Larry and Meta Reid, titled *Big Booze is Slowly, Softly Killing Women*).

There are means for preventing a portion of the harm induced by the intake of ethanol

There is a large compendium put together by Frank J. Chaloupka, Michael Grossman, and Henry Saffer (2002) addressing the utility of *reducing the harm of large intakes of alcoholic beverages via increasing the taxes on alcoholic beverages*. Their comprehensive analysis indicates that the taxes on alcoholic beverages have not increased markedly for years, and in effect, the actual cost of drinking is cheapened, as ordinary inflation and buying power has increased. After tabulation of the available information, their conclusion: a steep increase in taxes on alcoholic beverages (i.e., a large tax germane to the amount of ethanol in an alcoholic beverage) would indeed reduce the harm incurred by many as they bought and drank alcoholic beverages due mainly a limit on available cash to buy a lot of alcoholic beverages.

Among the reasons given that it was not a benefit to increase the taxes on alcoholic beverages was because it penalized those who drank only conservatively as well as those who drank excessively. However, please note that drinking conservatively is a step toward increasing drinking and such can be a setting condition for drinking excessively (i.e., yes, of course, ethanol can be addictive and often is). Ethanol is a weak poison when taken conservatively; however, when the doses of ethanol are large and taken often, they induce multiple diseases and asocial behaviors whose cumulative effects are paid for via care for the sick, and for the costs of accidents such as fatal car crashes, falls, and family-discord all made riskier by reduced coordination, alertness, and less overall cognitive efficiency.

It would be optimal if every prescriber of an opioid agonist had an at least a 15-minute counseling session with every patient prescribed an opioid agonist to counsel the patient on the advantages and dangers of using opioid agonists. Such consulting would surely caution patients on the use of alcoholic beverages while taking opioid agonists. The counseling might also instruct patients on how to cognitively reduce pain so that they can be active participants in their control of pain (e. g., Shpaner+ 6 coauthors, 2014). Long consultations, by usual prescribers, with the goal of managing pain while at the same time not inducing addictions are currently unlikely to happen. However, prescribers could provide a card to a patient prescribed an opioid agonist providing an address to an electronic version of a good counseling session concerning the dangers of misusing opioid agonists. Depending on the worth of the counseling (i.e., is it based in good science) and done by those experienced in developing excellent internet videos, such can be utilitarian.

Among people who regularly drink large numbers of servings of alcoholic beverages are prescribed naltrexone, there is marked reduction in numbers of servings taken daily (e. g., O'Malley+ 5 coauthors, 1992). Such clearly reduces the toxic load of daily intakes of ethanol. We gave rats taking large amounts of alcoholic beverage daily doses of naltrexone using the method of Reid & Hunter (1984). Rats were presented with an alcoholic beverage daily and their drinking was large enough to sufficiently slow righting reflexes. Then daily doses of naltrexone dramatically reduced intakes of an available alcoholic beverage. However, when we stopped the dosing, intake of alcoholic beverage resumed at the same level as before (Reid, Gardell & Hubbel, 1996). The effect was rather dramatic: when given naltrexone there was an extensive reduction in intake of alcoholic beverage; when no naltrexone was given, consumption of the alcoholic beverage returned to the amounts taken before dosing with naltrexone. We began a series of multiple 3 days on naltrexone and then three days of no naltrexone. We got the same results across rounds of dosing or no dosing. These data suggest that merely dosing with naltrexone will not by itself to be a cure for alcoholism.

With the advent of injections providing up to 28 days of continuous naltrexone being circulated, the overall therapeutic effect of naltrexone-dosing is enhanced, compared to the prescription of daily oral dosing of naltrexone. A reduction of near daily drunkenness allows for behavioral modifications that are protective. In brief, *injections of naltrexone are merely setting conditions for behavioral modifications that help and abate a more pleasant lifestyle.*

Taking drugs interfering with cholinergic systems of the nervous system are risk-factors for developing Alz, and other diseases.

The progression to dementia (loss of memory, loss of other skills, and becoming helpless) is a slowly developing disease, a manifestation of an insidious loss of brain tissue, particularly in the hippocampus, an anatomy critical to memory. Those studying the development of dementia have labelled stages on the progression of the disease: some normal loss of cognitive skills happening with nearly all older citizens, followed by what is labelled as mild cognitive impairment (MCI) (which is really not mild and a rather obvious loss of considerable cognitive and physical skills), signs of Alz, followed by dementia.

Epidemiologists have identified an array of correlations associated with MCI and later stages of disease. Each of those correlations can be a contributor of an acceleration of aging eventually ending with dementia and shortened life spans. Here we focus on a situation that clearly accelerates aging and is well within our grasp of modifying for the better, i.e., reducing the erosion of neural circuits involving the cholinergic components of the nervous system.

Not all persons have dementia prior to death and centenarians often retain many of their skills of younger years.

Acetylcholine (Ach) is the neurotransmitter of Cholinergic systems. There are 7 different kinds of receptors for ACh. Two of the 7, are classed as nicotinic receptors, and 5 are classed as muscarinic receptors (named after agonists that selectively activate a kind of receptor for ACh). Unfortunately, few if any of the current drugs with Abur are selective with respect to functions for a given kind of receptor. Consequently, drugs with a severe Abur are apt to have widespread effects on cholinergic systems.

ACh is involved with many functionalities such as sweating, muscle movement, the functions of the organs of the trunk, and circuits of the brain (manifest as insidious loss of cognitive and physical skills). Given the wide-spread involvement of ACh in many functions, it would seem prudent to not take drugs interfering with efficiency of cholinergic systems.

Nevertheless, there is a wide array of drugs interfering with functions of cholinergic components of the nervous system. When a drug acts at a receptor of a circuit within the nervous system involving a cholinergic component and that drug interferes with neural transmission, it is a drug with an anticholinergic burden (Abur) likely to interfere with homeostasis. There are drugs with different degrees of Abur. Nearly all drugs with an Abur act at muscarinic receptors.

Given that ACh is critical to many different features of the physiology and given there are commonly used drugs interfering with the actions of ACh, it just makes good sense to *not* use drugs interfering with circuits of the nervous system (and particularly if there are other drugs or procedures equally therapeutic and without interfering with cholinergic functionalities). Scientists have begun to correct the situation of the toxicity of drugs interfering with the normal functions of cholinergic systems by measuring the degree of interference a drug might have on systems involving cholinergic activity.

Drugs differ in their degree of interference with cholinergic systems, from no interference, to mild (labelled 1) to moderate (2), and to severe interferences (3). Not all assessments of the degree of interference of a drug on cholinergic systems yield the same Abur score. However, if one takes the average of multiple assessments there is a good chance that such reflects a degree of interference.

The consensus: the Abur of each taken drug can accumulate when taken during roughly the same times and the Abur scores can be added to yield an overall Abur score, e. g., 3 drugs with an Abur score of 1 is the equivalent to taking one drug with a Abur score of 3. Such does not consider that the scores are not on an equal interval scale, but adequate nevertheless for making judgments germane to managing the harm that can come from taking drugs with an Abur.

There is some controversy about what level of Abur is damaging to normal physiology. Some claim that an Abur score of 3 is undesirable while others claim that 6 is undesirable and more than 6 might be disastrous. Probably, the threat of disease or diseases associated with reduced efficiency of the nervous system is related to the specific disease or diseases being treated with a drug or drugs with an Abur. Given some lack of precision in the Abur scoring, nevertheless, such does not take away from the fact that a drug or drugs with an Aburis a setting condition for Alz and other causes of ill health (Coupland, CAC+5 coauthors, 2019; Salahudeen, M. S., Duffull S. B., Nishtala P. S., 2015; Ruxton K., Woodman R. J., Mangoni, A. A., 2015; Dyer A. H. + 4 coauthors 2020).

Drugs with a mild to severe Abur are being prescribed as treatments for a variety of diseases. Among them are treatments for depression, psychosis, cardiovascular diseases, asthma, overactive bladder, pulmonary diseases, and more. The drugs with an Abur being used to treat symptoms of diseases often result in cognitive losses.

Drugs with an Abur can contribute to polypharmacy. The accumulative side-effects from multiple drugs, with or without an Abur, can result in so much disruption of ordinary physiology to be considered a disease and often those side-effects are a cause to prescribe another drug for a supposed new disease. A consensus: more than 5 or 6 drugs taken concurrently is considered harmful.

There are as many as 25 marketable, approved by the FDA (USA), generic drugs with a severe Abur. There are as many as 140 brands associated with those generics (the number of brands seems to grow steadily). The proliferation of brands makes it difficult for patients and prescribers to discern the extent of a patient's Abur.

The ability to know the extent of Abur of medicines is obviously useful information and currently is not readily available. There are attempts to provide ways to determine if a given drug adds to a dangerous level of Abur, however, there needs to be a more comprehensive, easy way to assess the interference of drugs limiting cholinergic circuitry of the nervous system (Bell+ 5 coauthors, 2021). The world needs the community of scientists who have assessed the Abur of drugs to cooperate with some computer experts to provide

an easy way to assess extent of an Abur currently existing for a patient plus how a prospective prescription will contribute to the extant Abur. It will take money and time to develop and sustain a comprehensive, easy to use, digital way of computing the extent of Abur. There are efforts to alert practitioners on the problems with an accumulating Abur and other unwholesome features of drugs, such as the Beers Report. However, the tabulations are somewhat cumbersome. Further, there is little regulation of the cumulative effects of multiple drug use.

Circumstances reducing the viability of the heart and the circumstances of developing advanced diabetes are obviously major risk factors for all causes of mortality, hence for the development of Alz and eventual dementia. There is ample attention in the broad literature on sustaining the health of the heart and slowing the progression of diabetes. In so doing, that attention and science devoted to extending longevity can be countered by extensive use of alcoholic beverages, excessive prescriptions, or the inadequate management of drugs inducing anticholinergic effects. Further, such actions are well within prosperous nations ability to manage. The mentioned risks are interactive and attending or not attending to one of them is apt to have effects on the others. Attending to risks often involves behavioral modifications on the part of health-care professionals and their patients; hence specialists in behavioral modification should be involved in correcting risky behaviors. Also, specialists in public health have an important role to play (e. g., encouraging higher taxes on alcoholic beverages).

3. Summary

If citizens would (a) *stop* poisoning their physiology by ingesting large amounts alcoholic beverages, (b) stop taking multiple drugs with mild to severe anticholinergic burdens, (c) stop using benzodiazepines and similar drugs (GABA agonists similar to ethanol) for an array of illnesses such as anxiety & chronic insomnia (another salient risk of developing Alz) and start regularly treating those diagnoses via cognitive behavioral approaches, and (d) stop clogging arteries via regularly ingesting large amounts of sucrose and animal fats, it is highly likely such would avoid a goodly portions of onsets of Alz and be supportive of living a long time without dementia.

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