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The Great Nicotine Myth

Summary

Nicotine has a strong taboo surrounding it, especially within the medical profession - this is partly due to its conflation with smoking, but there is also a commercial agenda here that is continually reinforced by propaganda.

There are four nicotine myths perpetuated in modern culture that have no basis in fact. These are:

1. *The myth of nicotine's dangerous and alien nature*
2. *The myth of nicotine's toxicity*
3. *The myth of nicotine's potential for addiction*
4. *The myth of nicotine's potential for harm*

Not only is there no evidence to support any of these myths, in fact virtually all the evidence (not just some of it) is opposite to these assumptions. The article examines the propaganda, the commercial and institutional reasons for the propaganda, the latest collations and clarifications of evidence, and how the leading experts have demolished these myths.

Introduction - how propaganda maintains the taboo

Nicotine is one of the last great taboo subjects in the western world, and as a result has some powerful myths surrounding it. When we look closer, we find that there are strong commercial, institutional and ideological motives acting to promote these myths; and as a result the science is ignored.

Facts normally filter through gradually, so a continuous propaganda assault has been used in order to reverse this trend. If the desired public climate of opinion may swing the wrong way toward a correct evaluation of the facts rather than the distorted version needed commercially, then propaganda can be used successfully to manage public opinion and allow the desired regulation to be implemented or maintained, retaining access to a product only for the authorised commercial partners of government. No fact is immune to perversion by propaganda, and no lie is too big to be successful provided the resources are available.

As a good example of this, most people would be surprised - even amazed - to learn that there is not even a single published clinical trial of nicotine's potential for dependence; an extraordinary fact considering the almost-vitriolic description of its 'addictive' powers seen occasionally, for which, rather obviously since there are no CTs or RCTs or any other data source of any kind, there is not a shred of evidence. The lack of any published trial despite the intense interest in this subject, together with the extreme ease with which it can be tested and the easy availability of ethics committee approvals for this type of work raises many interesting questions.

The natural conclusion is to ask why such evidence, either pro or con, has not been published.

This does not mean that nicotine may not be mildly reinforcing for a small, statistically insignificant number of individuals; just that someone claiming knowledge of the subject who states that nicotine is 'strongly addictive' or similar, without any evidence, can hardly be regarded as a reliable source. Of anything, probably.

What the science tells us

- We know that smoking can create strong dependence, which can justifiably be described as addiction since there is a significant elevation of risk (addiction in modern usage implies dependence plus harm).
- We know that smokers can become dependent on nicotine as a result of smoking.
- No clinical trial has ever reported any potential for dependence on pure nicotine by never-smokers.
- Nicotine, by itself, has no observed potential for dependence. That is to say, pure nicotine administered to never-smokers or never-users of tobacco in clinical trials is not demonstrated to create dependence. Just to make this clear:
  a) Not a single one of the many clinical trials of pure nicotine administered to never-smokers, for investigation of its

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potential benefits in multiple clinical areas, report that any subject ever exhibited any sign of reinforcement, dependence, withdrawal syndrome or continued use - despite subjects being given high doses for months.
b) Nicotine cannot be shown to create dependence; in every clinical trial published, no reinforcement or dependence was demonstrated.
c) Dependence on nicotine has never been demonstrated in those not exposed to tobacco use in some form.
d) There are no published clinical trials that report dependence is observed when nicotine is administered to never-smokers. All such trials for investigation of nicotine's nutritional and medical value report no observed measure of dependence, withdrawal symptoms, or continuation of use - *no matter how much is administered or for how long*.

- This leads to the conclusion that tobacco contains synergens and other compounds that interact with nicotine to create dependence, and especially when delivered in tobacco smoke.
- The principal potentiators are believed to be the MAOIs in tobacco; both higher quantities and additional compounds of this type can be found in tobacco smoke as against, for example, oral tobaccos.
- The basic tobacco MAOIs include harman and norharman, and these are found in both unburnt and burnt tobacco; tobacco smoke contains additional MAOIs created by the combustion process, such as other aldehydes and pyrolytic derivatives.
- One or more of the WTAs may also play a role in creating the synergism responsible for nicotine dependence, anatabine being one such compound implicated.
- It is well-demonstrated that vapers (regular ecig users) commonly reduce the amount of nicotine consumed, and continue to reduce the strength used; therefore nicotine does not create tolerance, a key marker for dependence-creating drugs.
- Vapers can more easily reduce or eliminate consumption of nicotine than smokers. Over time, some may eliminate its use if desired for some reason.
- When other aspects of nicotine in popular culture are examined, we find the same pattern: a complete lack of evidence to support assertions that nicotine is a highly toxic, very harmful, dangerous, alien and highly addictive drug. All the evidence shows exactly the opposite.
- Current knowledge is therefore that nicotine requires potentiation in order to create dependence; that pure nicotine has no clinically-observed potential for dependence or tolerance; and that as tobacco usage history recedes, dependence reduces even in continuing users of nicotine, indicating that tobacco not nicotine is the problem.

MAOIs are mono-amine oxidase inhibitors; WTAs are whole tobacco alkaloids, i.e. all the other pharmacologically active alkaloids in tobacco apart from nicotine.

The Four Nicotine Myths

There are four nicotine myths perpetuated in modern culture that have no basis in fact. These are:

1. The myth of nicotine's dangerous and alien nature
2. The myth of nicotine's toxicity
3. The myth of nicotine's potential for addiction
4. The myth of nicotine's potential for harm

1. Nicotine - a dangerous, alien chemical?

Hardly. Consider this:

- Nicotine is a normal ingredient in the diet
- Everyone consumes it
- Everyone tests positive for it
- No person has ever tested negative for nicotine, in any of the large-scale clinical trials that looked at nicotine presence in the population
- No one can be shown to have ever been harmed by dietary nicotine

Indeed, it is very likely to be beneficial and very likely to be a nutrient since it is so closely associated with the B vitamin group, has multiple well-recognised beneficial effects many of which are in common with its sister compound nicotinic acid (vitamin B3), about 20% of the population appear to benefit by supplementing their dietary intake of it, lack of it is clearly linked with auto-immune disease, and it is commonly investigated as a component in medicines for such conditions as Alzheimers.

Since dietary nicotine supplementation by any method is very clearly linked with prevention of some neurodegenerative diseases, auto-immune diseases, inflammatory diseases (the latter three classes of disease are closely linked); and equally well-linked with successful treatments for those diseases and some cognitive function disorders; then it is quite likely that nicotine is an active dietary nutrient with specific application to those with a genetic predisposition to such conditions. It also provides other functions such as mood normalisation and stress reduction for those with issues in these areas. It also helps with alertness and task completion when tired for most if not all persons. This is not a complete list of nicotine's functions or benefits, which may depend on the specific genetic composition of the individual.

All vegetables of the Solanaceae family contain it, and this includes tomatoes, potatoes and aubergines / eggplants. Many foods contain it, including tea: when you drink tea, you are consuming five active alkaloids and nicotine is one of

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them. After all, that's why tea works.

Nicotine is closely linked with nicotinic acid, a sister compound that in some organisms is a metabolyte of nicotine, and both are generally co-located in the same vegetables. You may know it better as vitamin B3 or niacin [1].

Vitamin B3 is a necessary component in the diet and a deficiency may result in physical and psychiatric symptoms, the most serious of which is pellagra (a serious skin condition resulting in extreme deformities of the skin). B3 assists with cognitive function, memory, work capacity, alertness and stress relief; and so does nicotine. Because of this, it has been suggested that at some point in the future, when the taboo is less prevalent, nicotine may be allocated a B vitamin number. Currently, this may appear a spurious suggestion; but since its close cousin is a vitamin, and shares many of the same functions, and nicotine clearly protects against and treats certain auto-immune diseases, Parkinson's, and Alzheimers, and assists in some cases of cognitive dysfunction - then perhaps the suggestion is not so unrealistic.

There have been several large-scale clinical studies of nicotine presence in humans, one of which was a test of 800 people by the CDC in the USA: every subject tested positive [19]. Nicotine is a normal, safe ingredient in the diet. Just like any other active dietary ingredient, some people may require supplementation.

So nicotine is as normal to consume as vitamin B - unlike alcohol or coffee (caffeine), which are clearly more 'alien' as they are not part of the normal diet and not associated with a vitamin group. Active dietary ingredients, especially those with demonstrated benefits, cannot realistically be described as alien or harmful.

2. Nicotine - a highly toxic drug?

We used to think so, although apparently with zero evidence for it. Those of us who handle it on a daily basis always knew that it is far less dangerous than supposed, since otherwise - quite simply - many of us would be dead.

In October 2013, Prof Mayer of Graz demolished the myth: he showed that there is no evidence at all for the assumption that nicotine is highly toxic; and in fact the LD50 should be around 10 to 20 times greater than the current figure [2].

His work shows that:

- Evidence for the validity of the current LD50 simply does not exist
- The method used to arrive at the LD50 is based on a guess made more than a hundred years ago
- There is no evidence whatsoever that a dose equivalent to the current LD50 has ever killed anyone
- There is overwhelming evidence that doses of multiple times the LD50 have been survived
- Suicide by ingestion of 1,500mg of nicotine is known to have failed, the only result being abdominal pain and vomiting
- There is strong evidence that the lethal dose is 4mg plasma nicotine, and this equates to an absorbed 500mg - 1,000mg dose (an amount injected or efficiently absorbed by some route other than ingestion; or a massive dose by ingestion of which 1,000mg is absorbed before ejection by emesis; or a very large dose by ingestion, with concurrent anaesthesia)
- Because ingestion of 1,500mg nicotine is not fatal, a lethal dose would need to be administered by injection or similar (it is impossible to deliberately inhale sufficient nicotine to cause death).

Therefore it seems logical that a new LD50 for nicotine should be established at around 750mg, which is 12 times the current figure; and that this dosage must be administered intravenously or by some similar mechanism. There is no known fatal dose by ingestion for adults, because in the normal subject the result is copious vomiting that expels the material. It is also possible that, with a sufficiently large dose, enough could be absorbed in the mucous membranes of the mouth while swallowing to cause death. This dosage would presumably be in the multiple thousands of milligrammes.

The current LD50 of 60mg was simply a convenient addition to the ideological and commercial propaganda surrounding the compound and there was never any evidence for it.

Current legality

It has recently been suggested by legal affairs commentators that, given the demolishing of the nicotine toxicity myth by Prof Mayer, and current legal practice in determining toxicity issues, UK courts would take the Sprague-Dawley rat LD50 as the direct human equivalent: this is 50mg/kilo. Courts tend to operate with evidence as against ideology, and the evidence strongly suggests this is the correct figure to use; the rat LD50 is generally applied in cases of poisoning. A 70 kilo person would thus require a dose of 3,500mg for a 50% chance of fatality. This accords directly with experience in the area of suicide attempts with nicotine, where doses of 1,500mg are known to be survivable with no subsequent effects.

A new LD50 at least 12 times greater is needed. In addition we also know that there appears to be no reliable fatal dose by ingestion or inhalation, because it appears impossible for death to occur in normal circumstances. As a rough guide, approximately 1% of deliberate suicide attempts by use of nicotine appear to succeed, and these involve concurrent anaesthesia to block the normal physical responses that prevent nicotine poisoning. Thus, nicotine by itself is not dangerously toxic because the body recognises it and expels it (in the case of ingestion) or prevents further consumption (in the case of inhalation). Nicotine is a relatively safe material whatever measurement is applied; certainly no more dangerous than caffeine (coffee), in practice.

Update July 2014
ECITA have now been advised by consultant toxicologists who advise the UK government on EU toxicity compliance issues that e-cigarette refill liquid can - at the most - be labelled as CLP Group 4, which is the same as washing-up liquid [20]. This is because there is evidence that the courts will support a nicotine toxicity level in humans the same as for rats, which is the universally accepted model for this type of toxin, which is 50mg per kilo bodyweight or greater (depending on the administration route - dermal or ingested). This works out for a 70 kilo person to 3,500mg of nicotine, a fairly large amount (which also corresponds with Prof Mayer's analysis, and the facts: hardly any adult dies as a result of ingested nicotine, and then only when anaesthetics are co-administered).

This has thrown into doubt the legal basis for some of the new EU TPD regulations that attempt to restrict ecig refill liquid, since the UK government's own consultants advise that when mixed with other materials, the resulting liquid is less toxic than bleach and mostly no more toxic than washing-up liquid - a fact that anyone who works with it is well aware of.

3. Nicotine - a fiercely addictive drug?

Not likely at all; but of course we'd need some sort of evidence either way, and there isn't any. There is not one single published clinical trial of nicotine's potential for dependence.

This is incredible considering the intense interest in this topic, and begs the question: why? In the past it was usually considered that this is because of ethics committee issues; but we now know that ethics panels freely permit CTs where large quantities of nicotine are administered to unexposed individuals for long periods, and that such research is being carried out on an ongoing basis to examine treatments for neurodegenerative conditions and the like. There is no ethics committee issue since by now it is well-demonstrated that nicotine is both harmless and non-dependent, and the research that shows this is conclusive.

It must be obvious that trials to determine the dependence potential of nicotine on never-smokers must have taken place in the past and that the results could not be published. Such trials must have taken place before the current era in which ethics committees decide on which trials can and cannot take place; and there are many places in the world where such an issue would not be problematic anyway. We must therefore assume that the results were always known but not politically or commercially convenient.

And then we find that there have, in fact, been multiple clinical trials of pure nicotine administered to never-smokers, for the investigation of other effects such the benefit in cases of cognitive impairment. No subject, ever, in any of these trials, showed any sign of dependence.

If you are confused by the above (understandably, considering the volume of propaganda) then here are some further explanations:

- The ***only*** relevant trial is one in which **pure nicotine** is administered to people **never exposed to tobacco by consumption**. There is no such published trial where the objective was to examine subsequent dependence.
- Administration in a cocktail of 5,300 other compounds is irrelevant (i.e. in tobacco smoke) [3].
- Smokers are frequently dependent on nicotine, as a result of smoking. It is assumed that smoking causes some sort of change in brain chemistry. After smoking, people become dependent on smoking, and many become dependent on nicotine.
- There are many trials of dependence in smokers, but these are clearly irrelevant.
- There is no evidence that nicotine alone can create dependence. Without consumption in tobacco it has no evidence whatsoever for reinforcement (dependence creation).
- There is significant evidence that nicotine administered to never-smokers or never-users of tobacco has no dependence-forming capability. Several clinical trials are known where pure nicotine administered to never-smokers in high doses for extended periods for other purposes such as investigation of cognitive function improvement or treatment of auto-immune / inflammatory diseases reported that no subject experienced dependence or withdrawal symptoms, or continued to use nicotine.

Currently, therefore, the available evidence shows that nicotine is not 'addictive' unless supplied in a cocktail of synergens. The same could be said of many other normal dietary ingredients.

There is widespread confusion between dependence on smoking and on nicotine. There is no evidence that nicotine, by itself, is 'addictive'. Because this would be easy to demonstrate, but has not been, we must question the grounds on which beliefs in this area are held (we now know that ethics committees *do* permit this type of research).

This is not just a question of a lack of basic science; more a deliberate attempt to hide the facts for commercial and ideological reasons.

Terminology: addiction vs dependence

Another aspect worth consideration is the terminology related to a material's potential for reinforcement. The modern preference is to use the term 'addiction' for a compulsion to consume or act in a way that will often result in harm at some point; 'dependence' is used for compulsion to consume or act in a way considered harmless by modern urban living standards. 'Reinforcement', a process which can lead to dependence, is the potential for repeated use in the initial stages of dependence.

Thus, smoking, some types of drug use, and gambling compulsion, are considered addictions since there is significant risk of harm of some kind: either physical and/or social. In contrast, the need to drink coffee, although very common today and in some cases quite powerful, is regarded as a dependence since no observable harm results. Such things are unlikely to be harmless since there is likely to be a cost; but that cost is invisible in among the background noise and regarded as insignificant in modern life terms.

The consumption of nicotine, by itself, should be classed as a dependence if reinforcement has occurred as a result of smoking, since it is not possible to identify harm - see next section.

Evidence for dependence creation

As we have seen, there is no published evidence for nicotine's potential for reinforcement (dependence creation). All citations lead to studies on smoking or ex-smokers. We know that smoking creates dependence although there is no agreement on exactly what in tobacco smoke creates the dependence; there is agreement that nicotine is implicated as part of the cocktail in tobacco smoke that creates dependence, since after smoking people may be dependent on nicotine.

- The exact compounds creating the dependence have not been reliably identified by any process of elimination, or by administration of each separate compound to never-smokers in order to evaluate the potential for dependence
- There is debate about the compounds that might be involved, and the candidates include many of the other compounds present in tobacco smoke acting as potentiators, such as MAOIs, other active alkaloids such as anabasine, pyrolytic compounds such as carbon monoxide, or simply nicotine boosted by synergens
- The research that does exist on this topic provides strong clues but is not of sufficient quantity and repeatability to state without reservation that tobacco MAOIs and WTAs together with nicotine are the cause of dependence on nicotine after smoking; but there is no opposing evidence, so this explanation seems likely to be true
- There is also space here for inclusion of other synergens, since research on the exact cause of nicotine dependency after smoking is in its infancy

Smoking can create dependence (that can be termed an addiction due to the potential for harm); and smokers / ex-smokers can be dependent on nicotine. These are known facts. There is little evidence for the separate dependence-creative potential of any of the individual compounds, although MAOIs and/or some of the other active alkaloids are widely believed to be implicated. A combination of the various materials may be the cause of the change in brain chemistry that can make people dependent on smoking and/or nicotine. Above all, there is no evidence whatsoever that nicotine, administered alone and without smoke or any of the other compounds in tobacco smoke, can create dependence; all the evidence suggests the opposite.

Prof Killeen says (to paraphrase him slightly): "Nicotine is not addictive. Administering it together with MAOIs makes it addictive"; and: "People may disagree with me but, since there is no evidence, they have nothing on which to base an argument" [4]. In other words, since there are no published proper clinical trials of nicotine and dependence, there is no evidence to argue about.

As he says, people can disagree on (a) whether nicotine is dependence-forming or not, and/or (b) exactly what in tobacco or tobacco smoke causes the dependence on nicotine to be established [18]. There is plenty of argument about both issues; but until there is some evidence, argument is pointless.

"The risk of addiction to nicotine alone is virtually nil", states Dr. Paul Newhouse, of Vanderbilt University Center for Cognitive Medicine, who is almost certainly the world's leading expert on nicotine at this time, since he has administered more nicotine to more never-smokers in more clinical trials than anyone else [21].

Trials of pure nicotine with never-smokers

We now know of several clinical trials (eight published at the last count) that involved administration of pure nicotine to never-smokers [14] for purposes such as investigation of treatments for various disorders. *No subject has ever shown any signs of reinforcement.*

A typical example was one investigating nicotine therapy for cognitive impairment, where after high dosage administration for 6 months (equivalent to the amount delivered by 18 cigarettes daily), none of the subjects experienced any withdrawal symptoms or continued to use nicotine [10].

Current evidence therefore is that nicotine is not dependence-creating unless delivered with synergens of some kind, or perhaps in other exceptional circumstances. Until otherwise demonstrated, there is no evidence that nicotine is reinforcing (capable of producing dependence) and strong evidence that it is not.

We have to refer to the body of evidence that shows nicotine as having no potential for dependence as anecdotal, even though it is the result of clinical trials, because the trials were for purposes other than examining dependence issues. Because the trials were not specifically for the purpose of examining dependence, we cannot describe this evidence as demonstrating that nicotine has no potential for dependence (even though that is exactly what this evidence does demonstrate). No dependence was reported in any case (and the number of never-smokers exposed to large amounts of nicotine numbers several hundred in these trials), and dependence issues were in fact discussed; therefore it can be truthfully stated that:
- pure nicotine does not show any potential for dependence
- there is strong evidence to support this position
- no evidence exists to contradict this

We might also consider some related issues:

- If there is indeed no knowledge of nicotine's lack of potential for dependence, exactly what type of medical professionals would deliberately administer a compound rumoured to be 'highly addictive' to unexposed individuals, in large doses, for several months, in order to examine its benefits for another purpose?
- What sort of ethics committee would permit this type of experiment?

It seems rather obvious that those responsible know that nicotine has no potential for dependence, otherwise such trials would not be suggested, would not be approved, and would not be carried out by normal persons. The public profile of nicotine is clearly different from its medical one: those involved with the use of nicotine in medicine are clearly aware that it has no potential for dependence. No similar trial of heroin or amphetamines could be conceived of or approved, even if the expected result were that the compound cured all known ills and prolonged life for fifty years - it is known that such materials have strong potential for dependence/addiction for unexposed individuals and that they cannot be exposed to such materials for medical research. Nicotine may well be described in the same sort of derogatory terms in public; but it is abundantly clear that medics actually involved with nicotine know very well that it is harmless and has no potential for 'addiction'. Otherwise, the researchers carrying out these trials of nicotine on never-smokers and the ethics committees permitting them would be considered the same as having conducted trials of heroin on never-users.

Clinical trials of nicotine on unexposed subjects, with administration of high doses over extended periods of time, are recognised as safe by the medical community. Nicotine is recognised as harmless; as having no potential for dependence; and as having well-recognised benefits. *Otherwise, such trials would never be conceived, permitted, or carried out*.

Nicotine is certainly not capable of creating addiction, with its modern implied meaning of dependence plus harm, since nicotine (without smoke) cannot be shown to be dependence-creating or harmful (there is a vast data mountain that tells us so, in the case of the latter). It must therefore be classified (and regulated, and taxed) in the same class as coffee/caffeine as regards any harm caused. Even so, there are two probable caveats: it is unlikely that nicotine is as dependence-forming as caffeine; and it may be possible that it is less harmful, if/when harms of such low magnitude can somehow be identified reliably.

Finally, in the best Sherlock Holmes tradition, we should also consider what is *not* there as well as what is. If nicotine caused dependence (and especially the harm associated with addiction) then we would not only see a clinical trial demonstrating it; we would see dozens. We would also see a massive press release campaign trumpeting the alarming effects of this 'dangerous drug' (as is seen for every tiny little new trial that purports to show any harmful effect remotely associated with nicotine [17]). Such research would be of immense value to the commercial propagandists who have created the myths surrounding nicotine.

There are of course no such trials and no such publicity associated with them, and it is abundantly clear why not.

A note on MAOIs

Because there is significant clinical research with animal models that clearly demonstrates it, and no evidence that contradicts it, MAOIs are believed to be the prime candidate for the creation of nicotine dependence as a result of smoking. The MAOIs identified so far in tobacco smoke are harman, norharman, and assorted aldehydes. There is general agreement that the first two are important, and some researchers believe aldehydes are also separately active in addition to their precursor function with tryptophan in the pyrolytic creation of the primary MAOIs (additional quantities of the primary MAOIs are created in the combustion process). MAOIs are understood to boost nicotine activity and provide the primary synergism required to create dependence.

MAOIs are not the same as the other active alkaloids in tobacco such as nornicotine, anabasine, anatabine and myosmine. The effects of these additional alkaloids seem to be mostly unknown. Anatabine, though, is known to have

anti-inflammatory properties and is used in treatments for rheumatism. Anatabine is believed to increase the effect of other MAOIs and has been suggested as an MAOI in its own right; research on such issues is in its infancy.

The tolerance issue

E-Cigarette users, on average, seem able to reduce or even eliminate their consumption of nicotine if they find they have no measurable need for it (clearly, some do, as it improves certain aspects of cognitive function and acts to reduce stress for some people). This appears to demonstrate an additional factor: nicotine, by itself, does not create tolerance.

Although it is a different issue from dependence, tolerance - the requirement for ever-increasing doses for the same effect- is usually stated as a core factor for addictive drugs and is considered part of a dependence-creating drug's profile. Nicotine does not require ever-increasing doses for the same effect. Indeed, the opposite appears to be demonstrated: vapers routinely reduce the amount of nicotine they consume in proportion to the time since the last smoking event, and they report the same effect for these gradually reducing doses.

Some may transit into a zero-nicotine usergroup, and some may cease all ecig use. At any given time, about 7% of vapers are zero-nic users; this group is continually being refreshed by persons joining by reducing their nicotine intake to zero and persons leaving by quitting totally. We know that this group is generally reported as around 7% in surveys of ecig users; but we don't know what the figure is for those who join this group per year or who leave (although presumably they are equal).

Nicotine 'addiction': conclusion

- Nicotine is essentially harmless, therefore it cannot honestly be described as addictive even if it did have dependence potential (since addiction in modern usage implies measurable harm).
- There is substantial evidence that it does not create dependence, although such evidence has to be described as anecdotal, for technical reasons.
- There is no evidence whatsoever that nicotine has any measurable potential for dependence: such an outcome is always linked with tobacco consumption.
- The medical community involved with nicotine clearly recognise it as a harmless compound with no potential for dependence but many medical benefits, or they would not be happy to administer high doses for many months to unexposed individuals.
- Ethics committees clearly have no problem with nicotine; while in public it may be described in the same terms as heroin, in private it is rather clear that senior medical figures consider the inherent risk to be on a similar scale to coffee, or less.
- The cocktail of chemicals delivered in cigarette smoke appears to rewire the brain, in a manner of speaking, creating addiction in many individuals. Chemical changes are induced that remain permanently or semi-permanently, such that the brain is hardwired to need cigarettes or nicotine. Therefore we can describe the resultant nicotine dependence as 'persistent': long-lasting, often difficult to eradicate, but ultimately defeatable. Of course, some smokers never become dependent on nicotine as this is not a guaranteed result of smoking.
- The term 'addiction' is used correctly here, in the modern context, as harm often results from smoking.
- No one has ever shown that any of the individual materials in smoke have any potential for addiction, least of all nicotine, which in contrast has evidence showing that it does not create dependence. If it did have potential for reinforcement, the correct term would be dependence in any case because it cannot be decribed as addictive in the modern context, since there is proof (not just evidence) that extensive consumption has no clinical significance, as no significant harm can be demonstrated.
- Smoking is addictive, meaning that many people experience strong dependence and harm as a result. Nicotine cannot be shown to be dependence-forming or harmful.
- Some people appear to receive medical benefit from nicotine, whilst no harm can be demonstrated.
- Consumption of nicotine does not create tolerance; it is well-demonstrated that individuals can easily reduce their intake, in contrast to cigarettes.
- Nicotine should be considered separately from smoking. Individual compounds present in tobacco smoke may either be of no significance to health or, alternatively, beneficial to health, while smoke is clearly harmful.
- We know that anatabine, isolated from the tobacco plant, is a powerful anti-inflammatory and is now used in medicines for that purpose. Luckily it has no taboo surrounding it, otherwise the treatments for rheumatism and the like that employ it would perhaps not exist.

Strong and persistent

Above, we saw that dependence on nicotine is caused by a permanent or semi-permanent change in brain chemistry induced by smoking or other tobacco consumption. A better description of this effect is needed, and it can be expressed as follows:

Smoking often creates a *strong and persistent dependence on nicotine* by interaction with other compounds delivered concurrently that potentiate its effects. Pure nicotine has no measurable potential for dependence. It is well-demonstrated that ex-smokers can gradually reduce their dependence on nicotine as long as they cease smoking, even if they continue to consume nicotine: ongoing nicotine consumption by means of vaping is no bar to reduction of the quantity consumed or

cessation of nicotine or complete cessation of all inhaled materials. Thus, smoking causes dependence on nicotine; and as long as smoking is ceased, nicotine consumption can be reduced or ceased if desired. Vaping or any other form of consuming pure nicotine is equivalent to non-smoking as far as nicotine dependence is concerned.

Since many genetic variants of the human organism clearly derive significant medical benefit from nicotine, which is presumably why it is an active material present in the everyday diet in the first place, total cessation of nicotine supplementation should be approached with caution. In particular, family medical histories might profitably be examined first. Examples of neurodegenerative disease, auto-immune disease, inflammatory disease or cognitive function disorders in the family history should give cause for concern: there may be a requirement for nicotine supplementation.

4. Nicotine - a harmful and damaging drug?

Apart from the facts that:

- Nicotine is a normal component of the diet;
- And, that everyone tests positive for it;
- And, we now know it is between ten and twenty times less toxic than previously argued;
- And, that not only is there no evidence for it being dependence-forming, but there is reason to believe it isn't;

...apart from all that, there could be a valid question that either (1) an accidental or deliberate over-consumption at a single sitting, or (2) excessive consumption over an extended timescale, may cause harm. Naturally, this should be examined.

1. Accidental overdose

Those who consume nicotine on a regular basis know that its potential for harm by accidental over-consumption is about zero. This is because it is very similar to coffee in that when a certain threshold is reached, the experience starts to become unpleasant, and consumption ceases. If consumption continues, it can become very unpleasant; the only reason to continue would be to inflict deliberate self-harm, but this is difficult, increasingly unpleasant, and would require an iron will. It is equivalent to deliberate self-electrocution by starting at a barely noticeable voltage, then turning up the voltage in 1 volt steps, and taking 10-second shocks each time.The pain eventually becomes unbearable; and as it will take a hundred or more steps to cause permanent harm, it is probably impossible to get there. Collapse comes before harm.

As Prof Hajek says, "".....we now know these things are safe.....There is a built-in safety valve.....You just experience nausea and you stop.....and no health damage can come about. So these things are safe." [*discussion of dual-use or multi-use of e-cigarettes, NRT, smoking, etc.*] [11]

The unpleasant side effects and the speed with which nicotine is eliminated by the body mean that it would be very difficult indeed to cause harm, it would need to be deliberate, and it would be about as likely as a person attempting to drink enough coffee to hospitalise themself. It may be possible to do so, but it would seem to require a strength of will probably lacking in a person who might attempt it - and there must be easier ways of self-harming.

As regards deliberate or accidental ingestion of large quantities of nicotine, it appears that nicotine has little potential for harm except in anomalous circumstances. For example, multiple cases of ingestion of very large quantities of nicotine are known to have been survived with no harm resulting; for example, in a case of attempted suicide where 1,500mg of nicotine was swallowed, the only symptoms were abdominal pain and copious vomiting. However, it is believed that if other drugs are consumed in sufficient quantity to anaesthetise the subject and repress the vomit reflex triggered by ingestion of nicotine, then poisoning may result. There is a case known where a large quantity of valium appears to have had such an effect. Thus, nicotine by itself appears unlikely to cause harm in adults, but when consumed in a drug cocktail the effect may well be different. On the other hand, this could be applied to any number of other things such as cleaning materials.

In fact this is a recurring theme in anti-nicotine propaganda: the harm resulting from consumption of a toxic mix of multiple compounds is attributed, disingenuously, to nicotine.

2. Long-term consumption of substantial quantities

Then there comes the question of consuming nicotine in significant quantities for decades - perhaps this is a concern?

What if we could find a very large number of subjects who have consumed large amounts of supra-dietary nicotine over a lifetime, without smoke, and the data for whom is easily available: multiple studies with very large numbers of subjects including large cohorts [16] with identifiable health data? What if we could easily isolate this data demographically (e.g. by sex)? What if we had national health statistics for an isolated population of smokeless nicotine consumers, hundreds of clinical studies, numerous large scale meta-analyses of the studies, massive amounts of epidemiology, and in general a vast volume of data on such persons over many decades?

Well, we do, and it's called the Snus data [7]. There are hundreds of large-scale clinical studies over three decades utilising up to 100,000 subjects, together with unique national health statistics - Sweden has the lowest tobacco-related mortality of any developed country by a wide margin.

This huge volume of facts and evidence from Sweden shows that the average reduction of lifespan attributable to lifetime high-volume tobacco and nicotine consumption (without smoke) is only about 6 weeks [13].

Although there is no isolated data for pure nicotine consumption, indications are it has little risk (for example, from the far smaller NRT data resource) [15]; and the closest large data resource without inclusion of smoke, the Snus data, shows that harm resulting from consumption of this tobacco is on such a small scale it is difficult to identify statistically. Sweden has the lowest male lung cancer and oral cancer rates in the EU; the last item contrasts directly with the expectations people might have for an oral tobacco, since Snus has such a low elevation of risk for oral cancer that it cannot even be identified reliably.

Because of the very great size of the data resource, we know there is a small average lifespan reduction associated with long-term Snus consumption; there are now indications that this may be less than the equivalent for coffee consumption. In addition it can probably be assumed that tobacco consumption involves more risk than nicotine consumption alone (this is just a point of basic logic: consumption of 1,000 materials is not the same as consumption of 1 item from the list), and thus some subtraction from the lifespan reduction figure could probably be made to arrive at a suitable figure for nicotine consumption alone (until we have a 30-year data resource for e-cigarette users, who appear to be the only long-term pure nicotine users on a sufficiently large scale to potentially equal the Snus resource).

You can also see the latest expert medical position on nicotine's potential for harm from materials supplied by the UK's NICE, in their direction to doctors on this topic [5]; and from other experts in this area such as CV Phillips and B Rodu. Nicotine does not cause cancer, does not promote cancer, is not associated with cancer, and is not associated with heart disease [8].

It is interesting to note that even doctors are vulnerable to propaganda, when it is so pervasive as that propagated for nicotine: a recent survey revealed that 44% of British doctors thought nicotine is associated with cancer [12]. The UK doctors' official guidance authority, NICE, says they are wrong and in fact the opposite is the case: nicotine has no association with cancer (NICE PH45). (Also see [8] on this point.)

"I think the key point is that nicotine itself is harmless, which is something most people don't appreciate."
- Prof P Hajek
https://www.youtube.com/watch?v=SVS0_BGHHjM

Prof Hajek was comparing harms from smoking and nicotine rather than in an isolated situation. It is worth pointing out that 'most people' in his statement above includes a significant number of doctors.

Conclusion

There is probably no other subject surrounded by so much myth and propaganda as nicotine. The reasons are multiple and complex, and comprise ideology together with commercial, economic, political and social pressures.

Nicotine is a relatively harmless normal dietary component that many people appear to need to supplement. Because the required dietary supplementation was normally supplied in tobacco smoke and therefore entailed significant risk, it became tainted by association, and only because of that. No one considers the consumption of ketchup to be an addictive or harmful behaviour, and ketchup contains significant amounts of nicotine; no one considers it a bad idea to feed their baby mashed-up vegetables, which of course contain nicotine. You feed your baby nicotine and no one has ever suggested this is a bad idea - because it isn't. B-vitamins and associated compounds are normal and desirable.

If people wish to consider *supplementary* nicotine consumption undesirable, then they must apply the same logic even more forcefully to the far more 'alien' coffee, tea, sherry, wine, beer, and chocolate - or risk being classed as a gold-plated hypocrite [9]. If people wish to consider *normal dietary* nicotine consumption undesirable, then consumption of vegetables such as potatoes and tomatoes would need to be avoided, and this would probably lead to multiple nutritional deficiencies.

Supra-dietary nicotine consumption on average is harmless in terms of modern lifestyle choices [6].

Why do people lie about nicotine?

It is assumed, until better evidence is available, that this is for financial, practical or ideological reasons, or susceptibility to propaganda; or perhaps just ignorance. For example: for profit, for the benefit of funders, or in expectation of future benefit, or to protect prior positions, or for religious reasons, or due to the erroneous conflation of nicotine with smoking, or because of an idealised view of health that views all individuals as clones of a perfect human specimen and does not allow for nutritional supplements for individual needs. Or, because of the power of the

commercial propaganda - remember that 44% of British doctors answering a survey replied they believed that nicotine is associated with cancer, in direct contravention of their official clinical guidance from NICE, which clearly states there is no such association - see NICE PH45. Or, just simple ignorance.

No one really knows the reason for a taboo as its origins are lost in unrecorded history. It does help when strong commercial pressures exist to maintain the taboo. Transnational business interests combined with easily-controlled zealots and an effective propaganda machine appears to be a winning formula.

Notes

[1] When researchers discovered that nicotinic acid was a required nutrient, and allocated it to the B vitamin group as B3, they were worried that due to the nicotine taboo their work would be dismissed. As a result they invented a new name for the compound that avoided this problem: 'niacin', which is simply a selective contraction of nicotinic acid.

[2] References page: Nicotine, 1.

The LD50 is the median lethal dose, or the dose which will kill half of those who receive it. The current figure in use for nicotine is 60mg, which Prof Mayer demonstrated to be a fallacy. A new LD50 will need to be established at somewhere approaching 1,000mg. Nevertheless it cannot be applied to ingestion of pure nicotine without anaesthetics or anti-emetics (vomit reflex suppressors), since the material is expelled and too little is absorbed to cause harm.

[3] Until early 2013, the latest research into the identification of the ingredients of tobacco smoke had identified 5,300 compounds. Then in February 2013, a total of 9,600 compounds identified in tobacco and tobacco smoke were published:
References: Cigarettes - Technical, 1.

Not having a copy of the book, I cannot say which enumerated compounds overlap, being present in both the tobacco and the smoke; or which can only be found in tobacco and not the smoke generated - so I believe it still correct to state that, "At least 5,300 compounds have been identified so far in tobacco smoke".

[4] References: Nicotine, 14.

[5] References: Public Health, 1.

[6] This means that:
a. Consumption of significant amounts over an extended period of time probably has a cost, like any urban lifestyle decision; but the resulting average reduction of lifespan is hardly visible, especially considering that even the very small reduction in lifespan identified by the Snus data must also be attributed to and split with tobacco consumption. In any case it is probably far less significant than many other factors such as food choices, exercise choices, urban air quality, and so forth. The cost/benefit ratio is clearly favourable.
b. For persons who are not average, such as those with a genetic predisposition to stroke, the cost may be higher.

[7] The only source of isolatable long-term substantial nicotine consumption data (i.e. consumption of nicotine in significant supra-dietary amounts without tobacco smoke) is the Swedish data on Snus consumers. There are pros and cons to it:
a. There is a huge volume of it, from 30 years of intensive study (hundreds of clinical studies); plus the national health statistics, which are unique in some respects.
b. The data has some interesting isolation factors: primarily for one country and one sex: Swedish men (Snus is mainly consumed by men, and is banned in all other EU countries; Norway, being a non-EU country, permits its use, and therefore has significantly reduced tobacco-related mortality).
c. The data has two principal confounders: nicotine consumption is impossible to isolate from smokeless tobacco consumption; and Snus consumers are frequently ex-smokers.

[8] Note very carefully that animal nicotine models **do not** transfer to humans. There are numerous clinical trials of nicotine administration to animals that report promotion of cancer and other effects. None of these can be replicated in humans and we have a huge volume of facts and data that does not just provide evidence for this, it is proven.

Clinical trials or studies do not prove anything, even if there are hundreds of them: they provide evidence to support an argument and no more. Therefore the hundreds of clinical studies of Snus consumers demonstrating that harm cannot be reliably identified in clinically significant quantity is not considered proof, no matter how great the volume.

National health statistics however are facts and can be referred to as proof, since, assuming that the data is correctly obtained and interpreted, they refer to the real world not the lab. Since there may be anomalies in any statistics, it may be acceptable to debate the accuracy of national health statistics. Eventually, though, there comes a point at which sufficient statistics, epidemiology and clinical study data tell you that something is a reality and not a hypothesis, and the Swedish data is long past that point: nicotine is proven harmless. To be completely accurate: nicotine consumption on average is harmless in terms of modern lifestyle choices (see #6, also #17).

[9] All these contain pharmacologically-active materials that are not a normal part of the diet. Coffee contains caffeine, tea (commonly) contains 5 active alkaloids: caffeine, nicotine, and 3 of the 'theos'. Chocolate contains an active alkaloid, one of the 'theos'. Neither is alcohol a normal dietary ingredient.

[10] See: References page, Nicotine, 2, 3.
Also: www.ecigarette-politics.com/nicotine-clinical-trials-why-aren-t-there-any.html

[11] References: Nicotine, 15.

[12] References: Nicotine, 5.

[13] Multiple citations exist for expected lifespan reductions in Snus consumers of between 2 weeks and 10 weeks. We use 6 weeks, as the median figure.

[14] a. A 'never-smoker' in medical parlance is a person who has never smoked a single cigarette.
b. An 'ever-smoker' is a person who has smoked one or more cigarettes. (It tends to be used for a subject who once smoked, but not to any great extent; it is an undefined, somewhat loose term.)
c. A 'non-smoker' is someone who used to smoke (so medically, a non-smoker is an ex-smoker: note the difference in the medical definition of non-smoker to the common meaning, which might also include someone who never smoked).
d. A 'smoker' is a person who has smoked during the past 30 days (usual definition); it is sometimes applied more loosely, to those who occasionally smoke and intend to in the future, but have not done so recently.
e. A 'daily smoker' is a person who smokes at least once per day.
f. A 1PAD smoker, 2PAD smoker, are smokers who consume 1 pack a day or more.
In general, published statistics refer to those classified under item #d. Occasionally the #e definition is used, normally by those who wish to present smoking prevalence as lower than might be expected and who sometimes deliberately obfuscate the mechanism they use for doing so.

It has often been argued that these classification systems are unwieldy or erroneous or worse, but no positive alternative has been offered. In addition, all current statistics globally are based on the 'past 30-day' figure. However, it has recently been shown that a new class, 'past 5 days' could be an improvement and would probably appeal to many. The problem is changing a global system, though.

[15] The data resource for NRT consumption is microscopic in size compared to that for Snus consumption; the timescale is also restricted in comparison. (Although NRTs have been available since 1984, NICE say they have only 5 years data at 2013; the reason for this is not clear.) This is why the Snus data is used in discussions about (and even the licensing of) the long-term safety of NRT therapy: no harm can be reliably identified from population-level consumption of large quantities of nicotine over multiple decades. (To be accurate: an average lifespan reduction of ~6 weeks is identified, but since this is probably far less than for any lifestyle decision such as diet or exercise and so on, it is ignored for all practical purposes.) As a separate issue, incidences of any type of cancer reported by studies (and not by the majority, incidentally) are so few in number that, even if correctly identified, they are many times lower than a clinically signicant figure. Cancer of any kind is not statistically or clinically associated with Snus consumption, and not at all with nicotine consumpion.

'Clinical significance' generally refers to repeatedly demonstrated effects of a size that cannot be attributed to statistical error. This is generally taken to mean a reliable measurement of a 3% effect or greater. Consumption of Snus has no clinical significance, and consumption of nicotine certainly doesn't.

[16] The strict definition of 'cohort' is a group of the same age. It is also used for a group with some other common factor such as date of smoking cessation. There are large cohorts of both types in the Snus research data (with subject numbers of up to 98,000 individuals in a single study, for example).

[17] Every now and then, a university announces the conclusion of a new trial of nicotine with animals that appears to demonstrate a newly-found effect such as promotion of tumours. This happens regularly. These events are always accompanied by a press release campaign and numerous articles in newspapers. Headlines announce, "New danger from nicotine". The problem is that we already have the facts together with a vast mountain of data from a population that has used nicotine without smoke for decades and shows no significant effects. Animal modelling of nicotine and morbidity does not transfer to humans (see #8).

The same applies to cell modelling studies using *in vitro* methods - we already know these are irrelevant because we have a large population where none of these effects can be seen. It is very hard to see these events as anything other than funding drives of some kind, unrelated to any real health concerns.

[18] Currently we don't know for certain if tobacco has to be smoked in order to create dependence on nicotine, or whether oral tobacco consumption can also create it. It is difficult to locate solid evidence here because many/most ST users are likely to have been exposed to tobacco smoke. It does look as if the level of and variety of MAOIs in tobacco smoke is much higher than that encountered in oral tobacco consumption. Research here is minimal since it is discouraged, by means of restriction of funding.

[19] The CDC have done their best to hide this clinical trial, and it would almost certainly have been removed entirely had it not been cited and thus impossible to be 'disappeared'. See References page.

[20] See: http://www.ecita.org.uk/blog/index.php/how-toxic-is-e-liquid/

[21] See: Vaping Quotes page.

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