Dr. Vince Clinical Research

White Paper

Assessing the Abuse Liability of Tobacco and Nicotine Products

Tobacco Harm Reduction Series

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Background

Abuse liability is a term used to describe the harm caused to an individual and to others in Society through the use, misuse and abuse of CNS active substances. It therefore comprises both personal and social elements, all of which need to be assessed to reach a full determination. While several theoretical frameworks have been proposed, the core features of abuse liability have been identified by Stitzer and De Wit (1998)[1] as:

• Evidence of self-administration

• Evidence of adverse consequences – e.g., physical or mental harm (to self and others), intoxication, performance impairment

• Evidence of subjective or mood-altering effects in humans – e.g., feeling "high", bad experiences, liking/enjoyment

For many CNS active substances, the most significant adverse consequence related to abuse liability is developing an addiction – and the terms "abuse potential", "dependence potential", or "addictiveness" all refer to

"…the pharmacological potential of a substance to cause addiction, a state which affects an individual's ability to control his or her behaviour, typically by instilling a reward or a relief from withdrawal symptoms, or both" (EU TPD 2014)[2]

Furthermore, since collection of the totality of data to determine abuse liability may take several years, "abuse potential", "dependence potential" or "addictiveness" serve as useful proxies for the larger concept, since addictive processes appear to underlie or drive many of the core features of abuse liability.

For biopharmaceuticals designed with CNS activity or possibly exhibiting such activity as a side-effect, abuse potential is commonly evaluated as part of non-clinical safety assessments using endpoints such as chemical similarity to existing drugs of abuse, behavioural studies in animals, and receptor binding studies. If any markers of abuse potential are present, further exploration during clinical development is required. This approach is described in the FDA CDER 2017 guidance[3], and DVCR has established a strong reputation in offering the clinical assessment of the human abuse potential of pharmaceuticals.

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Regulatory Demands

Given the common understanding that tobacco and nicotine products are addictive, and the fact that regulatory responsibility for oversight of such products increasingly lies with health organisations (e.g., the World Health Organisation, the US Food and Drug Administration, DG Sante within the European Union), it is perhaps not surprising that the determination of abuse liability has also become a core issue when seeking an authorization for the sale of new tobacco or nicotine products. However, the approach taken varies somewhat from that taken with biopharmaceuticals.

The most advanced tobacco regulatory frameworks have been developed by the European Union and the United States. Relevant industry guidance states:

• "Member States and the Commission require comprehensive information…to assess the attractiveness, addictiveness and toxicity of tobacco products…" (EU TPD 2014)[2]

• "The (PMTA) discussion should include

information such as... Assessment of abuse liability (i.e., the addictiveness and abuse and misuse potential of the new product…)". (US FDA 2016)[4]

These complimentary frameworks not only identify addictiveness as the core feature of abuse liability but also introduce the additional concept of "attractiveness", which is a feature of recreational commercial products that is absent from biopharmaceutical products. A definition offered by a scientific advisory committee to the European Union provides a succinct explanation:

"Attractiveness is defined as the stimulation to use the product…The attractiveness of tobacco products may be increased by a number of additives but is also influenced by external factors such as marketing, price etc." (SCENIHR 2010)[5]

Traditional combustible products (i.e., cigarettes) which dominate in the current tobacco market meet abuse liability criteria because they are attractive, cause physical harm to the user, cause harm to others due to the impact of second-hand smoke or the effects of tobacco waste upon the environment, and they are addictive because of the presence of nicotine. Even modern non-combustible tobacco or nicotine products (e.g., e-cigarettes, nicotine pouches) which have likely led to overall reductions in combustible cigarette use and have mitigated some of the adverse effects associated with traditional combustible products may still be attractive to the consumer and addictive due to the presence of nicotine.

Another difference in emphasis between the characterization of abuse liability for biopharmaceuticals and for nicotine and tobacco products is the aim of assessment. Most pharmaceutical compounds are now designed to minimize the risk of abuse potential i.e., the primary (ideal) endpoint is an absolute removal of such effects. In contrast, the aim for new tobacco and nicotine products is to demonstrate a relative level of abuse liability, ideally less than that of combustible tobacco, such that current smokers will be able to switch to a product with a potential lower physical health risk. Furthermore, it needs to be shown separately (commonly in studies of perceptions and intentions) that this level of abuse liability will not encourage current non-users of tobacco and nicotine, particularly youth, to initiate use of the product.

This characterization of abuse liability may be seen as a facet of tobacco harm reduction and bears some similarities to the harm reduction approaches taken to provide medicinal biopharmaceutical substitutes for illicit drugs of abuse. For tobacco and nicotine products, this balance of outcomes has been made explicit in the US FDA interpretation of "Appropriate for the Protection of the Public Health" (APPH), the unique public health standard included in the US Tobacco Control Act[6].

Novel Challenges

In addition to the theoretical differences outlined above, mapping tobacco and nicotine products onto the general definition of abuse liability given by Stitzer and DeWit (1998)[1], shows a difference in the relevant core features and therefore data which can be collected to characterize abuse liability.

• *Evidence of self-administration*

While it may seem obvious that users will self-administer

tobacco and nicotine products, it remains unclear to what extent this is driven by a pathological process or simply a reflection of an everyday habit. Nevertheless, gross behavioral changes to rates of use (e.g., number of cigarettes smoked per day, amount of nicotine consumed in a day) have been employed to quantify the abuse liability of tobacco and nicotine products.

• *Evidence of adverse consequences – e.g., physical or mental harm (to self and others), intoxication, performance impairment*

There is no question regarding the physical harm caused by combustible tobacco products, and the mental harm is predicated upon the possible development of addiction. However, there is no clear evidence of intoxication or performance impairment associated with everyday tobacco or nicotine use. The percentage of individuals who meet diagnostic criteria for addiction (e.g., those given in DSM-5[7] or ICD-11[8]) among total users of a particular tobacco or nicotine product could be employed as an alternative gross measure of abuse liability.

• *Evidence of subjective or mood-altering effects…in humans – e.g., (feeling "high", bad experiences, liking/enjoyment)*

When provided as consumer products, there can be no doubt that tobacco and nicotine are attractive, liked, and enjoyed although there is scant evidence of feeling "high" during use. As with self-administration, it remains unclear to what extent such subjective effects are driven by a pathological process, or simply reflect the operation of normal everyday habits. Nevertheless, measures of subjective or mood-altering effects, which relate most closely to the psychological experience of abuse potential have been widely employed as the best proximal measures to quantify the abuse liability of tobacco and nicotine products.

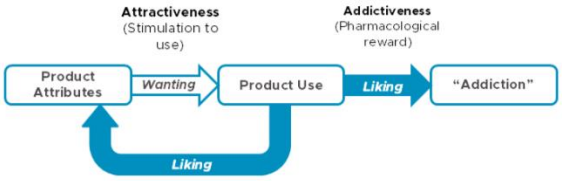
In addition, blood samples for measures of plasma nicotine concentrations are typically collected, as faster uptake and onset of action has been associated with greater abuse liability. This is evident with the high abuse potential of combustible cigarettes where nicotine is rapidly delivered to the brain. Plasma nicotine concentrations provide an objective, physiological measure which compliments the measurement of subjective, psychological effects.

A Conceptual Model

Drawing these various threads together, it is possible to conceive of a model which captures the theoretical abuse liability framework for tobacco and nicotine products, reflects the concerns of regulatory bodies, and provides both an approach to gather data and a narrative which will meet with acceptance from regulators.

Attractiveness is experienced by the consumer as aspects of wanting (desire, craving etc.) in response to product attributes. These attributes can be as diverse as marketing, price, packaging, ingredients, flavour, or method of use (i.e., e-cigarette, smokeless tobacco, nicotine pouch etc.) and can be represented as follows:

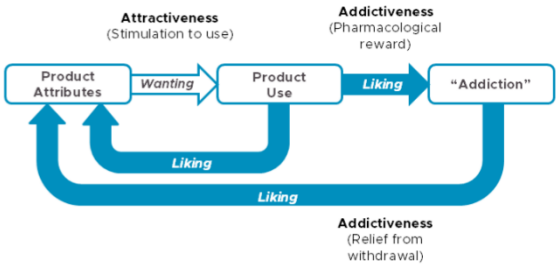
Addictiveness is experienced by the consumer as liking (satisfaction, enjoyment etc.). Above a certain threshold this liking becomes pathological, and addiction is the result. However, it is important to note that the normal experience of liking can become an attribute of the product without contributing to the addictive process. A feedback loop therefore exists. These processes can be added to the model as follows:



The full definition of addictiveness adds to the conceptual model:

"Addictiveness' means the pharmacological potential of a substance to cause addiction, a state which affects an individual's ability to control his or her behaviour, typically by instilling a reward or a relief from withdrawal symptoms, or both" (EU TPD 2014[2])

This updated definition adds "…instilling… a relief from withdrawal symptoms" and strongly implies that pharmacological potential not only causes addiction but also maintains addiction. Nevertheless, the core concepts of instilling a reward or relief from withdrawal are both experienced by the consumer as aspects of "liking" (satisfaction, enjoyment etc.). So, the model must be expanded one more time:

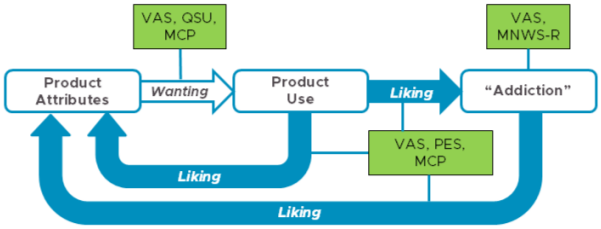


What Can Be Measured?

Measures of abuse potential for tobacco and nicotine products should primarily focus upon the consequences of product liking during and after use, which is represented in the blue arrows above. Simple liking questionnaires, presented as visual analogue scales (VAS), have proved valuable in profiling different tobacco and nicotine products and are able to distinguish between the subjective effects of smoking combustible tobacco, using an alternative tobacco or nicotine product, and the "medicinal" delivery of nicotine through nicotine replacement therapy (NRT) e.g., a patch or gum. VAS for liking, good/positive effects, bad/negative effects, intent to use the product again, relief from withdrawal can all be employed. Turning to product wanting before and after product use, visual analogue scales of overall craving and withdrawal, and cigarette craving VAS have been successfully employed.

If existing standard measures are also to be included, Product Evaluation Scales (PES) and Multiple-Choice Procedures (MCP) can relate to liking, the Questionnaire on Smoking Urges (QSU) and Multiple-Choice Procedures (MCP) can relate to wanting, and the Minnesota Nicotine Withdrawal Scale – Revised (MNWS-R) can index how far along the addiction pathway an individual lies. These measures can all provide additional granularity to the subjective VAS endpoints, if required.

Placing these different measures on the conceptual model, it can be seen how the various mechanisms which impact abuse potential are assessed:



The DVCR Approach

Recent Dr. Vince Clinical Research (DVCR) studies have compared the abuse liability of nicotine pouches to nicotine gum and combustible cigarettes in a cross-over study among regular cigarette smokers, using a selection of measures from those outlined above and behavioural measures of product consumption. Throughout, data collection was assured and enhanced through digital administration using the validated Cambridge Cognition platform. More information

regarding the conduct of DVCR clinical trials for tobacco and nicotine products can be found at:

Nicotine Studies | Tobacco Studies | Tobacco Study | Clinical Trials

Conclusions

The addictiveness / abuse potential of tobacco and nicotine products can be assessed by (proximal) measures of liking (e.g. VAS, PES, MCP during and after consumption). Some measures which have been used (e.g. VAS, QSU, MCP before and after consumption) measure wanting and are more closely related to "attractiveness" and help explain its contribution to abuse liability. Other measures (e.g. VAS MNWS-R) relate to Smoker Status. Behavioural endpoints such as gross changes to rates of use (e.g., number of products used per day, amount of nicotine consumed in a day, etc. etc.) may supplement these data and, where it is not possible to bridge existing pharmacokinetic (PK) data, regulatory bodies may also request PK measurements as a compliment to the subjective and behavioural data. Importantly, the interpretation of this abuse liability is currently made in relation to combustible tobacco products and medicinal nicotine replacement therapy.

References

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About Dr. Vince Clinical Research

Dr. Vince Clinical Research (DVCR) is a full-service contract research organization (CRO) specializing in early phase trials in both healthy normal volunteers and patient populations across a wide range of trial designs and therapeutic areas such as neuroscience, substance abuse, pain, cardiometabolic disorders, infectious diseases and many others. CRO services include project management, data management, biostatistics, statistical programming, PK/PD analysis, medical writing, monitoring, site feasibility and management for multi-site trials.

Additionally, DVCR operates one of the most innovative and technologically advanced clinical pharmacology units in the world with over 90 beds for overnight confinement, a clinical laboratory, a surgical suite, a cGMP compliant pharmacy, as well as luxurious amenities to support diverse study participant recruitment and retention. By leveraging technology and one of the country's most

experienced leadership teams in early clinical development, DVCR provides Smarter Faster Data® to their biopharmaceutical clients.

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