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The Importance of Estimating Causal Effects for Evaluating a Nicotine Standard for Cigarettes

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Abstract

Recent evidence from randomized clinical trials (RCTs) of very low nicotine content (VLNC) cigarettes indicates that smokers randomized to VLNC cigarettes had significantly lower cigarette use, dependence, and biomarkers of exposure than smokers randomized to normal nicotine content control cigarettes. In these trials, a substantial number of participants did not adhere to their randomized treatment assignment, i.e., they used commercial cigarettes not provided by the trial in place of or in addition to the VLNC cigarettes provided by the trial. As with most RCTs, the analysis of these trials followed the intention-to-treat principle, where participants are analyzed according to their randomized treatment assignment regardless of adherence. Alternately, the analysis of an RCT could focus on the estimation and testing of the causal effect of the intervention, which is the treatment effect if all subjects were to adhere to their randomized treatment assignment. In this commentary, we compare these two approaches, highlighting the important role of causal estimation and inference for evaluating the regulatory effect of a nicotine standard for cigarettes. Additionally, we review the results of the secondary analyses of randomized trials of VLNC cigarettes using causal inference methodology to account for non-adherence to the assigned treatment and discuss the implications for a nicotine standard for cigarettes.

Introduction

Recent evidence from randomized clinical trials (RCTs) of very low nicotine content (VLNC) cigarettes indicates that smokers randomized to VLNC cigarettes had significantly lower cigarette use, dependence, and biomarkers of exposure than smokers randomized to normal nicotine content (NNC) control cigarettes.[1,2] A challenge to the interpretation of these trials is nonadherence to randomized treatment assignment, that is, the use of commercial cigarettes not provided by the trial in place of or in addition to the VLNC cigarettes provided by the trial.[3] The presence of nonadherent smokers is potentially problematic because it could obscure the effects of the intervention, and, as a result, extrapolating the results of these trials to a future regulatory environment in which a new nicotine standard is enacted is challenging.

Nonadherence to randomized treatment assignment is common in RCTs, and the analysis of RCTs in the presence of nonadherence has been studied extensively in the statistical literature.[4–7] The standard framework for analyzing RCTs is to perform an intention-to-treat (ITT) analysis, where subjects are analyzed according to their randomized treatment assignment regardless of adherence to the assigned treatment.[8] Alternately (or in addition to an ITT

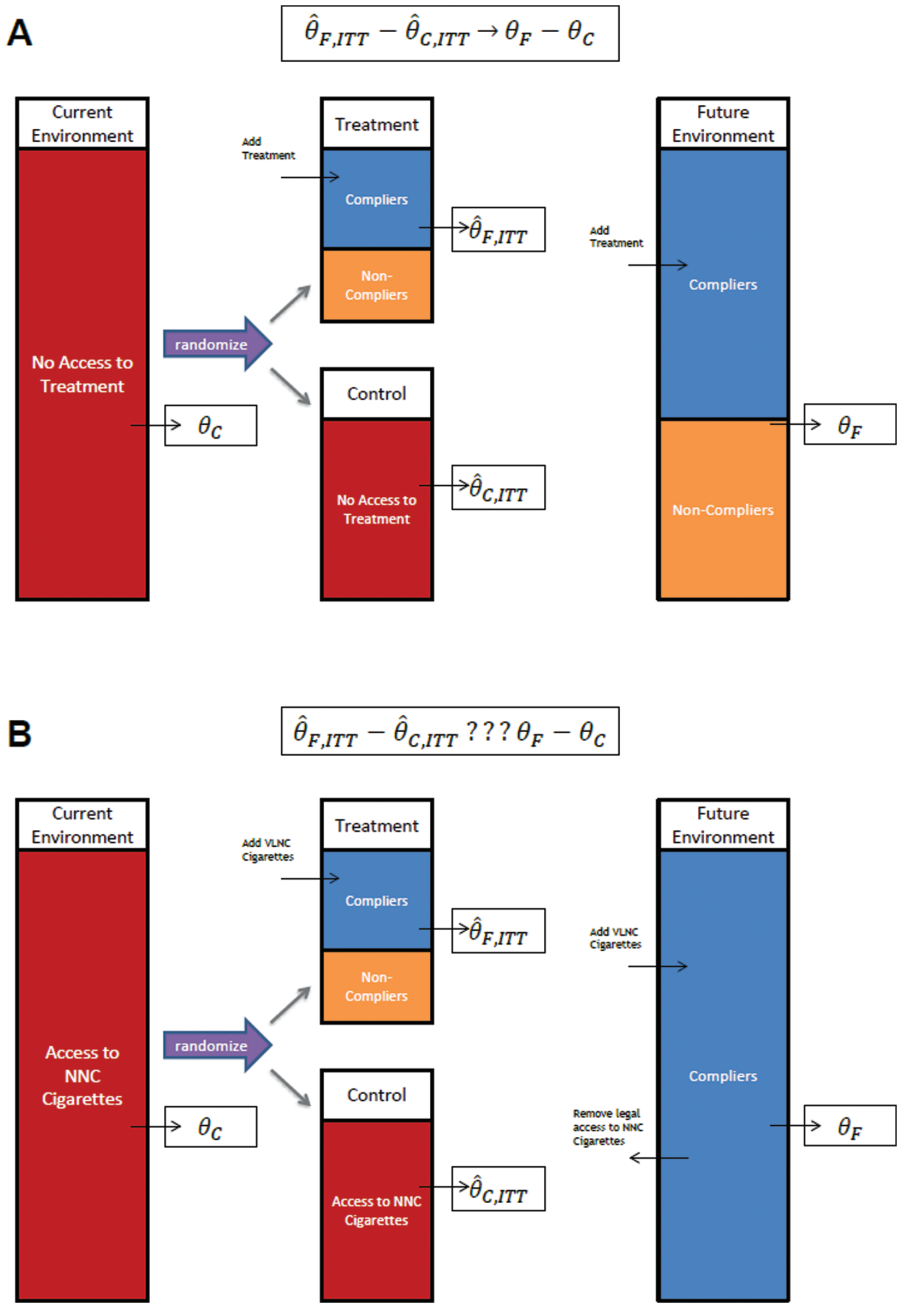

Figure 1. (A) Conceptual diagram of the relationship between a randomized clinical trial and the target of inference in the context of evaluating a novel therapeutic agent. (B) Conceptual diagram of the relationship between a randomized clinical trial and the target of inference in the context of a new nicotine standard for cigarettes. In both cases, $\theta_{F,ITT} - \theta_{C,ITT}$ is the ITT estimate of the true difference between the current and future environments, $\theta_F - \theta_C$.

analysis), the analysis of a clinical trial can focus on the estimation of causal effects (ie, the effect if all subjects were to adhere to randomized treatment assignment)[9] using methods from the causal inference literature.[9–15] In this commentary, we compare these two approaches, highlighting the role of causal inference in evaluating the effect of a nicotine standard for cigarettes, and we review the results of the secondary analyses of randomized trials of VLNC cigarettes using causal inference methodology to account for nonadherence to the assigned treatment.

Intention-to-Treat Versus Causal Inference

RCTs of Novel Therapeutics

Figure 1A presents a conceptual diagram for RCTs of novel therapeutics and illustrates why an ITT analysis is most appropriate. The far left side of the figure represents the current environment where all patients with the target diagnosis are prescribed the standard of care. Because the experimental treatment is not approved for clinical

practice, none of the patients would be able to access the experimental treatment outside of the RCT. The far right side of the figure represents the future environment, where the new treatment is approved for clinical practice and all patients with the target diagnosis were prescribed the experimental treatment. Even if all patients were prescribed the experimental treatment, not all patients will take the treatment as prescribed. The middle section of the figure represents an RCT in which participants are randomized to receive either the new treatment, or a control treatment, which may be either a placebo or the current standard of care. As with the future environment (far right), participants in the trial may or may not adhere with their treatment assignment. The objective of an RCT is to estimate the difference in outcomes between the current environment and the future environment (ie, mean difference, odds ratio, hazard ratio, etc.), which we denote as θ_F-θ_C. Under the assumption that the adherence patterns are similar in the conduct of the trial to what would be observed in the general population, the ITT analysis provides a consistent estimator of the difference between the anticipated outcomes in the current environment and future environment where the treatment is approved. That is, θ_F, ITT- $\theta_{C,ITT} \rightarrow \theta_F$-$\theta_C$ in an infinite sample size. The ITT comparison is justified because, in some contexts, it can provide an unbiased estimator of the use-effectiveness of a treatment or intervention, that is, how well the treatment works in everyday practice in an environment where patients may or may not adhere to a prescribed treatment.[5–7] For this reason, it is recommended as the primary analytical approach for analyzing RCTs of novel therapeutics.[8]

RCTs of VLNC Cigarettes

This is in contrast to RCTs of VLNC cigarettes, which are represented by the conceptual diagram in Figure 1B. In this case, the current regulatory environment is defined by the legal availability of NNC cigarettes. An RCT to evaluate nicotine reduction will randomize participants to receive either NNC cigarettes (control group) or VLNC cigarettes (treatment group) but will be completed in an environment where NNC cigarettes are commercially available. As a result, the participants randomized to receive VLNC cigarettes have the option to smoke NNC cigarettes in place of or in addition to VLNC cigarettes. In contrast, the future regulatory environment where a nicotine standard is in place is defined by *removing* NNC cigarettes and *replacing* them with VLNC cigarettes. As a result, in the future environment, all smokers would "adhere" to the intervention in the sense that legal access would be restricted to only VLNC cigarettes, albeit some illicit NNC use would likely occur (see Section "Causal Effects and the Black Market"). This creates uncertainty as to the relationship between the ITT effect and the effect of a nicotine standard.

In the statistical literature, the effect of an intervention if all subjects were to adhere to the intervention is referred to as the *causal effect*.[9] Estimating the causal effect in the presence of nonadherence is challenging because, although treatment *assignment* may be randomized, *adherence* to treatment assignment is not. As a result, a comparison of only adherent participants will introduce confounding. A number of approaches to estimating causal effects from RCTs in the presence of nonadherence have been proposed in the causal inference literature, including inverse probability weighting, principal stratification, instrumental variable analysis, and structural equation modeling.[9–11,13–15] Secondary analyses of RCTs of VLNC cigarettes using causal inference methodology can provide crucial information as to the effect of a new nicotine standard for cigarettes.

Evidence for the Causal Effect of Nicotine Reduction

The results of a 20-week, three-arm RCT comparing immediate reduction in nicotine content, gradual reduction in nicotine content, and a control arm were recently reported and included a secondary causal analysis of biomarkers and cigarettes per day (CPD).[2] In the causal analysis, smokers randomized to the immediate reduction group (randomized to receive cigarettes with 0.4 mg of nicotine/gram of tobacco) had significantly lower breath carbon monoxide (CO), and biomarkers of exposure to carcinogens and toxicants, and smoked significantly fewer CPD than smokers randomized to the control group (randomized to receive cigarettes with 15.5 mg of nicotine/gram of tobacco) at 20 weeks. More importantly, when compared to the primary ITT analysis, the estimated treatment effects from the causal analysis were similar, and, in fact, larger, in many cases. This suggests that, in a reduced-nicotine content regulatory environment (where NNC are not legally available), smokers would smoker fewer CPD and have lower biomarkers of exposure than the current regulatory environment. Similarly, secondary analyses of a 6-week randomized trial of VLNC cigarettes[1] resulted in an estimated causal effect on CPD that was similar to the primary, ITT analysis.[12,16]

Causal Effects and the Black Market

A limitation of the conceptual diagram presented in Figure 1B is that it does not reflect the black market that would likely develop in the presence of a nicotine standard for cigarettes. In this case, the future environment would still include NNC cigarettes and some smokers would not adhere to the reduced nicotine intervention. However, the extent of nonadherence is unknown and likely to be less than was observed in RCTs because they would be less available than in the current regulatory environment and more costly (with one "cost" being that use would be illicit). Estimating the effect of a nicotine standard in the presence of a black market is difficult and may not be reflected by either the ITT or causal analysis. The best approach to evaluating the effect of a nicotine standard in the presence of a black market is through population modeling, which requires assumptions about the scope of the black market. In this case, estimated causal effects provide an important building block for population modeling by providing an estimate of the treatment effect in the sub-set of the population not participating in the black market. The causal effects may need to be "calibrated" if the sub-populations that do and do not participate in the black market differ by important effect modifiers.[17] That said, the similarity of the ITT and causal treatment effect estimates in the published literature, which represent the extremes of perfect adherence and substantial nonadherence when NNC cigarettes are legally available, suggests that the treatment effect would not vary dramatically if one assumes illicit cigarette use is unlikely to exceed the use of currently available NNC cigarettes by participants in clinical trials.

Summary

RCTs of VLNC cigarettes provide important evidence in support of a new nicotine standard for cigarettes but are challenging to interpret in the presence of nonadherence to randomized treatment assignment. Causal inference methods provide powerful tools for understanding the effect of VLNC cigarettes had all participants been adherent to their randomized treatment assignments. Secondary analyses of RCTs of VLNC cigarettes indicate a consistency between

the ITT and causal effects, which provides important evidence in support of extrapolating the results of these trials to a future environment where nicotine reduction is mandated by regulation.

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Declaration of Interests

None declared.

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