Method for Estimating Non-study Cigarette Use Among Switchers to Very Low Nicotine Content (VLNC) Cigarettes in Ambulatory Clinical Trials

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Abstract

Background: In March 2018, FDA issued an advance notice of proposed rulemaking (ANPRM) on a nicotine standard for cigarettes to make them "minimally"- or "non-addictive." Some studies have reported reductions in the number of cigarettes per day (CPD) smoked after switching to very low nicotine content (VLNC) cigarettes, while others reported no change. Non-compliance is a common limitation in VLNC studies where smokers continue to have access to conventional nicotine content (CNC) cigarettes. While methods for estimating the prevalence of non-study cigarette use have been reported, no method for estimating its magnitude (i.e., CPD) has been published. We describe a method for estimating non-study CPD and the implication of the resulting estimates in interpreting data from VLNC studies.

Methods: This method is based on the same principle used in published methods for estimating the prevalence of non-compliance. Among participants exclusively smoking assigned cigarettes, the biomarker of exposure (BOE) level for a smoke constituent is proportional to the amount of the constituent per cigarette (Yield) and CPD, i.e., BOE = Yield*CPD*k, where k represents a pharmacokinetic factor that integrates the intake, bioavailability, distribution and clearance of the constituent. When non-study cigarettes are also smoked, the equation needs to be modified to account for both sources as such: BOE = $Yield_{study}$*CPD_{study}*k_{study} + $Yield_{non\text{-}study}$*$CPD_{non\text{-}study}$*$k_{non\text{-}study}$. The equation can be solved for non-study CPD when relevant BOE, Yield, CPD, and k data are available.

Results: The method was verified against data from a published VLNC study where participants did not have access to non-study cigarettes. Estimates using data from published VLNC studies where participants had access to CNC indicate that (1) under-reporting on the magnitude of non-study cigarettes use was common, (2) estimates of non-study CPD vary by study, and (3) estimated non-study CPD under-reported can exceed the reduction in self-reported CPD after switching to VLNC.

Conclusions: Controlling and accurately estimating non-study cigarette use is critical for ambulatory VLNC switching studies to ensure the resulting data can be appropriately evaluated for use in science-based regulatory decision making.

Introduction

To assess the impact of VLNC cigarettes on smokers' cigarette consumption, multiple clinical studies have switched smokers to VLNCs. Some of these studies have reported a reduction in the number of cigarettes smoked after switching to VLNC cigarettes, while others reported no change in CPD. Non-compliance is a common limitation in ambulatory studies, where smokers continue to have access to CNC cigarettes. Donny et al.[1] reported that participants' self-reported non-compliance prevalence rates were inversely correlated with the nicotine content of the assigned VLNC cigarettes, and 73–81% of the participants in the groups assigned cigarettes with nicotine content of 5.2 mg/g or less reported smoking at least one non-study cigarette during the study. In addition, study participants substantially under-report the prevalence of non-study cigarette use. In the same study, while 39% of the participants assigned to cigarettes with 0.4 mg/g nicotine self-reported smoking non-study cigarettes during week 6, biochemical measures showed that 76–78% of them were non-compliant.[2] As pointed out by Goldstein and Goldstein,[3] the 30-fold difference between the expected and measured urinary nicotine levels in the 0.4 mg/g VLNC group (0.5 and 15 nmol/mg creatinine, respectively) provides an indication on the magnitude of non-study CPD under-reporting. If not adequately considered, under-reporting of non-study cigarette use poses significant challenges to accurately interpreting the resulting data. While methods for estimating the prevalence (i.e., percent of participants) of non-compliance have been reported,[2,4,5] there is no published method for estimating the magnitude (i.e., CPD) of non-compliance. We describe a method for estimating the magnitude of non-study cigarette use among switchers to VLNC cigarettes in ambulatory clinical studies that is based on the same mass balance principle used in the published methods for estimating the prevalence of non-compliance.

Methods

If participants in a study use assigned study cigarettes exclusively (per protocol), the level of the biomarker of exposure (BOE) to a smoke constituent should be proportional to the quantity of the constituent per cigarette (in smoke or tobacco, reffered to as "Yield" for simplicity) and the number of cigarettes smoked per day (CPD):

$$BOE = Yield*CPD*k,$$

with the k representing a composite factor encompassing the intake (dose), distribution and clearance of the constituent.

When non-study cigarettes are smoked in addition to assigned VLNC cigarettes, this equation needs to be modified to account for both sources:

$$BOE = Yield_{VLNC}*CPD_{VLNC}*k_{VLNC} + Yield_{non\text{-}study}*CPD_{non\text{-}study}*k_{non\text{-}study}$$

The k value for each constituent/biomarker combination depends primarily on the actual intake per cigarette relative to the constituent Yield (referred to as "bioavailability" here for simplicity and consistency with the existing literature[2,4,5]) and the distribution and clearance of the constituent. Within the same individual or between randomized groups of participants, the difference in the k value between study and non-study cigarettes is mainly driven by the bioavailability of the constituent, with compensatory smoking behavior (i.e., puffing and inhalation) being the primary factor. Based on smoking topography and exhaled CO measures, published VLNC clinical studies generally reported no or limited compensatory smoking behaviors between VLNC, CNC and usual brand (UB) cigarettes.[1,6] Therefore, the k values can be expected to be similar between study and non-study cigarettes and are assumed to be the same to simplify the equation into:

$$BOE = Yield_{VLNC}*CPD_{VLNC}*k + Yield_{non\text{-}study}*CPD_{non\text{-}study}*k$$

The most likely non-study cigarettes smoked by the study participants are the commercial CNC cigarettes they have been smoking prior to enrolling into the study. SPECTRUM® cigarettes with a nominal nicotine content of 15.8 mg/g filler were designed to be representative of the average US commercial cigarettes and are commonly used as CNC references in VLNC clinical trials. Therefore, the constituent Yields of the SPECTRUM® CNC can be used as surrogates to represent the averages for the non-study cigarettes in the equation:

$$BOE = Yield_{VLNC}*CPD_{VLNC}*k + Yield_{CNC}*CPD_{non\text{-}study}*k$$

The k value can be derived using data from the SPECTRUM® CNC group, based on the equation $BOE_{CNC} = Yield_{CNC}*CPD_{CNC}*k$, as:

$$k = BOE_{CNC} / (Yield_{CNC}*CPD_{CNC})$$

The number of non-study cigarettes smoke by participants in a VLNC group can then be calculated as:

$$CPD_{non\text{-}study} = (BOE - Yield_{VLNC}*CPD_{VLNC}*k) / (Yield_{CNC}*k)$$

Therefore, the magnitude of non-study cigarette use among VLNC groups can be estimated for studies when relevant BOE, Yield, and CPD data are available for both VLNC and CNC (or UB) groups.

Results

Method Verified by Data from a Controlled Study

The validity of the proposed method was verified with data from a published study reporting exposure data among smokers who did not have access to non-study cigarettes and were smoking assigned VLNC cigarettes exclusively.[7]

TABLE 1. Data from Denlinger et al.[7]

Cigarette	VLNC (0.4 mg/g)	UB	
Yield (mg nicotine or µg anatabine per gram of tobacco filler)			
Nicotine	0.295	16.5	
Anatabine	30	1158.5*	
CPD	28.3	20.09	
BOE (nmol/mg creatinine)			Non-study CPD Estimate
Nicotine	0.47	11.47	0.3
Cotinine	1.23	17.79	0.9
TNE	3.45	63.38	0.6
Anatabine	0.003	0.06	0.4

*mean of the range for 50 top-selling cigarettes

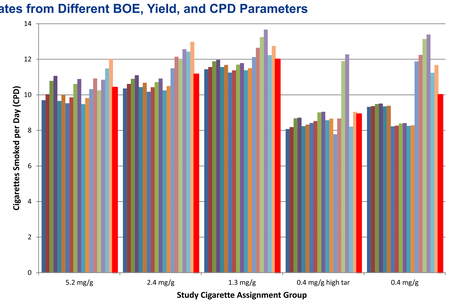
Based on the reported BOEs for nicotine, cotinine, TNE (total nicotine equivalent) and anatabine, the estimated numbers of non-study CPD using this method are 0.3, 0.9, 0.6 and 0.4, respectively. They are within 1-3% of the actual average CPD smoked (28.3). The highest estimate (0.9 CPD) was from cotinine which has the longest half-life, whereas the lowest (0.3 CPD) was from nicotine which has the shortest half-life among the four biomarkers, suggesting the small discrepancies likely reflect the carryover of the biomarkers from baseline as suggested by the authors rather than flaws in the method used. These results provide evidence supporting the validity of the proposed method.

Method Produces Consistent Estimates from Different BOE, Yield, and CPD Parameters

Data from a large VLNC switching study with SPECTRUM® cigarettes[1] permitted 18 separate non-study CPD estimates for each of the 5 VLNC groups in the study using different BOE/Yield/CPD combinations (Table 2), with the 15.8 mg/g CNC group as reference.

TABLE 2. . BOE/Yield/CPD combination for each group in Donny et al.[1]

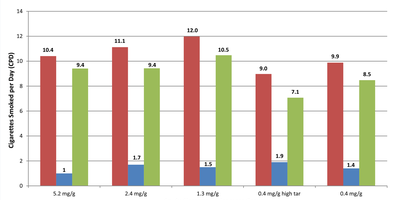
	BOE	Yield	CPD
1	Cotinine	Nicotine in smoke (CI)	Total cigarette
2			Study cigarette
3		Nicotine in smoke (ISO)	Total cigarette
4			Study cigarette
5		Nicotine in tobacco filler	Total cigarette
6			Study cigarette
7	NE	Nicotine in smoke (CI)	Total cigarette
8			Study cigarette
9		Nicotine in smoke (ISO)	Total cigarette
10			Study cigarette
11		Nicotine in tobacco filler	Total cigarette
12			Study cigarette
13	NNAL	NNK in smoke (CI)	Total cigarette
14			Study cigarette
15		NNK in smoke (ISO)	Total cigarette
16			Study cigarette
17		NNK in tobacco filler	Total cigarette
18			Study cigarette



The first 18 columns in each group are individual estimates from different BOE/Yield/CPD combinations as described in Table 2; the last column is the mean of the preceding 18 estimates.

The estimated numbers of non-study CPD within each group from different input combinations are generally consistent. Estimates from NNAL tend to be higher, particularly for the groups assigned cigarettes with 0.4 mg/g nicotine.

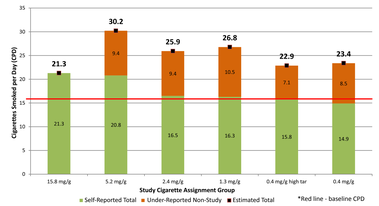
Under-Reporting of Non-study CPD Common at Different Nicotine Levels



Average estimated, self-reported, and under-reported number of non-study CPD for each VLNC group in Donny et al.,[1] with 15.8 mg/g CNC as the reference.

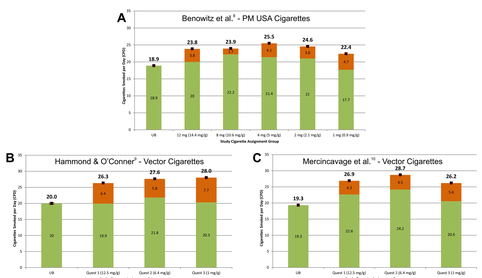
Under-reported non-study CPD numbers were derived by subtracting self-reported non-study CPD (difference between self-reported Total and Study CPDs in Donny et al.[1]) from the estimated non-study CPD. The results show that participants in the VLNC groups under-reported non-study cigarette CPD by 73–89%.

Non-study CPD Estimates Exceed Self-Reported CPD Reductions



The average under-reported CPD estimates are higher than the corresponding self-reported CPD reductions after switching to VLNC for 6 weeks, with 15.8 mg/g CNC as the reference.[1] Using participant's UB as the reference resulted in non-study CPD estimates that are about 10% higher for each group (data not shown). Therefore, when the magnitude of under-reporting is taken into consideration, there was no reduction in the total number of CPD for any VLNC group in the study compared to the reference group. The red line indicates the baseline CPD.

Under-Reporting of Non-study CPD Common Across Studies



Non-study CPD estimates in VLNC switching studies using different cigarettes manufactured by Philip Morris USA® and the Vector Group.[9-10] Self-reported, estimated under-reported and estimated total numbers of CPD are based on reported nicotine exposure using participants' UB as reference. The numbers in the parentheses indicate the nicotine content per gram of tobacco filler of each cigarette used in the studies. The results show that under-reporting of non-study CPD is common across switching studies using different VLNC cigarettes whereas the magnitude of under-reporting varies by study.

We estimate that an average of 8.6 non-study cigarettes were smoked per day among the immediate reduction to 0.4 mg/g nicotine SPECTRUM® cigarette group in Hatsukami et al.[11], based on ISO smoke nicotine and NNK yields and the reported mean TNE and NNAL levels, which is consistent with the 8.5 non-study CPD estimated for the group assigned to the same VLNC cigarette in Donny et al.[1]

Assumptions and Limitations

Non-study CPD estimates using this method can be affected by compensatory smoking, which was assumed to be minimal based on published data. Due to the limited amount of nicotine in the filler, compensatory smoking of VLNC cigarettes with the lowest nicotine content will have the least impact on non-study CPD estimates, where the highest non-compliance rates have been observed[1]. For example, if we assume participants are exposed to three times the amount of nicotine yield under Canadian Intensive (CI) smoking conditions from each VLNC cigarette, which is equivalent to the conservative assumption of 40% nicotine bioavailability used by Benowitz et al.[8]in setting the threshold for non-compliance, the estimated non-study CPD for the 0.4 mg/g group in Donny et al.[1] would only change by less than 1 (or about 10%). Caution is still warranted when applying this method to data from studies in which substantial compensatory smoking are observed among groups smoking VLNC, particularly for VLNCs with intermediate levels of nicotine content (e.g., 5.2 mg/g or above). It is also important to note that BOEs of nicotine will not be suitable when applying this method to VLNC studies in which other forms of nicotine products (e.g., NRT, ENDs) are expected to be used in conjunction with VLNC cigarettes. For such studies, measures of BOEs to other smoke constituents that are either not present or present at much lower levels in the alternative nicotine products (e.g., NNK, anatabine) should be considered. Anatabine data from Denlinger et al.[7] yielded a non-study CPD estimate very close to those based on nicotine, cotinine and TNE, whereas estimates based on NNK tend to be higher than those based on nicotine in Donny et al.[1] This observation, albeit based on limited data from a single study, suggests that biomarker for anatabine exposure might be superior to that for NNK for non-study CPD estimation, particularly for short-term switching studies due to the longer half-life of NNAL. Additional research will be needed to confirm if this is true. Another limitation of the study is the use of average CPD and biomarker values estimated from graphs in the cited publications when the actual numbers were not reported. This can be addressed with the availability of raw data.

Conclusion

We report a method for estimating the number of non-study CPD in ambulatory VLNC switching studies where participants continue to have access to CNC cigarettes. Results from our study indicate that, while the estimated number of non-study CPD vary by study, under-reporting on the magnitude of non-study cigarettes use is common for VLNCs at different nicotine content levels and across studies using different VLNC cigarettes. In addition, the number of under-reported non-study CPD can exceed the reduction in self-reported CPD after switching to VLNC, which would lead to conclusions contrary to those based on self-reported CPD alone. In planning future ambulatory VLNC switching studies researchers should consider including measures that could (1) control/minimize non-study product use, (2) enhance the accuracy of self-reported data, and (3) enable objective assessment of both the prevalence and the magnitude of non-study cigarette use. Incorporating such measures in the study design will be critical to ensuring the resulting data can be appropriately evaluated for use in science-based regulatory processes for establishing a product standard for nicotine in conventional cigarettes.

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