Population Modeling of Modified Risk Tobacco Products Accounting for Effects of Cigarette Smoking

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ABSTRACT

The FDA’s draft guidance on Modified Risk Tobacco Products (MRTPs) applications recommends simulation models to evaluate net public health impacts of MRTP candidates such as electronic cigarettes (e- cigarettes) and snus. These products might reduce mortality risk compared to cigarettes, but switching to the new product will lead to increased use of dual use, increased total initiation to tobacco products, relapse of former smokers, role as a gateway to, and smoking-related harm of new smokers. We developed a two-product simulation model to explore possible population impacts of an MRTP. The conventional cigarette (CC) sub-model incorporates effects of age, gender, cigarette per day (CPD), and time since quitting. The MRTP sub-model allows transitions to and from dual use and the MRTP alone, and effects of dual use on CC quit rates. A product use history generator for MRTPs, who are accepted by a large random sample, this approach provides greater flexibility than Markov state models, allowing detailed CCD modeling for example, to reflect the high panel support in long-term prediction, we model a broad range of probability-weighted scenarios.

Smokers who add an MRTP without fully switching tend to smoke fewer CPD, reducing mortality risk based on studies of large cohorts of smokers. The relationship of relative mortality risks to CPDs appears steep at very low CPDs (e.g., < 10 CPD), indicating that quitting even from a low CPD level reduces mortality risks more than reducing CPDs would. The simulation of effects of different levels of CPD reduction, starting with distributions of CPDs and age and sex from National Survey on Drug Use and Health (NSDUH), varying the CPD reduction from 5% to 90% had a greater effect on cardiovascular deaths than varying other assumptions, such as transitions to dual use and relapse from use and, with dual use by age, had from the MRTP CC. Therefore, to facilitate the model and include benefits from CPD reduction by dual users, in conjunction with added risks from the MRTP in addition, following up dual use CC CPD histories and quit rates over time should be an essential part of post-market studies.

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METHODS

• Extend a simulation model of present and future use of CC and MRTP (Poland et al., 2015, 2014), to account for effects of CPD changes over time on mortality
• Evaluate & estimate the impact of MRTPs on the population mortality, addressing FDA expectations for quantifying net public health impact (FDA 2012).

OBJECTIVES

• An annual individual simulation model with two tobacco products (CC, MRTP (Poland et al., 2015, 2014), was extended to incorporate differential transition rates of relative risk when an individual changes tobacco product use, including CPD.

• Exposes CPDs (CC) defined in terms of Relative Risk (RR), relative to a newer user: RR = 1.0.

• When a change in tobacco product use changes exposures (long-term target) ES, exposure exponentially toward the new equilibrium: ES = ES old * (1-e^(-delta TI*RR)).

RESULTS

• The slope of change 1 depends on age and sex and was fitted to a prior model of the decay of risk over time since quitting (Mendolia et al., 2015).

• The same slopes were used to make RR change gradually after any tobacco product initiation, addition, change in use level, or cessation.

• MRTP users were estimated to be in equilibrium based on large cohort studies (Fig. 2).

• A hypothetical MRTP (such as an e-cig or snus) was assumed to be available in the first simulation year, with transition rate data & risk relative to CC as shown in Table 1. Dual users were assumed to reduce CPD.

• CC relapse rates for the MRTP alone and dual use were estimated 90% for 3 years, 75% for 2 years, and 50% for 1 year.

• A population of 560,000 was simulated over 2032 and 2066, and smoking and mortality rates were aggregated from individual smoking and MRTP use histories (Fig. 4).

Table 1. Hypothetical MRTP Inputs (reference case).

<table>
<thead>
<tr>
<th>Input</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC initiation</td>
<td>20%</td>
</tr>
<tr>
<td>CC reduction</td>
<td>5% to 90%</td>
</tr>
<tr>
<td>MRTP users increase</td>
<td>42%</td>
</tr>
<tr>
<td>MRTP users quit CC</td>
<td>50%</td>
</tr>
<tr>
<td>MRTP users quit CC and MRTP</td>
<td>50%</td>
</tr>
</tbody>
</table>

Fig. 1. Two-product (CC and MRTP) smoking history. Each node represents a subpopulation, and each arrow represents a flow proportional to the current subpopulation (except for new users). The number of users corresponds to numbered MRTP inputs and outputs.

Fig. 2. Dashed arrows indicate transitions not currently implemented. Only one transition occurs at a time (e.g., C<->B but not B<->A or C<->B and not B<->A). The arrow [A->B] is the only form of relapse allowed; otherwise, smoking is permanent. The CC-only model has no transitions to and from MRTP.

Fig. 3. Sensitivity of MRTP effects on mortality through 2060.

Fig. 4. Change in Illustrative simulated cumulative US death relative to two-product reference case. Case C includes only CC. The line is the two product reference case. Other cases also reflect changes over time of low and high input values of the key five drugs in Fig. 4.

DISCUSSION

The model combines strengths of other smoking prevalence and mortality prediction models: two tobacco products, full age sex demographics, and time-varying effects of CPD and years since quitting on mortality.

Individual relative reduction provides the flexibility to model gradual relative risk changes over time, after changes in tobacco product use.

Hypothetical MRTP inputs show that CPD reduction is important to model because it can make the difference between no net mortality reduction and substantial reduction.

A long time horizon is necessary to properly assess public health impacts.

Future research may include: 1) refining input distributions with more data, 2) refining sub-models such as CPD-mortality accounting for full CPD history, 3) varying demographics currently fixed in [4], 4) reflecting possible future changes in age smoking patterns, and 4) increasing sample size and time horizons for better accuracy.

REFERENCES

Barnes & Thalberg 2001: Health consequences of smoking 1-4 cigarettes per day. Subst Use Misuse 36:513-326.