
**eAppendix.** Caveats of the smoking cessation drug rapid query

**eReferences.**

This supplementary material has been provided by the authors to give readers additional information about their work.
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Although we wished to restrict the analysis to individuals who used varenicline or bupropion for smoking cessation to reduce confounding by smoking, the use of a tobacco use disorder code within the preceding 180 days identified only a minority of current smokers and its predictive value has not been assessed. Among varenicline initiators (presumably all of whom were smokers) and bupropion initiators, those with the code had a higher rate of the combined cardiovascular outcome than did those without it. This higher event rate suggests that the smoking code identified a high-risk subset of users.

Product-based inference about the indication for therapy can also be problematic. Although separate bupropion preparations are marketed for depression and smoking cessation, only 1.5% of all bupropion initiators received formulations specifically approved for smoking cessation. This may underrepresent the intended use, since the bupropion product dispensed may reflect product availability, formulary structure, physician preference or familiarity, and reimbursement policies. In sum, neither approach allowed us to identify with complete confidence individuals who used bupropion solely for smoking cessation purposes.

Choice of an appropriate reference population is often a challenge. Although bupropion initiators with a smoking indication were a logical comparator group, bupropion increases blood pressure and may thus increase cardiovascular risk.\(^1,2\) With regard to selection of outcomes, the acute myocardial infarction end point has been shown to have a high positive predictive value,\(^3,4\) including in the Mini-Sentinel population.\(^5\) The other two cardiovascular end point codes have not been rigorously validated.
It is also important to focus on the period during which risk is likely to be observed and on a population that is representative of the users of the product. This rapid query focused on short-term cardiovascular risk during the first treatment episode. The relatively brief average exposure for both drugs (Table) was a reflection of actual use patterns. Although the exposure patterns are likely typical, they limit the information on risk associated with longer use. Since we excluded individuals with recent cardiovascular outcomes, the analysis provides no information about this high-risk population.

The analysis adjusted only for age group, sex, and data partner, so there may be residual confounding by other variables. Since the average follow-up length differed between the varenicline initiators and all bupropion initiators, the results might be biased if there were time-varying hazards or confounders that affected treatment persistence.6, 7
eReferences


