Wrong-way driving (WWD) is a dangerous behavior, especially on high-speed divided highways. The nature of WWD crashes makes it difficult for agencies to combat them effectively. Advanced WWD countermeasures equipped with flashing lights, detection devices, and cameras have been shown to significantly reduce WWD. However, the cost of these countermeasures means that agencies often cannot deploy these countermeasures at all exit ramps. To help agencies identify the most cost-effective deployment locations, an innovative WWD countermeasure optimization approach was developed. This approach consists of a WWD crash risk (WWCR) model and a WWD countermeasures optimization algorithm. The WWCR model uses non-crash WWD events, interchange designs, and traffic volumes to predict the number of WWD crashes on multi-exit roadway segments. Then, the optimization algorithm uses these WWCR values to identify the optimal exits for advanced WWD countermeasure deployment based on available resources and other applicable constraints. This approach was applied to the Central Florida Expressway Authority (CFX) and Florida’s Turnpike Enterprise (FTE) toll road networks. In both applications, the optimization algorithm helped the agencies achieve significant WWCR reduction while meeting investment and other constraints and better allocate their resources compared to only following the results of the WWCR model. The optimization algorithm was also used to identify mainline sections on the CFX network with high WWCR. Finally, the optimization approach was used to evaluate the existing Rectangular Flashing Beacon (RFB) advanced WWD countermeasures on the CFX network and the Light-Emitting Diode (LED) and RFB advanced WWD countermeasures on the FTE network. These evaluations showed that the crash reduction and injury reduction benefits of these advanced WWD countermeasures currently deployed by FTE and CFX have exceeded the costs since these countermeasures have been deployed. By using this WWD countermeasures optimization approach, agencies throughout the United States could proactively and cost-effectively reduce WWD.