Wrong-way driving (WWD) has been problematic on United States highways for decades despite its rare occurrence. Since WWD crashes are rare, recent researchers have studied WWD non-crash events such as WWD 911 calls and WWD citations to understand the overall nature and trend of WWD. This paper demonstrates the regional nature of the WWD problem and proposes regional transportation systems management and operations (Regional TSM&O) solutions to combat this problem. Specifically, it was found that 11% of all WWD multi-data events (e.g., multiple 911 calls for the same WWD event) traveled from one county to another. Additionally, 30% of all WWD single-data and multi-data events occurred at or near interchanges between two limited access highways in counties with multiple operating agencies. This indicates that a significant proportion of WWD events could potentially travel from one limited access facility to another. Moreover, 28% of WWD events occurred on limited access facilities shared by multiple agencies. To emphasize the regional nature of WWD, this paper determined the vulnerable demographic groups in different regions of Florida by developing WWD crash and citation prediction models. The models’ findings indicate that certain demographic groups (such as elderly or Hispanic) increase WWD risk. The models’ results can be used to improve driver education and increase law enforcement presence in high risk WWD locations. Regional TSM&O solutions, such as coordination and communication among agencies and regional traffic management centers (RTMCs), law enforcement co-location with RTMCs, and strengthening statewide TSM&O programs to manage WWD events are also proposed.