Abstract: For care of the chronic disease (e.g., depression, diabetes, hypertension), it is critical to identify the effective treatment pathway which aims to promptly switch prescriptions following the change of patient state and disease progression. However, this task is challenging because the optimal treatment pathway for each patient needs to be personalized due to the significant heterogeneity among individuals. Therefore, it is naturally promising to investigate how to use abundant electronic health records (EHRs) for effective and safe treatment recommendation, which needs to consider multiple aspects of life-critical evidence. In this work, we propose a novel prescription recommendation framework named OntoPath to predict the next drug in treatment pathway, by integrating multiple medical evidence from domain knowledge guidance, medical history profiling, and side information utilization. Extensive experiments on a large-scale depression patient cohort from a real-world medical claims database with over 37-thousand patients are performed for evaluation. The results demonstrate the effectiveness of OntoPath through the consistent outperformance over the state-of-the-art baselines, and the interpretability of model mechanism in case studies.