OBJECTIVE: To evaluate the relationship between antidepressant medication adherence and short-term disability (STD) in an employed population. **STUDY DESIGN:** Retrospective observational cohort study of 2112 employees with a new episode of treatment with an antidepressant medication (selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors). **METHODS:** Both Health Plan Employer Data and Information Set (HEDIS) acute and continuation treatment guidelines were applied to categorize patients' medication adherence. STD events were followed for 365 days after the date that an initial antidepressant medication prescription was filled. The association between STD and adherence was analyzed with multiple logistic regression models, adjusting for demographic and other confounding factors. **RESULTS:** A total of 1301 employees (61.6% of 2112) adhered to acute phase treatment, and 966 (45.7% of 2112) remained adherent to continuation phase treatment. After adjusting for sociodemographic factors, employees nonadherent with acute treatment were 38.7% more likely to have STD claims than adherent employees (odds ratio [OR] = 1.387; 95% confidence interval [CI] = 1.025, 1.876; P = .0339); and employees nonadherent with continuation treatment were 46.1% more likely to have STD claims than adherent employees (OR = 1.461; 95% CI = 1.071, 1.993; P = .0167). **CONCLUSIONS:** A higher incidence of STD was associated with antidepressant medication nonadherence in both acute and continuation treatment phases. Employers may save indirect costs by providing assistance to encourage employees to adhere to their antidepressant medication treatment.