Abstract: Mental health refers to a wider range of activities directly or indirectly related to mental well-being. Mentally ill patients in Kenya are increasingly becoming prone to a high risk of poly-pharmacy, complex therapeutic regimen and frequent modification of therapy. The objective of this study was to assess the prevalence and severity of potential drug-drug interactions among mentally ill patients admitted at Mathari Mental Hospital in Nairobi County, Kenya. The study was designed in a retro-active descriptive cross-sectional study of medical records data of patients who had undergone mental treatment and were admitted at Mathari Mental Hospital between July and December 2013. This study focused on a population comprising of all mentally ill patients of either gender who were admitted and put on a medication during the study period and aged between 13 and 75 years. One hundred and seventy five patient files were sampled. Married and unemployed patients had a statistically significant (p<0.05) association with a prevalence and severity of potentially serious drug interaction. Participants with a bipolar mood disorder had a statistically association with potentially serious drug interactions [OR 4.39 CI (1.09, 17) p=0.04] there was a statically significant association of potentially serious drug interactions with fluphenazine [OR 10.38 CI (4.66, 23.1) p<0.01], haloperidol [OR 4.39 CI (2.29, 8.41) p<0.01] and amitriptyline [OR 3.39 CI (1.36, 8.41) p=0.01]. Married, unemployed and patients on Fluphenazine, haloperidol, amitriptyline ad chlorpromazine were at a higher risk of having potentially serious drug-drug interactions. We recommend continuous electrocardiogram for patients on specific anti-psychotics like haloperidol. Key words: Mental health, Drug Interaction, Prescriptions