Drug-related deaths have reached epidemic levels in the United States and are partly responsible for recent declines in U.S. white life expectancy. Rising deaths from drug use are said to reflect an epidemic of despair among U.S. whites, evidenced also by increases in deaths related to alcohol use and self-harm. These “deaths of despair” are thought to be caused by rising economic distress and hopelessness among certain cohorts of U.S. whites. An alternative explanation for U.S. drug-related mortality trends emphasizes rising availability of opioid-based pain relievers (OPRs). This study documents state- and county-level trends in U.S. white men’s and women’s drug-related mortality rates between 1990 and 2015 and tests the despair-based explanation and availability-based explanation by examining: 1) how states’ drug-related mortality rates have changed across periods and across birth cohorts, 2) how county-level trends in drug-related deaths track with deaths from alcohol use and suicides, 3) how worsening economic conditions affect counties’ drug-related death rates, and 4) how an exogenous “pill dump” in Mingo County, West Virginia affected drug-related death rates. The popular despair-based explanation for rising drug-related mortality among U.S. whites is not supported by empirical evidence. Increases in drug-related death rates among U.S. whites have been unrelated to worsening economic conditions and independent of mortality trends from alcohol use and suicides. Changes in drug-related mortality rates track strongly with the timing of increased availability of OPRs and other changes in the U.S. drug environment.