FDA Black Box Warning and Suicide

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| **Project Name:**  Longitudinal Analysis of SSRI Warnings and Suicide in Youth |
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| **Principal Investigator institution**:  Harvard Pilgrim Health Care |
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| **Abstract:**  Approximately 14-25% of youth experience major depression before adulthood; about 9% of adolescents attempt suicide and 2.9% make a suicide attempt requiring medical attention. Treatment with antidepressant medications has been shown to improve mood and decrease suicidal ideation. However, there has been concern that antidepressants paradoxically increase the risk of suicidal behaviors following initiation of SSRI treatment. The FDA issued several public health advisories and a boxed warning since October of 2003 and, beginning in 2005, all SSRI labeling has required a “black box” warning (BBW) regarding the increased risk of suicidality in children and adolescents taking antidepressants. However, conflicting evidence concerning the true effects of SSRIs on the risk of suicidal behaviors in youth has generated much controversy. Studies following the BBW reported decreased rates of pharmacologic treatment for depression. Another study reported an 18% *increase* in completed suicides among youth in 2004 and 2005.  This research will contribute to research regarding unintended consequences of regulatory actions. The secondary aim is to assess the utility of sequential analysis for prospectively assessing signals of health policy impacts using the antidepressant warnings as a policy example. |
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| **Participating Sites:**  Harvard Medical School Department of Population Medicine and Harvard Pilgrim Health Care Institute, Boston, MA (Lead Site)  School of Pharmacy, Northeastern University, Boston, MA Center for Applied Health Research, Baylor Scott & White Health jointly with Central Texas Veterans Health Care System, Temple, TX  Department of Health Service Research, Kaiser Permanente Washington (Formerly Group Health), Seattle, WA  HealthPartners Institute, Minneapolis, MN  Center for Health Policy and Health Services Research and Behavioral Health Services, Henry Ford Health System, Detroit, MI  Kaiser Permanente Colorado, Institute for Health Research, Denver, CO  Health Management & Policy, Georgia State University School of Public Health and Kaiser Permanente Georgia, The Center for Clinical and Outcomes Research, Atlanta, GA  Center for Health Research, Kaiser Permanente Hawaii, Honolulu, HI  Division of Research, Kaiser Permanente, Oakland, CA  Center for Health Research, Kaiser Permanente Northwest, Portland, OR  Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA  Center for Biomedical Informatics, University of Tennessee Health Science Center, Memphis, TN  Department of Medicine, Division of Pharmacoepidemiology and Pharmacoeconomics, Harvard Medical School, Brigham and Women’s Hospital, Boston, MA |
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| **OBJECTIVE:** To investigate if the widely publicized warnings in 2003 from the US Food and Drug Administration about a possible increased risk of suicidality with antidepressant use in young people were associated with changes in antidepressant use, suicide attempts, and completed suicides among young people. |
| **DESIGN:** Quasi-experimental study assessing changes in outcomes after the warnings, controlling for pre-existing trends. |
| **SETTING:** Automated healthcare claims data (2000-10) derived from the virtual data warehouse of 11 health plans in the US Mental Health Research Network. |
| **PARTICIPANTS:** Study cohorts included adolescents (around 1.1 million), young adults (around 1.4 million), and adults (around 5 million). |
| **MAIN OUTCOME MEASURES:** Rates of antidepressant dispensings, psychotropic drug poisonings (a validated proxy for suicide attempts), and completed suicides. |
| **RESULTS:** Trends in antidepressant use and poisonings changed abruptly after the warnings. In the second year after the warnings, relative changes in antidepressant use were -31.0% (95% confidence interval -33.0% to -29.0%) among adolescents, -24.3% (-25.4% to -23.2%) among young adults, and -14.5% (-16.0% to -12.9%) among adults. These reflected absolute reductions of 696, 1216, and 1621 dispensings per 100,000 people among adolescents, young adults, and adults, respectively. Simultaneously, there were significant, relative increases in psychotropic drug poisonings in adolescents (21.7%, 95% confidence interval 4.9% to 38.5%) and young adults (33.7%, 26.9% to 40.4%) but not among adults (5.2%, -6.5% to 16.9%). These reflected absolute increases of 2 and 4 poisonings per 100,000 people among adolescents and young adults, respectively (approximately 77 additional poisonings in our cohort of 2.5 million young people). Completed suicides did not change for any age group. |
| **CONCLUSIONS:** Safety warnings about antidepressants and widespread media coverage decreased antidepressant use, and there were simultaneous increases in suicide attempts among young people. It is essential to monitor and reduce possible unintended consequences of FDA warnings and media reporting. |
| **Major Goals:**   * Examine the combined effects of FDA warnings and media coverage on changes in antidepressant use, suicide attempts, and suicides among children/adolescents, young adults and adults. * Evaluate the utility of sequential analysis for prospectively assessing signals of health policy impacts using FDA antidepressant warnings and related media coverage as policy example. |
| **Description of study sample:**  Records data from 11 MHRN health systems were used to examine time trends in rates of antidepressant use, suicide attempt, and suicide death before, during, and after FDA advisories regarding suicidality during antidepressant treatment.  The combined sample included approximately 1.1 million adolescents aged 10-17, 1.4 million adults aged 18-29, and 5 million adults aged 30-64. |
| **Current Status:** *(write 1-2 sentences describing the project status; include current date)*  We investigated the reliability of E-codes within the 11 MHRN health systems over the study period and found e-codes were largely incomplete in these databases; this analysis has been published (see below). We have completed the analyses using the interrupted time series methods. This analysis has been published in the BMJ (see below). We have completed the sequential analysis that will be published soon in Medical Care. |
| **Study Registration:**  N/A |
| **Publications:**  Lu CY, Stewart C, Ahmed AT, Ahmedani BK, Coleman K, Copeland LA, Hunkeler EM, Lakoma MD, Madden JM, Penfold RB, Rusinak D, Zhang F, Soumerai SB. [How complete are E-codes in commercial plan claims databases?](https://www.ncbi.nlm.nih.gov/pubmed/?term=How+complete+are+E-codes+in+commercial+plan+claims+databases%3F) Pharmacoepidemiol Drug Saf. 2014 Feb;23(2):218-20. doi: 10.1002/pds.3551.  Lu CY, Zhang F, Lakoma MD, Madden JM, Rusinak D, Penfold RB, Simon G, Ahmedani BK, Clarke G, Hunkeler EM, Waitzfelder B, Owen-Smith A, Raebel MA, Rossom R, Coleman KJ, Copeland LA, Soumerai SB. [Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study](https://www.ncbi.nlm.nih.gov/pubmed/?term=Changes+in+antidepressant+use+by+young+people+and+suicidal+behavior+after+FDA+warnings+and+media+coverage%3A+quasi-experimental+study). BMJ. 2014 Jun 18;348:g3596. doi: 10.1136/bmj.g3596. |
| **Resources:**N/A |
| **Lessons Learned:**   * Completeness of e-codes varies significantly over time, across treatment settings and across study sites. Improvements in e-coding in commercial health plan datasets are critical for injury research. * In the meantime, poisoning by psychotropic drugs appears to be a useful proxy for identifying suicide attempts leading to emergency room visits and hospitalizations. * There were substantial reductions in antidepressant use among all age groups and simultaneous, small increases in psychotropic drug poisonings, a validated measure of suicide attempts, among adolescents and young adults following the FDA warnings. These results were consistent across 11 geographically diverse U.S. study sites. Media exaggeration about FDA reports of drug risks may reduce appropriate drug use and increase adverse outcomes. We did not detect changes in completed suicides after the warnings, which is an extremely rare outcome. |
| **What’s Next?** The Virtual Data Warehouse (VDW) provides a rich resource for multi-site research.  The longitudinal nature of the VDW enables longitudinal analyses that are necessarily part of the interrupted time series method, a strong quasi-experimental study design.  *Manuscript in-press publication at Medical Care*: Lu, CY, Penfold RB, Toh S, Sturtevant J, Madden JM, Simon G, Ahmedani BK, Clarke G, Coleman KJ, Copeland L, Daida Y, Davis RL, Hunkeler EM, Owen-Smith A, Raebel MA, Rossom MA, Soumerai SB, Kulldorff M. Near real-time surveillance for consequences of health policies using sequential analysis.   *Manuscript in-press publication at Medical Care:* Lu, CY, Simon, G, Soumerai, SB, Kulldorff, M. Early warning systems are imperfect, but essential.  *Manuscript in-press publication at Medical Care:* Lu, CY, Simon, G, Soumerai, SB. Staying honest when policy changes backfire. |
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