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Counterpoint: Staying Honest When Policy Changes Backfire

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Abstract

Despite the good intentions of FDA, many drug warnings are ineffective or have unintended consequences, particularly if the media exaggerates the messages and scares the public. The controversial 2003–04 FDA warnings on youth suicidal ideation associated with antidepressant use are a case in point. In a 10-year interrupted time series analysis (ITS) in 11 health plans, we found that the warnings and hyped media coverage led to substantial reductions in antidepressant use (declines in antidepressant use and overall care corroborated in several studies), and small, visible increases in ER and inpatient poisonings with psychotropic drugs. In a gross misunderstanding of the method, Dr. Stone calls ITS, "an intuition based upon false analogies, fallacious assumptions and analytical error." We demonstrate visually in landmark studies that ITS is one of the oldest (hundreds of years) and strongest quasi-experimental study designs, and that his alternative data analyses do not even have rates (denominators), nor baselines, so the measures of change are invalid.

Dr. Stone's commentary mixes concerns about our current paper[1] regarding surveillance methods (that is, hypothesis generating) with criticisms of our 2014 British Medical Journal paper[2] using interrupted time series analysis to examine consequences of the antidepressant warnings and media coverage (that is, hypothesis testing). Before responding to his specific concerns, we should clarify the important distinction between the two papers. Our 2014 paper[2] used an interrupted time series (ITS) design to examine changes in rates of antidepressant prescribing and suicide attempts following the antidepressant warnings and associated worldwide press coverage (often exaggerated—see below). We concluded that "…the FDA warnings and media coverage led to substantial reductions in antidepressant use, which were associated with small increases in suicide attempts by poisonings among young people." We also referenced multiple papers showing that the chilling effects of the warnings and media reports were also associated with decreases in mental health care. We stand by that report and we believe our conclusions were reasonable and prudent. We should

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conduct such studies carefully because they suggest a continuing public health threat in a vulnerable population. Our more recent paper[1] uses sequential analysis to assess whether signals of a policy effect could have been detected earlier rather than to make a causal inference regarding the effects of FDA antidepressant warnings. We concluded that "…the advantage of sequential analysis is to quickly and efficiently detect signals of excess risk that can then be thoroughly investigated in rigorously designed studies." We did not and would not claim that sequential analysis supports strong causal inference. It is instead a method for early signal detection. See our first Counterpoint.[3]

Dr. Stone is Deputy Director for Safety, Division of Psychiatric Products at the US FDA, and served as a Medical Reviewer pertaining to Antidepressants and Suicidality in adults.[4] While we believe that Dr. Stone and colleagues recommended antidepressant warnings with the best of intentions, our earlier paper demonstrates that the warnings and associated publicity had unfortunate unintended consequences. We are not surprised that Dr. Stone vigorously defends the FDA's warnings, but based on professional and ethical standards he should acknowledge his role and his conflicts of interest upfront and transparently.

Our responses to Dr. Stone's methodological criticisms common to both papers are presented here. Several of Dr. Stone's comments imply that our work involved post-hoc searching for a desired result. This is simply false. Our study questions, data sources, exposure definition, outcome definitions, and analytic methods were specified in advance and vetted by NIH peer review.

The policy and media exposures

Dr. Stone states repeatedly that we evaluated only the independent effect of FDA warnings when we stated repeatedly in both papers that we were studying the combined effects of the warnings and the much more powerful worldwide publicity accompanying them. In fact, warnings or regulatory actions generally have been shown to have little or no effect on clinical behavior (including several of our studies).[5–8] Major reinforcement by media was found to be a consistent factor in all studies finding significant impacts of FDA regulatory actions (e.g., aspirin use in Reye's Syndrome[7], antidepressant use and suicidality in youth[2], propoxyphene misuse[8]). Furthermore in the systematic review conducted for FDA by Briesacher et al,[6] the authors concluded: "Additionally, in all cases where significant intended impacts were detected, the investigators noted intensive communication efforts including widespread media attention as a key to successfully changing prescribing patterns." Consistent with our findings, they concluded that "50% found no impact or weak/modest impacts of FDA actions and 33% detected unintended consequences."[6]

The antidepressant warnings were widely publicized by media reports.[9] Many news stories used anecdotes and emphasized the risk of antidepressant use by children and adolescents.[9] Thus, well intended safety warnings became frightening alarms to clinicians, parents, and young people. Examples are: A *New York Times* headline stated "FDA links drugs to being suicidal;"[10] The *Washington Post* reported "FDA confirms antidepressants raise children's suicide risk;"[11] *USA Today* reported "Could antidepressants prescribed for…children and teenagers cause some of them to attempt suicide?"[12] *The New York* Post reported "Federal

health experts yesterday declared that…antidepressants may be dangerous to children…and may make youngsters suicidal;"[13] and USA Today's headline stated "Suicide alert has parents rethinking antidepressants."[14]

Given the widespread media coverage, we stated consistently that the combination of FDA warnings and media reports were the policy exposure, not the warnings alone, as misunderstood by Dr. Stone. We did not attempt to isolate warnings on package inserts, and assess their effects independent of media reports, which was impossible.

It is important to state that we agree with the FDA boxed warnings and advisories based on the less-than-optimal data available at the time. We agree with the time-honored practice of erring on the side of public health, despite these threats to validity. The advisories suggested that clinicians be alert to such suicidal thoughts at the start of treatment. We stated that this message was appropriate. FDA did not recommend withholding potentially life-saving treatment or that antidepressants "caused" suicide. But, as we discuss above, the worldwide media often exaggerated the warnings into fear appeals, often stating that antidepressants "*caused*" suicide in youth. What would common sense dictate about the behavioral effects of such exaggerated headlines on parents and youth? It is these communications that likely reduced antidepressant use by 20–30% among all youth and those who had a depression diagnosis in our and several other studies.[2, 15–20] Outpatient mental health visits did not increase as intended after the warnings,[19, 21] probably because the media did not cover the recommendation of increased monitoring of treated patients.

Dr. Stone questions our specification of time period for exposure to antidepressant warnings and associated publicity. We agree that this exposure was complex, involving FDA announcements, implementation of labeling changes, and associated publicity. Consequently, our original study protocol specified that observations from the fourth quarter of 2003 to the fourth quarter of 2004 (about one year in the 10-year observation period) would all be considered part of the implementation period and excluded from our earlier ITS analyses. Our more recent sequential analyses adhered to that a priori decision.

Dr. Stone asserts that we could not begin to evaluate the FDA warnings (again, actually, the media) because they stretched out so long over time. In contrast to Dr. Stone's assertions, Figure 1 shows that the major advisories, warnings and news reports were concentrated in the 2003–2005 period. Dr. Stone is concerned with events occurring years after the warnings. The single advisory in 2007 concerning young adults was simply not covered by the press and had no apparent effects. Appropriately, our analyses concentrated on the earliest changes in antidepressant use or suicide attempts after the warnings and media reports, and we did not even calculate effect sizes beyond two years after the policy. The thousands of news reports by major media outlets likely outweighed any direct effects of drug labelling.

The data source and study cohorts

Dr. Stone questions our methods of selection of 11 participating health systems. Again, our NIH protocol showed that our participating health systems were selected a priori, based on

three criteria: comprehensive records for a defined and stable population, consistent and complete ascertainment of antidepressant medication dispensings from 2000 through 2010, and complete and consistent ascertainment of suicide attempts (psychotropic drug poisoning diagnoses) and suicide deaths from 2000 to 2010. *None* of the alternative data sources Dr. Stone suggests satisfy those criteria (discussed below).

Dr. Stone also questions the generalizability of our study cohorts. The 11 participating health systems are members of the Mental Health Research Network (MHRN), a national network of health systems that has received funding for 12 federal studies. Together these systems provide care to a diverse population of 10 million people in 12 states. Members are enrolled through employer-sponsored insurance, individual insurance plans, and capitated Medicare and Medicaid programs. Members served by these systems are generally representative of each system's geographic service area. See our previously published article[2] for a comparison of demographic characteristics between the study cohort and the US general population. The generalizability of this data source is beyond doubt.

This Network, funded by the NIH since 2010, was *not* created *arbitrarily* for this project, as implied by Dr. Stone, nor are the effects "cherry picked". Study aims and details of methods were specified in advance and only implemented after NIH peer review. We suggest that there should be a registration of observational studies, as it is the case for clinical trials. If such a registry had existed, we certainly would have registered our studies so there would be no questions about post-hoc searching for a desired result.

Inappropriate "alternative" databases for studies of this policy

Dr. Stone suggests a number of databases that might contain information on suicidality in the US over time. But there are major limitations in terms of their suitability for examining the antidepressant warnings and media coverage.

- ***Non-fatal injury database produced by the Centers for Disease Control and Prevention***[22]: WISQARS Nonfatal provides data from the National Electronic Injury Surveillance System-All Injury Program (NEISS-AIP).[23] The main limitation of this dataset for evaluating this policy is that only yearly data are available from 2001; thus, there are only 3 pre-policy data points (2001, 2002, 2003), making it impossible to measure historical trends (the counterfactual) and policy effects.[24–26] It is not an acceptable design by international standards, i.e., Cochrane Systematic Reviews.[27] It is impossible with such a meager baseline to estimate what would have happened in the absence of the policies. (It is impossible to reliably fit a trend line to three points.) What's more, as a hospital system, it is impossible to know the rates of hospital events because there is no denominator of patients in the community. It is impossible to observe antidepressant dispensings in a hospital database. We used events and denominators of enrolled patients in both studies.[1, 2]
- ***Data from the Drug Abuse Warning Network (DAWN)***[28]: Dr. Stone emphasizes DAWN in major critiques over several pages of his commentary. It has similar flaws for this work. DAWN provides a surveillance system to monitor drug

related emergency department (ED) visits to hospitals since the early 1970s. These are counts of events without denominators and therefore there is no population rate over time, disqualifying it from studies based on elementary criteria. In addition, the survey methodology of DAWN has been modified for improvement over time with the current approach implemented in 2004. Thus, use of this dataset for investigating this policy likely introduces instrumental bias. In essence, this dataset can only provide post-policy data for this policy. Studies of effects of policies without a baseline would never be considered evidence from the start, a fact known by our doctoral students. And, yet again, this data set does not include routine data on outpatient antidepressant dispensings.

- ***Data from Youth Risk Behavior Surveillance System (YRBSS)***[29]*:* YRBSS includes national and local school-based surveys to monitor health-risk behaviors among youth and adults. The main limitation of this dataset is that it is based on an in-class pencil-and-paper survey of school children's suicidal ideation and behaviors.[30] Self-reported measures are severely compromised by recall and social desirability biases.[31]
- ***Health Care Utilization Project (HCUP)***[32] ***databases***: The National (Nationwide) Inpatient Sample (NIS)[33] approximates a 20-percent stratified sample of all discharges from U.S. community hospitals. However, inpatient encounters represent only about a third of medical encounters for suicide attempts.[34, 35] The Nationwide Emergency Department Sample (NEDS)[36] approximates a 20-percent stratified sample of U.S. hospital-based EDs. Unfortunately, the NEDS data are available only from 2006, which would provide post-only data that are inadequate for evaluating this policy with an acceptable research design. Of course, the hospital and ED data include no denominators and, yet again, it is impossible to construct rates of adverse outcomes over long observation periods, as we did.
- ***California injury data***[37]: This data base contains information about nonfatal injuries comes from both hospital discharge data and ED data for the entire state including external cause of injury (E-code). The main limitation of this dataset is that the ED data on self-harm are only available from 2006; two years after the warnings; thus, it is inadequate for examining this policy without a baseline using an acceptable research design.[26] The hospital visit data on self-harm are available from 1991 but as noted above, inpatient encounters represent only about a third of medical encounters for suicide attempts.[34, 35] Again, as a hospital database, it excludes denominator patients and cannot construct population rates of outcomes over time. It simply fails basic criteria for studying the outcomes of policies.

Inappropriate explanations for policy effects

Dr. Stone suggests that generic penetration of several antidepressants around the time of the 2004 warnings and media reports as alternative explanations for changing patterns of

antidepressant use over the study period. However, the literature does not support his hypothesis. In fact, the study by Pamer et al[38] found that promotional spending on all antidepressant drugs declined between the first quarter of 2004 and the first quarter of 2007 (after the 2004 warnings and media reports). Market entry of low-cost generic antidepressants occurred throughout our observation period; thus, it could not explain the sudden change in trend. Ventimiglia et al[39] actually found that generic antidepressants substituted for branded antidepressants; thus, overall use of antidepressants did not change due to market changes. In addition, both studies presented post-only information (only after the policy), which is the weakest and most invalid evidence on effects of policies.[26] There are no data on pre-post changes in medication use so no valid inferences are possible. In addition, there are multiple studies that corroborate our finding that the warnings and media reports were followed by 20–30% reductions in antidepressant use.[2, 15–20]

Dr. Stone further suggests regression toward the mean as a possible explanation for our findings on reduced antidepressant use. This bias occurs when investigators select a group above the mean at baseline for a particular outcome (e.g., health care use); then the utilization almost always falls at follow-up due to the imperfect reliability of measures. While very important, Dr. Stone's "punt" of this bias has no relevance to our study because we did not select outlier study subjects. We followed the entire experience of all members of 11 health systems. Regression toward the mean is not a plausible alternative explanation.

The outcome measures

Dr. Stone questions our use of psychotropic drug poisoning diagnoses as a proxy for self-harm or suicidal behavior. In this one area, our published analyses do depart from our original study protocol. We originally proposed to examine changes in rates of diagnosed self-harm as indicated by ICD9-CM E-code diagnoses regarding intent of injury (self-inflicted, accidental, undetermined, etc.). Unfortunately, our quality control analyses[40] demonstrated marked variability in use of E-code diagnoses across health systems and over time within health systems. Consequently, our published analyses consider a proxy measure, diagnosis of psychotropic drug poisoning (positive predictive value, 79.7% and specificity 99.3%) regardless of E-code diagnosis. High specificity is an important criterion for outcome measures as it estimates the extent to which positives really represent the outcome of interest (that is, we can believe what we are observing is true with few false positives). There is no evidence suggesting ICD-9 coding practice changed over time. Obviously, by using this measure we are underestimating suicide attempts because attempts by other means are not counted. Nevertheless, our analyses found an abrupt change in the rate of this proxy outcome. It is important to note that the completed suicides – our other measure – are derived from state death registries with causes of death information; this measure is not vulnerable to similar limitations. We are puzzled by Dr. Stone's references to emergency department encounters for marijuana use and to data from the Drug Abuse Warning Network. Our outcome definition (ICD9-CM code: 969) included only poisonings by prescription psychotropic medications (antidepressants, antipsychotics, benzodiazepines, stimulants, etc.). We did not have any hypotheses regarding effects of the antidepressant warnings and media coverage on drug abuse or drug abuse diagnoses.

The interrupted time series method

We are puzzled by the dramatic tone of Dr. Stone's blanket statement regarding the lack of utility of ITS designs in causal inference, "an intuition based upon false analogies, fallacious assumptions and analytical error." We of course recognize that no study or design is perfect (what a boring science that would be). The ITS is a well-established and important method that has been used in thousands of research studies[41] over hundreds of years (see below). It has demonstrated health effects of policies that could never be randomized.[41] Medical Care has published dozens of ITS studies (including our own).[42–46] An FDA sponsored review identified ITS as one of the preferred methods to evaluate FDA regulatory actions.[6]

Dr. Stone claims that ITS is only used to predict future trends. This is incorrect.[41] But interrupted time series is exactly what its name implies. It controls for secular trends in study outcomes and assesses whether or not a policy causes abrupt changes in the level or the pre-existing trend (slope) of study outcomes.[2] This method is accepted in leading texts on experimental and quasi-experimental research design[26] and worldwide as a strong design in natural experiments. It is robust against most threats to internal validity.[26] Figure 2 is an example of visible effects of the combined warnings and media reports on both antidepressant use and psychotropic drug poisonings among adolescents.

Figure 3 is an example of a clear non-effect of FDA's warnings *alone* attempting to reduce refills of the narcotic analgesic, propoxyphene (it was removed from the market decades later, in part due to this study). This further supports the view[6] above that media reinforcements are usually necessary to affect prescribing change.

One example (Figure 4) is a landmark study showing the lives saved after implementation of a hospital hand-washing policy by the preeminent medical researcher, Ignaz Semmelweis,[47] in the mid-1800s. The link between the start of handwashing and a marked reduction in maternal mortality could not be clearer, despite the variability of the rare maternal mortality outcome.

Another example (Figure 5) is the initiation and removal of a cap on medication reimbursements in Medicaid, a natural experiment that does not allow an RCT to show its disturbing effects on medication access among the poor and chronically ill.[48–50] The instantaneous level changes are so large that the findings are as clear as an RCT. The immediate reversal in the trend of study outcomes one year later when the policy was withdrawn further enhances its validity. This and its follow-up studies have been used by CMS and Congress, numerous state Medicaid agencies, and advocacy organizations for the elderly and mentally ill to provide low income subsidies in Medicare Part D and reverse restrictions in medication access among vulnerable populations throughout the US.[51–53]

Conclusions

We agree with Dr. Stone that our two papers used relatively old data to address a question regarding a policy exposure more than ten years in the past. Our purpose, however, was to make two generalizable points. We believe our 2014 paper[2] demonstrated that well-intended policies can have unintended negative consequences, particularly when accompanied by

widespread media coverage that distorted the original messages. Our current paper[1] indicates that sequential analyses might allow earlier detection of signals of those unintended consequences that can then be thoroughly investigated in rigorously designed studies, such as ITS. Those generalizable points are certainly not obsolete. As we confront a national crisis of increasing opioid overdose deaths, regulators and legislators must consider various urgent policy responses. Random assignment to alternative policies is not a realistic option. The methods we have used in our two papers (sequential analyses for early detection, interrupted time series for causal inference) will be essential tools in examining the impact of those policy responses. We sincerely hope that we are able to accurately identify and evaluate effects of opioid policy changes in less than ten years.

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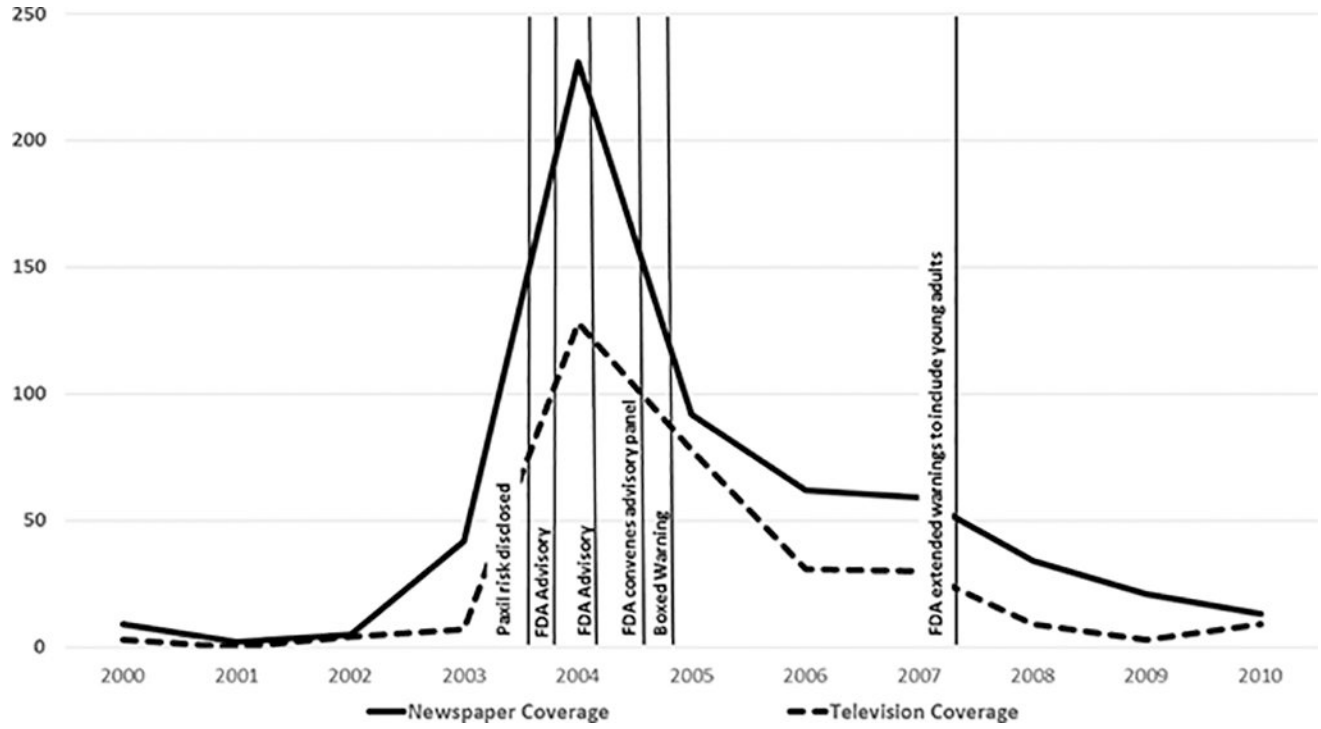

Figure 1.

U.S. newspaper and television coverage of stories on pediatric antidepressant use and suicidality 2000–2010 from LexisNexis. We used LexisNexis database to collect data from all U.S. newspapers and U.S. TV transcripts from four major news networks CNN, ABC, CBS, and NBC. The search terms used were: suicid! AND (antidepressant! OR anti-depressant! OR antidepressiv! OR SSRI!) AND (child! OR pediatric!) AND FDA!

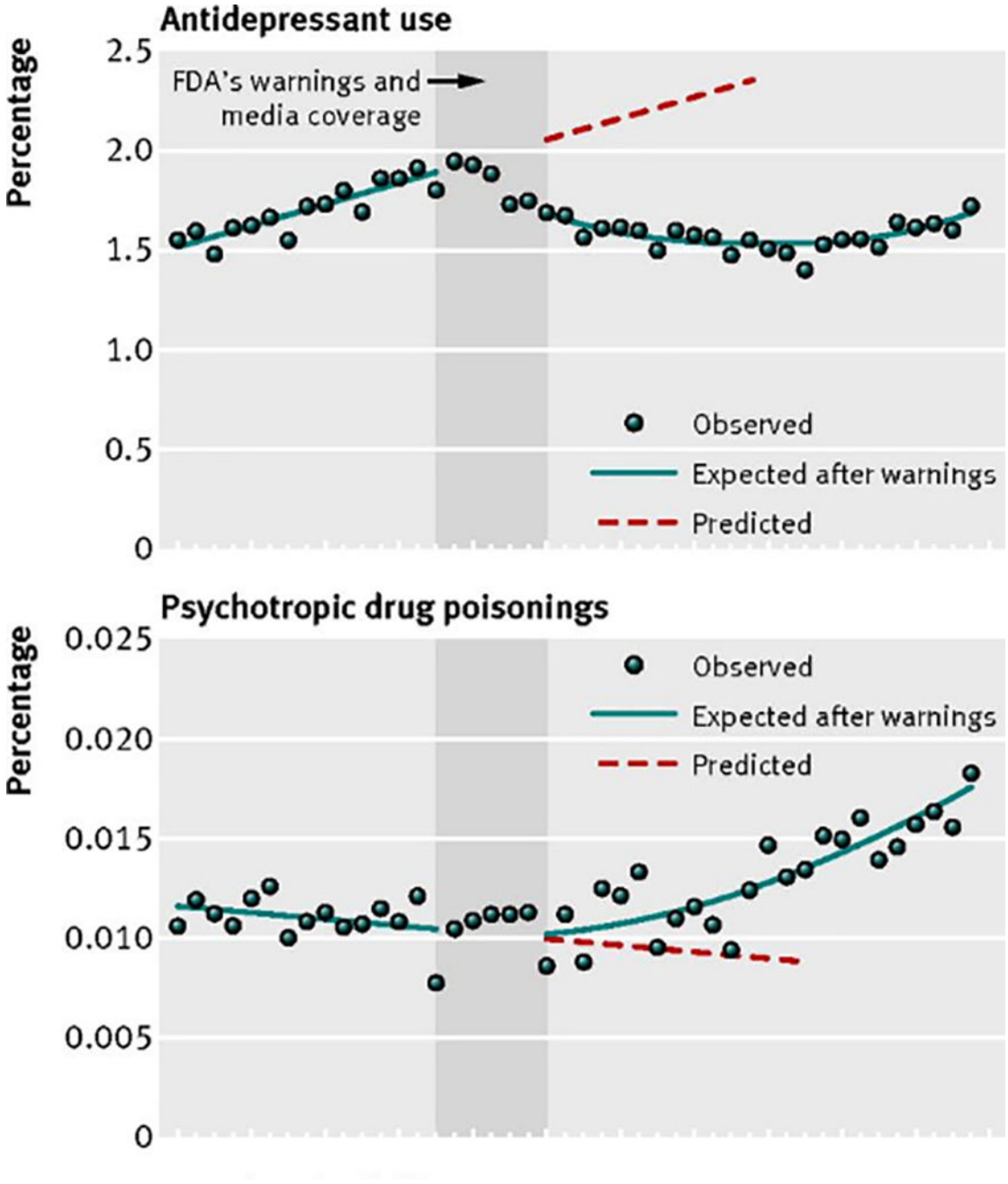

Figure 2.

Rates of antidepressant use and psychotropic drug poisoning per quarter before and after the warnings among adolescents enrolled in 11 health plans in nationwide Mental Health Research Network. Reproduced with permission from British Medical Journal.

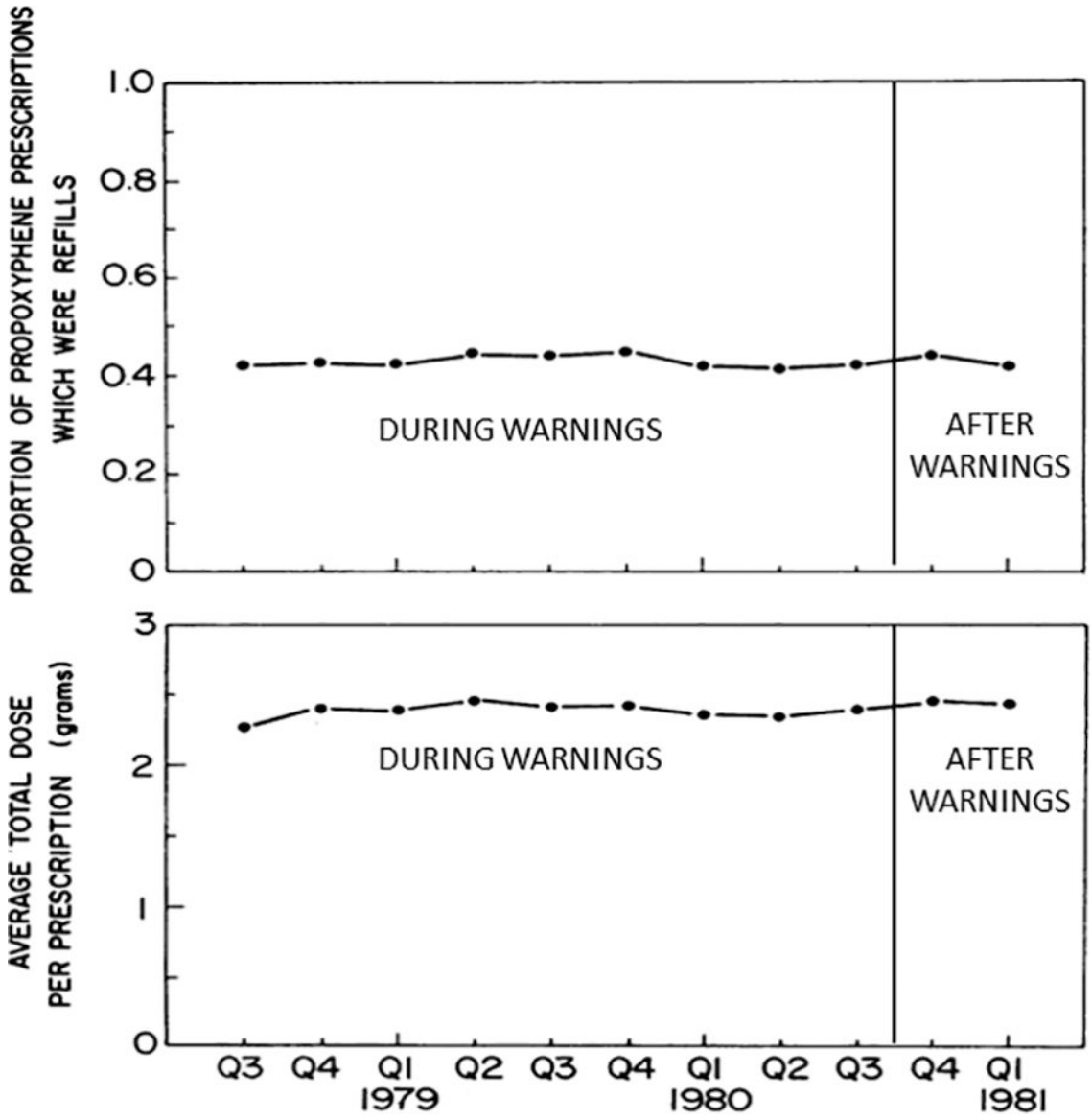

FIGURE 2—Trend in Propoxyphene Refill Rates (top half) and Dose per Prescription (bottom half) Dispensed by Retail Pharmacies in the US by Quarter from July 1978 through March 1981
Data provided from US FDA, based on National Prescription Audit.[23,26]

Figure 3.

No Effect of FDA Warning to Reduce Refills of Propoxyphene Reproduced with permission from American Journal of Public Health.

Trend in Propoxyphene Refill Rates (top half) and Dose per Prescription (bottom half) Dispensed by Retail Pharmacies in the US by Quarter from July 1978 through March 1981 Data provided from US FDA, based on National Prescription Audit.[23,26]

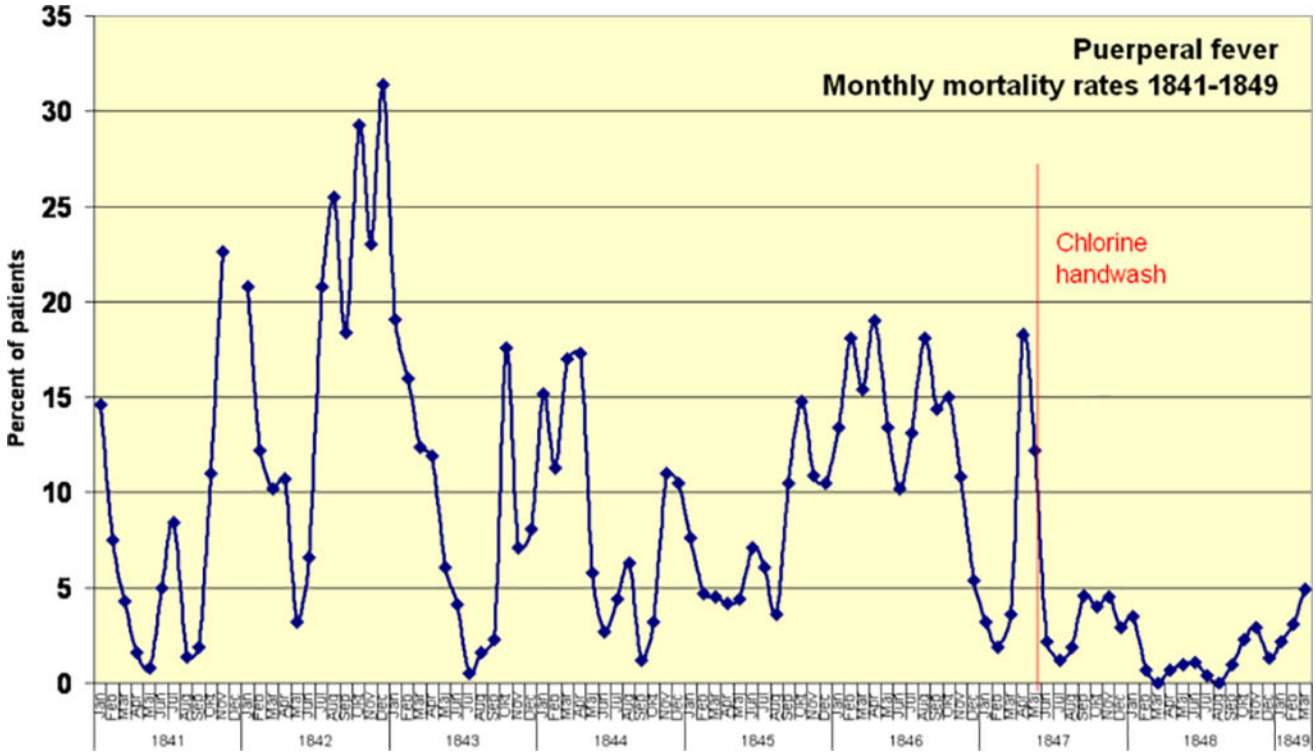

Figure 4.

Puerperal fever monthly mortality rates at Vienna Maternity Institution 1841–1849. Rates drop when implementing handwashing. Available publicly. Semmelweis I (1861). Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebers. [The etiology, concept, and prophylaxis of childbed fever]. Budapest and Vienna: Hartleben.

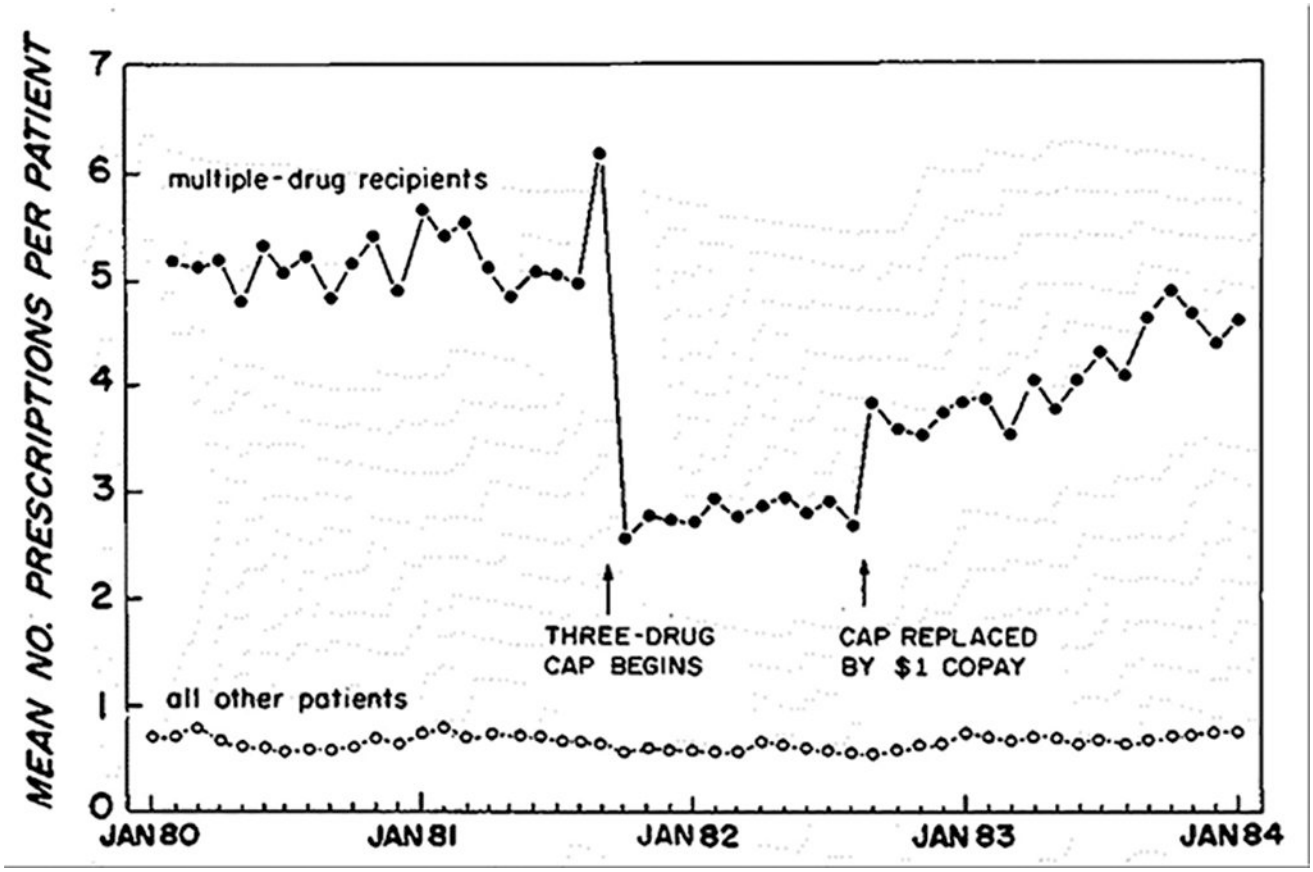

Figure 5.

Time Series of Average Number of Constant-Size Prescriptions per Continuously Eligible Patient per Month among Noninstitutionalized Patients Receiving Multiple Drugs (N=860) and Other Outpatients (N=8002). Reproduced with permission from The New England Journal of Medicine.