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The statistics of suicide

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1. Why is suicide so important to study?

Worldwide, there are about one million suicides annually. In the United States (USA) approximately 750,000 people died by suicide over the last 25 years. Suicides outnumber homicides by at least a 3:2 ratio in the USA. Deaths from suicide exceeded deaths from AIDS by 200 000 in the past 20 years. Four times as many Americans died by suicide during the Vietnam War than from wartime fatalities. [1] More deaths by suicide were recorded among American military during the recent Iraq and Afghanistan wars than were recorded for military related casualties.[2] Nonetheless, suicide is a rare event with an annual rate in the US of 12 per 100 000, making it an extremely difficult phenomenon to study using conventional approaches. Suicide is the third leading cause of death in adolescents 10 to 14 years of age in the US and the leading cause of death in this age group in several other countries including China, Sweden, Ireland, Australia and New Zealand.[1]

The enormous human cost of suicide in youth makes research and prevention a national priority. Over 90% of youth suicides in the USA are associated with psychiatric illness;[1,3,4] however, only 2% of youth suicides were on medication at the time of their suicide.[5,6] In a study of 49 adolescent suicides in Utah State, 24% had been prescribed antidepressants but none of them tested positive for antidepressants at the time of their death.[7] In a post-mortem study conducted on 66 youth suicides in New York City,[5] only four had measurable levels of antidepressants (2 with imipramine and 2 with fluoxetine).

Suicide is rare in younger children (less than 1/100 000 per year in 5- to 14- year-olds[1]), but it is more common after mid-adolescence. The annual rates in the US of 15- to 19-year-olds are 3 per 100 000 for girls and 15 per 100 000 for boys.[8] In contrast to suicide mortality, suicidal thinking and suicide attempts are relatively common: every year, 19% of teenagers 15 to 19 years of age in the general USA population have suicidal ideation and nearly 9% make a suicide attempt.[9] The rate of suicidal behavior is even more frequent in youth receiving care for depression; 35 to 50% have made, or will make, a suicide attempt[10-12] and between 2 and 8% will die by suicide over the decade following their first treatment.[10,11,13]

2. Why is suicide difficult to study?

For many reasons, suicide is one of the more difficult adverse events to study. First, suicide is a rare event so it is generally not possible to study completed suicide in RCTs or even in reasonably large pharmacoepidemiologic studies. Consequently, the suicidal events that form the basis for prevention measures (such as the FDA black-box warnings) are usually suicidal thoughts, which are far more prevalent than suicide completions or suicide attempts (particularly in psychiatric populations) but may be of limited value in predicting completed suicide.

Large scale pharmacoepidemiologic studies generally focus on suicide attempts or acts of deliberate self-harm, though in some cases they also include a small number of completed suicides, particularly in countries where national death registries are linkable to health services utilization data, which is generally not true in the USA. These observational studies often suffer from selection bias that can result in 'confounding by indication' and other problems which limit our ability to draw causal inferences. For example, patients with depression have both an increased risk of suicidal behavior and an increased likelihood of taking antidepressant medications; hence the appearance of an association between taking antidepressants and suicidal events that is invariably found is confounded by the indication for the use of antidepressants, namely depression. While antidepressants may increase risk of suicidal events, suicidal events definitely increase the

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likelihood of antidepressant treatment. As shown by Simon and colleagues,[14] the greatest risk of suicidal behavior is in the month prior to treatment initiation. The same confounding by indication problem exists for the purported role of anti-smoking medications and anti-epileptic medications in suicidal behavior: patients with psychiatric illness have elevated rates of smoking so they are more likely to use anti-smoking medications and several anti-epileptic medications are often prescribed as adjunctive treatment of bipolar disorder.

Selection effects are generally eliminated in RCTs, but RCTs are not without their own set of problems which limit inferences. As discussed above, given their limited size, RCTs are generally only able to examine suicidal ideation, which may tell us little about suicide risk. Traditionally, RCTs have not been designed to examine suicide risk; they are usually focused on retrospective spontaneous reports of suicidal thoughts and behaviors of study participants. Such data are subject to ascertainment bias[15] in which the method of eliciting the suicidal information can result in apparent differences in the rates of these events between treated subjects and untreated controls. For example, patients randomized to active medication will have more side-effects in general than patients randomized to placebo; this will result in greater contact with study staff and more opportunity to report suicidal thoughts and behavior. Similarly, suicide attempts in which the individual ingests the study medication will result in increased likelihood of detection among actively treated subjects because overdose of active medication (e.g., an antidepressant) will have a greater likelihood of emergency room contact than overdose of an inert placebo.

3. What do we know about suicide and antidepressants?

One of the greatest recent controversies in the safety of pharmaceuticals is the question of whether certain classes of medications (e.g., antidepressants) increase the risk of suicidal thoughts, behavior, and completion. In 2004, the US Food and Drug Administration (FDA) placed a black-box warning on all antidepressants because of concern that such medications increased risk of suicidal thoughts and behavior in children and, in 2006, extended the warning to young adults. These warnings are not limited to antidepressants, but have also been placed on anti-epileptics, smoking cessation drugs (varenicline), acne medications such as isotretinoin, beta blockers, reserpine and drugs for weight loss.[16] This topic was discussed in a recent paper in the Shanghai Archives of Psychiatry.[17] A recent review by Gibbons and Mann[18] provides a detailed summary of the recent research about the relationship between medication use and suicide.

Questions regarding a possible relationship between antidepressants and suicide emerged in 1990 with the publication of a series of case reports in which the then newly introduced selective serotonin reuptake inhibitors (SSRIs) were associated with the apparent emergence of suicidal thoughts and behavior.[19] These early observations led to US FDA hearings in 1991 that did not find evidence of an increased risk of suicidal acts associated with antidepressants. These early case studies set the stage for the development of new approaches to the analysis of pharmacovigilance data in general and with respect to suicide in particular. Attention to the potential relationship between antidepressants and suicide led to a US black-box warning for children under 18 years of age in October 2004. The evidence supporting the warning was a meta-analysis conducted by the FDA,[20] which combined spontaneous reports of suicidal thoughts and behaviors from 25 placebo-controlled pediatric RCTs of newer antidepressant medications. The conclusion was that higher rates of self-reported suicidal ideation and behavior occurred in children treated with antidepressants than in those receiving placebo (OR=1.78; 95% CI=1.14, 2.77). The FDA also presented results of an analysis of prospective data (based on a suicidal ideation or behavior rating-scale item), which showed no effect of antidepressant use on the emergence or worsening of suicidal thoughts and behaviors (OR=0.92; CI=0.76, 1.11). The difference between prospective clinician ratings and spontaneous patient reports of suicidal ideation and behavior has never been adequately explained; it may be due to ascertainment bias between active treatment and placebo groups.

In January 2006, the FDA conducted a second meta-analysis[21] of 372 RCTs of newer antidepressants in adults with a pooled sample of approximately 100 000 individuals. The analysis was based solely on spontaneous adverse event reports from these RCTs; no data on prospective clinician ratings were provided in the studies. While the overall analysis revealed no evidence of an association, stratification by age revealed that for the primary endpoint of suicidal ideation or behavior, 18- to 24-year-olds taking antidepressants had an increased risk compared to those taking placebo that approached statistical significance (OR=1.62; CI=0.97, 2.71). However, adults aged 25 to 64 years had a significantly decreased risk (OR=0.79; CI=0.64, 0.98), and geriatric patients had a markedly significantly decreased risk (OR=0.37; CI=0.18, 0.76). On the basis of these results, the FDA extended the black-box warning to include 18- to 24-year-olds.

Since the FDA warnings, several studies have raised serious questions regarding the results of the FDA analyses. Bridge and colleagues[22] analyzed an expanded set (27 studies) of pediatric RCTs of antidepressant treatment and suicidality; they found that the association between antidepressant treatment and suicidality was much weaker than reported in the FDA's original findings. Gibbons and colleagues[23] studied a cohort of 226 866 veterans with a new episode of major depressive disorder and found a significantly lower rate of suicide attempt in those treated with monotherapy SSRIs compared with those treated without antidepressant medication (123/100 000 for SSRIs versus 335/100 000 for no antidepressant; OR 0.37; p<0.0001). Moreover, among veterans treated with monotherapy SSRIs the rate of suicide attempts after treatment (123/100 000) was significantly lower than the rate before treatment (221/100 000; relative risk 0.56; p<0.0001). Analyses stratified by age did not confirm the FDA's findings of increased suicidality for 18- to 24-year-olds. The veterans data have also been re-analyzed using person-time logistic regression.[24] This analysis found a significant decrease in suicide attempt rate during monotherapy SSRI treatment (hazard ratio [HR], 0.17; CI=0.10, 0.28; p=0.0001); the suicide attempt rate decreased with time from the index episode and the hazard rate is much lower for patients treated with monotherapy SSRIs (versus non-pharmacological treatments) during the first few months following treatment initiation, but the difference between the different treatment groups becomes indistinguishable by 9 months following the index episode.

Ecological studies conducted following the FDA's black-box warning revealed that there may have been unintended consequences of the warning. Several authors[25-28] have now shown that antidepressant prescription rates precipitously dropped following the warning. Both Gibbons and colleagues[26] and the US Centers for Disease Control and Prevention[29] documented a 14% increase in child and adolescent suicide rates following the decrease in antidepressant prescriptions. Libby and colleagues[30,31] found a 44% reduction in the diagnosis of new cases of child depression among general practitioners following the black-box warning and a 37% reduction in the diagnosis of new cases among young adults.

Recently, Gibbons and colleagues[32,33] synthesized all the longitudinal data from 40 drug company sponsored and one large National Institute of Mental Health placebo-controlled RCTs of fluoxetine for youth, adults and the elderly, and of venlafaxine in adults. Both drugs were shown to be efficacious in all age cohorts although the maximum benefit was observed for children and only marginal benefit was observed for the elderly following six weeks of treatment. With respect to suicidal thoughts and behavior, significant benefits of antidepressant treatment were observed in adults and the elderly, and these benefits were mediated by larger decreases in depressive severity observed in treated patients relative to placebo controls. In children, despite statistically and clinically significant benefits in terms of depression observed with active treatment, no significant difference between treated and control patients was observed in the rates of suicidal ideation and behavior. These results indicate that suicidal thoughts and behavior are driven by depression in adults but this does not appear to be the case for children. This finding is consistent with a recent finding by Kessler and colleagues[34] who found that over 80% of suicidal adolescents received some form of mental health treatment, but the treatment failed to prevent suicidal behavior.

4. Are there more effective methods for measuring suicide risk?

As noted, the use of spontaneously reported retrospective accounts of suicidal thoughts and behavior even in the context of RCTs can lead to invalid statistical inferences. Previously, prospective measurements of suicidality were usually based on ratings of a single symptom item that has response categories ranging from suicidal thoughts to planning to behavior. Recently, the US FDA[16] has endorsed use of the Columbia-Suicide Severity Rating Scale (C-SSRS)[35] for routine prospective assessment of suicidal risk in RCTs involving any central nervous system related drug. The C-SSRS provides direct classification of suicidal events into 11 categories, 5 of which concern suicidal ideation (ranging from passive thoughts to active ideation including method, intent and planning), 5 suicidal behaviors (ranging from preparatory actions to completed suicide), and self-injurious behavior with no suicidal intent. The advantage of the C-SSRS is that it standardizes what we mean by suicidal events and eliminates the ascertainment bias that can be produced by spontaneous reports when comparing patients receiving an active treatment versus a pharmacologically inactive control. This is an important advance for RCTs in which suicide is an adverse event of concern, and it will be of considerable interest to examine the association between antidepressant treatment and suicidal events in youth as more data using the C-SSRS become available.

Identification of individuals with significant suicidal

ideation or those who have already made a serious attempt may be too late for the purpose of prevention. [1] In adults and the elderly, we know that depressive severity is an important mediator of suicidal thoughts and behaviors and therefore the ability to more widely and less invasively measure depression and screen for suicidal risk is still sorely needed. This is particularly true in high-risk populations such as veterans of military actions who in the US are at greater risk of death by suicide than death from a battle-related injury. Recently Gibbons and colleagues[36] developed a computerized adaptive test of depressive severity (the CAT-Depression Inventory, CAT-DI) that can be self-administered in two minutes, requires an average of 12 items per subject yet maintains a correlation of 0.95 with the total item bank score based on almost 400 items. Using a simple empirically derived threshold, the test has a sensitivity of 0.92 and a specificity of 0.88 for identifying a major depressive disorder (using the diagnosis derived by a clinician using the Structured Clinical Interview for DSM-IV as the gold standard). The test is based on multidimensional item response theory (MIRT)[37,38] and one of the subdomains includes 14 suicide items. In the event that a suicide item is not administered as a part of the adaptive test, 1 to 4 additional suicide screening items are administered and if any item is endorsed at a moderate level or above, a suicide alert is sent to the treating clinician or managed care provider. The advantage of an adaptive self-report measure of depressive severity and suicidal risk is that it can be administered to large populations via the internet from a cloud computing environment. Furthermore, unlike traditional brief, fixed-length instruments such as the PHQ-9 (Patient Health Questionnaire), which involve repeatedly administering the same set of items (which can result in response set bias), the CAT-DI adapts to changes in depressive severity within individuals and asks different questions depending on the current level of impairment. Reduction in respondent burden is achieved by initiating the next CAT testing session based on the estimated depressive severity from the previous session and, thus, reducing the number of items that need to be administered. Another advantage of CAT is that the termination criterion (which determines the required level of precision of the estimate and is inversely proportional to the number of items required) can be different for different applications. For example, in an RCT we may want extremely precise estimates that will enable us to obtain the most accurate estimate of a treatment effect of interest and will, thus, require a larger number of items (e.g., 20-30). In primary care, we may require a somewhat less precise estimate which is sufficient to detect depression when present and monitor the effectiveness of treatment so it will require an intermediate number of items (e.g., 10-12). In psychiatric epidemiology, we may require a less precise estimate based on fewer items (e.g., 5 or 6) that is sufficient for determining the prevalence of depression within a specified population. All that is required is to change the termination criterion (i.e. the required standard error of the severity level estimate) depending on the requirements of the specific application. The paradigm shift is from a traditional fixed-length test that has a small number of items and may result in variable measurement precision, to a variable length test with a small but optimally selected set of items for the specific respondent and leads to constant measurement precision across individuals. Additional CATs for anxiety, hypomania/mania spectrum and a brief depression diagnostic screening test have also been developed using this methodology.

5. What improvements in statistical methodologies are possible for the study of suicide?

From a statistical perspective, the analysis of suicide and related events are among the most challenging and interesting drug safety problems. There is no other area where the indication for treatment is so strongly confounded with the adverse event of interest. Even in well-controlled observational studies, selection effects can lead to severely biased results. Since suicide events are rare, RCTs in and of themselves generally have sample sizes that are too small to draw valid inferences. Furthermore, patients enrolled in RCTs may have little resemblance to those patients who are the ultimate consumers of the medications of interest. In the following, I provide a brief overview of several areas of promising statistical research.

5.1 Meta-analysis

Most meta-analyses of rare binary events in medical research (including suicidal events) are based on the fixed-effect model or 'Mantel-Haenszel Method' or the random-effect model of DerSimonian and Laird.[39] The fixed-effect model assumes that the treatment effect is constant over studies and the random-effect model allows the treatment effect to vary from study to study. Recently, Bhaumik and colleagues[40] studied these estimators and found that the estimated treatment effect can be grossly over-estimated when there is significant variability in the treatment effect across studies. The bias is smaller for the random-effect model than for the fixed-effect model, but still appreciable. These estimators also require a continuity correction to

zero cells from a given trial and if the number of events in both arms is zero, then the study must be removed from the computation. Alternative methods based on non-linear mixed-effects regression models[41] do not require continuity corrections or removal of zero-event studies and do not suffer from bias due to treatment effect heterogeneity across studies. The disadvantage of these more advanced meta-analysis procedures is that the results are dependent on the particular model specification (random background event rate, random treatment effect, both random effects and their correlation). While the correct model specification is an empirical question, a model with two correlated random effects (random background incidence and random treatment effect) generally works well in all cases.[42]

While meta-analysis combines effect sizes such as standardized mean differences or odds ratios, 'research synthesis' provides a re-analysis of the complete set of person-level longitudinal data from each study. As an example, the previously discussed papers by Gibbons and colleagues[32,33] performed 3-level linear (efficacy) and non-linear (safety) mixed-effects regression analyses[37] of the data from a series of 41 RCTs on the efficacy and safety of antidepressants. In these analyses, the intercept and slope of the temporal trends in efficacy and safety measures are allowed to vary from individual to individual and the study means of these same effects are allowed to vary from study to study. With proper specification of the variance component structure, the overall pooled estimate of the treatment by time interaction tests the overall efficacy (or safety) of the medication of interest.

5.2 Person-time models

Person-time regression or discrete-time survival analysis[43] is an ingenious approach to fitting a time to event or survival analytic model in a parametric way using standard logistic regression software. The basic idea is to discretize time into a set of smaller intervals and to then record the number of subjects at risk in each interval, the number experiencing the event (e.g., suicide attempt), and the number censored. A similar approach can be taken using unstructured data in which each subject contributes n_i records either to the point in time in which the event was first experienced or to the end of the follow-up period. Advantages of the approach are that: (a) time-varying predictors are easily accommodated, (b) random-effects such as the nesting of patients within hospitals or clinics, or counties can be easily included, (c) competing risks such as death by suicide or other causes of mortality can be examined, and (d) non-proportional hazard models can be estimated.[41,44] The net result is that we can relax the assumption that once a subject is exposed they are always exposed and replace it with any exposure pattern (e.g., monthly) and produce a within-subject estimate of the effect of the exposure on the probability of experiencing the adverse event. Note that unlike a traditional mixed-effects logistic regression for a repeated binary event, these models are restricted to a single event per person and as such, the repeated observations within individuals are conditionally independent.[43]

5.3 Causal Inference

Since larger sample sizes are required to study events such as suicide attempts, this generally leads to large-scale pharmacoepidemiologic studies of medical claims data, which suffer from the usual problems associated with the analysis of observational data. To insulate inferences from bias produced by the selection of patients to treatments (either self-selected or selected by their treating physician based on observable characteristics such as severity of illness) we turn to methods designed to draw causal inferences from observational studies. The now classic approach is based on propensity score matching[45,46] in which patients who do or do not receive a particular treatment of interest are matched on a large number of potential confounders (e.g., age, sex, concomitant treatments, comorbid diagnoses, prior attempts) and the likelihood of receiving treatment (e.g., an antidepressant). The fundamental idea is to carve a RCT out of an observational study, without eliminating so much of the data that the 'RCT' is no longer generalizable.

While propensity score matching is useful conceptually, drug exposures are typically dynamic and the exposure status takes on different values over time. Traditional propensity score matching assumes that treatment status does not change over time. While some work has been done in the area of dynamic propensity score matching,[47] an equally if not more promising approach for dynamic treatment exposures is based on the idea of marginal structural models (MSM).[48] The basic idea of MSM is that we compute the probability of treatment at each of T time-points and then combine these probabilities to compute the likelihood of treatment up to a particular point in time. These probabilities are then standardized and used as weights in a second stage regression that models the dynamic effects of treatment on the adverse event of interest (e.g., suicide attempt) weighted by the likelihood to receive treatment at any

particular point in time. While the traditional approach described by Robins and co-workers rests strongly on the assumption that all of the important confounders have been measured and are available for the analysis, the analysis may be further expanded to include the effects of unmeasured confounders by adding one or more random effects to the treatment selection model as described by Leon and Hedeker[49] in the context of computing dynamic propensity score adjustments.

6. Where do we go from here?

The area of drug safety in general and suicide in particular is an enormously important problem that has traditionally been investigated using quite simple approaches which often yield questionable results. Improving the quality of analytic work in this important area should be a major goal of future applications.

Conflict of interest

This work was supported by NIMH grant R01MH8012201. Dr. Gibbons has served as an expert witness for the US Department of Justice, Wyeth and Pfizer Pharmaceuticals on suicide-related cases.

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ERRATUM

In the February 2013 issue, there were two errors on the right column of page 56 of the Biostatistics in Psychiatry (13) article. (Lê Cook B, Manning WG. Thinking beyond the mean: a practical guide for using quantile regression methods for health services research. Shanghai Archives of Psychiatry 2013; 25(1): 55-59.) The phrase '…a 75th quantile regression fits a regression line through the data so that 90 percent of the observations…' should read: '…a 75th quantile regression fits a regression line through the data so that 75 percent of the observations...' And the phrase '…and the observed values above the line (positive residuals) by 1.75.' should read: '…and the observed values above the line (positive residuals) by 1.5.' We apologize for the errors.