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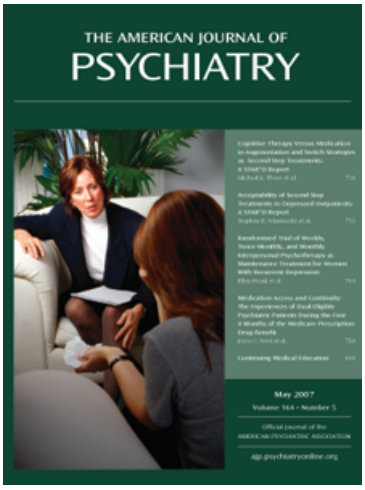

Editors' Column

Sooner or later, residents who read research articles in *The American Journal of Psychiatry* or in other journals wonder how they can interpret the statistical analyses in the article. Frequently, statisticians are coauthors of major papers, and other statisticians are among the reviewers of these papers. How a resident without formal statistical training can understand and then validate these statistics and the conclusions derived from them is a daunting issue. The *Journal's* editors and reviewers are responsible for making sure the statistical analysis and their conclusions are correct, but we do not expect readers to trust our judgment without question. Therefore, papers routinely present the details of their statistical methods and analytic results. Unfortunately, these details often further intimidate and alienate readers.

For this issue of the Residents' Journal we examine a clinical research article from the April issue of *The American Journal of Psychiatry* as an illustration of why and how statistical analyses are used in clinical research. Dr. Melissa DelBello's paper, "Twelve-Month Outcome of Adolescents With Bipolar Disorder Following First Hospitalization for a Manic or Mixed Episode," asks a very straightforward question: What happens to children during the year following hospitalization for an episode of bipolar disorder, and can we determine which factors influence their course of recovery?

This study is particularly interesting because it looks exclusively at adolescents hospitalized for their first manic episodes, before the effects of repeated hospitalizations and chronic illness have a chance to influence their clinical picture. To achieve their goal of assessing what affects 12-month outcomes after the first manic episode, DelBello et al. specified at the start of their study what they expected to find. This is an "a priori" hypothesis, which is an important feature of good research. A priori means literally "from what is before." The idea is that the investigators must propose a hypothesis to test based on what is already known, and prior to starting the study. DelBello et al. cleverly chose to test bipolar disorder outcomes from three different perspectives of recovery: 1) syndromic (do the subjects continue to fulfill criteria for illness?), 2) symptomatic (does the intensity of remaining symptoms fall significantly?), and 3) functional recovery (have the subjects returned to school?).

To measure recovery, DelBello et al. used the Longitudinal Interval Follow-up Examination (LIFE), which is a semistructured clinical interview that is used to track the longitudinal severity of axis I disorders. One might ask why the investigators simply do not accumulate all the data and then sift through it to find what is changing and what factors influence these changes. However, open-ended analyses are frequently subject to error because some associations between factors and outcomes are expected to occur by chance. In any large database, so many associations are potentially testable that investigators might find only a few chance associations and then report these as meaningful. If investigators find such chance associations, we ask them to report them as investigational or preliminary and then to test them in another group of patients as a priori hypotheses.

In the DelBello et al. study, syndromic recovery was defined as 8 weeks with a LIFE overall score of ≤4. Symptomatic recovery was defined as 8 weeks with a LIFE overall score of ≤2, and functional recovery was defined as achieving a rating equal to or better than premorbid psychosocial functioning. The first goal of this study was to describe the rate of recovery using these three perspectives. The second goal was to test different predictors of outcome. For this second goal, the investigators' a priori hypothesis was that psychosis, socioeconomic status, poor medication adherence, and co-occurring substance use disorders would predict worse outcome in first-hospitalization bipolar adolescents.

To test the probability of recovery, the authors used the Kaplan-Meier estimate of cumulative probability. This method is a technique for estimating time-related events, sometimes called a "survivorship function," or "survival analysis." This term comes from the fact that this method is often used in actuarial science to analyze death as an outcome. However, it may be used effectively to analyze time to an endpoint for any outcome, including remission and recovery from illness. Calculating the Kaplan-Meier estimate essentially involves dividing the number of people who have

recovered by a certain time point by the number of people who were eligible to recover at that time. The result is a "survivorship curve," as shown in Figures 1–3 in the DelBello et al. paper. From these curves, the investigators calculated the overall probability of recovery (0.86 for syndromic recovery, for example) and the mean time for recovery (20 weeks).

During most studies, it is inevitable that some people will drop out for various reasons, including moving away or refusal to participate. Their data, which was previously included, is then not available from that time forward. Since they are no longer in the study, their data cannot be in the numerator, nor can it be in the denominator, since investigators cannot know if they will recover eventually or not. Because they are removed from the data analysis, they are said to be "censored." Circles on the curves show when this censoring occurred. The investigators also calculated different curves depending on different subgroup characteristics such as alcohol use, etc., to test their a priori hypotheses. The other curves in Figure 1 allow a comparison between the time course and probability of different aspects of recovery.

Figures 2 and 3 then look at different factors that might affect recovery from an initial episode of bipolar disorder. Figure 2 (left panel) looks at the presence or absence of attention deficit hyperactivity disorder (ADHD) as one factor. Recovery curves are calculated for both conditions and then compared using Cox proportional hazards modeling. A hazard ratio of 2.4 is calculated for the effect of ADHD, meaning that symptomatic recovery is over twice as likely to occur in the time period examined in the absence of ADHD than when ADHD is present. If there was no difference, the hazard ratio would be 1.0. By inspecting Figure 2, one can see how the patients with ADHD are less likely to recover than the patients without ADHD.

Dr. DelBello decided to pursue a master's degree in statistics and epidemiology as part of an NIMH career development award while she was completing her research training after her residency in child psychiatry. This article was part of that graduate work. Dr. DelBello now joins us to explain why she chose to complete this training and why she chose the methods used in this study:

"As part of my research training I realized the importance of learning how to examine longitudinal data, in particular examining factors related to outcome. However, patients in our studies often move away or are lost to follow-up, and therefore those data are missing. Survival analyses account for these missing data points so that you can still use subject data acquired up until the patients drop out of the study or are lost to follow-up. As previously discussed, there are statistical methods for comparing two survival curves, allowing the effects of clinical variables (e.g., specific co-occurring disorders) on outcome to be examined. Survival analyses will help inform patients and their families about the probability of having a favorable versus poor outcome based on their clinical characteristics. Although at times it is challenging to learn new statistical methodologies, I found the most effective method for learning statistical analyses has been to apply them to a specific dataset that is then used to answer a clinically related question."

While statistical methods and calculations may initially seem daunting for residents without research experience, good papers such as this one are able to illustrate in figures or tables the "take home" message of the clinically relevant knowledge resulting from the study. Parents whose adolescent children are first hospitalized for bipolar disorder often want an idea of what the next year might bring. Dr. DelBello's paper gives the information to help residents, families, and patients make useful plans for the next year. There are many other methods for statistical comparisons of clinical conditions that we will explore from other papers in future editions of the Residents' Journal.

Susan Schultz, M.D.
Robert Freedman, M.D.
with Melissa DelBello, M.D.

Quetiapine and Cataracts in an Adolescent With Down's Syndrome

Qazi U. Javed, M.D., PGY3
Department of Psychiatry, University of Wisconsin Hospitals and Clinics

TO THE EDITOR: There have been reports of quetiapine's role in cataract formation (1, 2). I report the case of an adolescent with Down's syndrome who developed cataracts following treatment with quetiapine.

The patient is a 15-year-old male diagnosed with Down's syndrome at birth. Since the age of three he had been taking methylphenidate for the treatment of attention deficit hyperactivity disorder. His past medications also included imipramine and risperidone for the treatment of behavioral outbursts and compulsive behavior. At the age of 12, his dose of methylphenidate was augmented with quetiapine. At the age of 14 his ophthalmologic exam was normal. One year later he had developed bilateral cortical cataracts. At the time of presentation to the mental health clinic, he had been taking quetiapine, 50 mg b.i.d., for the last 16 months. Ophthalmology was unclear of the etiology of the cataracts.

Studies show that children with Down's syndrome are at risk for cataract formation (3). The prevalence has been estimated as being between 12% to 54% (3, 4). Cataract frequency increases with age and is most likely to appear between ages 12 to 15 (5). In the study of ocular lenses in mice by Frederikse and Ren, oxidative stress is considered as a model to explain the pathophysiology of cataracts in Down's syndrome (6).

The manufacturer has reported that quetiapine may interfere with cholesterol biosynthesis and thus could cause changes in lens cholesterol (AstraZeneca, personal communication, 2005). Changes in lens cholesterol are associated with cataract formation (7). Lens changes have been observed in human subjects in phases II and III of clinical trials with quetiapine. However, no causality was established because of confounding factors. A change in lens cholesterol is an additive risk factor for cataractogenesis in individuals with Down's syndrome.

There have also been reports from the manufacturers of cataract formation following treatment with olanzapine and ziprasidone, but no causal relationship has been found. Even though it is unclear if quetiapine contributed to cataract formation in this particular patient, clinicians dealing with Down's syndrome should be aware of the possible risk when initiating treatment with an atypical neuroleptic.

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Can the Heritability of Psychosis be Accounted for by the Epigenetic Variations of a Single Gene?

Tanuj Sidhartha, M.D., PGY3
Department of Psychiatry, University of Texas Southwestern Medical Center

In the January 2007 issue of *The American Journal of Psychiatry*, Dr. Timothy J. Crow summarizes the major findings to date in the genetics of schizophrenia and bipolar disorder (1). Genetic epidemiological studies (twin and adoption studies) have convincingly demonstrated the heritability of these psychotic illnesses (2). Linkage analysis is one of the two main methods of locating disease-inducing genes, and to date, this approach has led to the identification of a few candidate genes of small to modest effects, for an even smaller number of psychiatric illnesses. For psychotic disorders, the specific susceptibility genes have been hard to come by. Nonreplication has been the norm after the initial finding of a gene linkage, and even after genomewide scans, none of these candidate susceptibility genes can be considered as definitely contributing to the heritability of psychosis.

This could mean that the best-case scenario for the future is the discovery of multiple genes of small effect for the heritability of psychosis. Dr. Crow argues though that it need not be so, and presents an alternative hypothesis based on certain schools of thought in phenomenology, genetics, and human evolution. He draws our attention to the following facts and possibilities.

First, there is enough in the literature to suggest that the expression of a single gene can explain the phenotype of psychosis. Uniform incidence of psychosis across populations, homogeneous structural brain changes (such as ventricular enlargement), etc., are all consistent with this hypothesis.

Second, there are heritable changes in gene function that can occur without a change in the DNA (e.g., epigenetic variations such as processes of DNA methylation and X chromosome inactivation). The linkage approach looks for variations in the genetic code and thus is blind to epigenetic sources of variation that might account for the heritability of psychosis.

Third, Dr. Crow has long considered the symptoms of psychosis to be the result of disturbances in the *Homo sapiens*-specific capacity for language. It is of interest that capacity for language and brain asymmetry are both specific to *H. sapiens* and are generally regarded as an abrupt step in the evolution of the species. If this is so, then the genetic changes associated with this genetic event could hold the key to the genetic basis of psychosis. One such genetic change is the X to Y translocation followed by paracentric inversion on the Y short arm. The rearrangement of genes in this region assumes importance because of the epigenetic process of X inactivation (1, 3). The gene pair protocadherin X/Y (which codes for cell surface adhesion molecules) is proposed as a promising candidate for further research.

It would be difficult to get very enthusiastic about the possibility of the above as the one answer everyone is waiting for, especially as it depends on proving the validity of a number of assumptions and testing an even larger number of hypotheses. It can be argued though that the lack of success with current methods calls for "going back to the drawing board" and considering alternative approaches. It also calls for appreciation of and attention to developments in related fields of study that could provide much awaited leads. The above theory does all that and more by providing a new challenge, direction, and hope to residents at the beginning of their careers.

Hopefully, someday all this will have some clinical relevance. The finding of genetic origins of illnesses does not often lead to benefits in disease management beyond genetic counseling (for example, Huntington's disease). Furthermore, it has been argued that we will probably never find such strong genetic associations for psychiatric illnesses as for Huntington's (4).

As residents, it is important to become familiar with reality; it might be years or decades before we have a new, simple, and effective genetic intervention for any of the illnesses that we deal with. Unfortunately, advances at the intracellular level (post receptor) have also not yet led to documentable benefits for inpatient management. So it is highly probable that for a fairly long time to come our success in managing our patients will continue to be dependent on our expertise with psychopharmacology and psychotherapy.

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2007 APA Annual Meeting

We would like to invite all residents to participate in a jointly sponsored *CORF-AJP* focus group to take place at the 2007 APA Annual Meeting in San Diego, California. In this meeting, thoughts on the Residents' Journal and ideas on how the *American Journal of Psychiatry* can be of further use to residents will be discussed. The meeting is scheduled for Tuesday, May 22, 2007, 2:30 to 3:30 p.m. in the San Diego Marriott Hotel and Marina, Columbia Rooms 1-3, North Tower. For information on the 2007 APA Annual Meeting, including registration and housing, please visit http://www.psych.org/edu/ann_mtgs/am/07/index.cfm. For further information please contact ajp@psych.org.