

2015 in Review

The Editors are pleased to offer personal selections of some of the articles they found particularly interesting and important in this year's *Journal*.

Revisiting Early Drug Discovery

Robert Freedman, M.D.

"The Clinical Discovery of Imipramine" by Walter A. Brown and Maria Rosdolsky (1) excerpts the *Swiss Medical Weekly's* 1957 publication in German of Dr. Roland Kuhn's original clinical description of the effects of imipramine. He was the first to administer imipramine as an experimental drug to psychiatric patients. He treated several hundred patients in his hospital and reported on the positive effects seen in 40 of them. He initially assessed imipramine's effect in schizophrenia, because it had been synthesized as an antipsychotic neuroleptic, and then recognized that its antidepressive effects surpassed any antipsychotic use. The administrations lasted 4 to 6 weeks, with responses sometimes taking that long to develop. He observed that a delayed effect increased suicidal tendencies. He noted that despite the wide range of clinical manifestations of depression, effects of imipramine unexpectedly occurred in both melancholic and nonmelancholic patients and even in some patients whose depression was induced by stressful life circumstances. He reported that only about three-quarters of patients responded and of those fewer than one-half had full remission. He noted that responses were more transient in grieving patients. In brief, in 40 patients he saw almost all currently known therapeutic effects of the first antidepressant. Most clinicians today would be hard-pressed to say much more about the therapeutic effect of antidepressants. It is tempting to read the report and long for a return to the age of the first discovery of the major classes of psychotropic drugs. Conflict of interest, informed consent, clinical trials registration—none of these enhancements have resulted in new and better treatment for depression, ultimately the goal of research. The clock cannot roll back, however. To my reading, the object lesson for today is that careful clinical observation in the hands of a treating physician contributes much to improve the treatment of patients.

Trajectories of Illness in Individuals at Ultra-High Risk for Psychosis

David A. Lewis, M.D.

Much attention has been directed, and rightly so, in recent years toward identifying youth and young adults at elevated risk for

developing a psychotic disorder. The goal of this attention has principally been to inform and guide attempts at preemptive interventions; that is, to implement therapeutic strategies that will, by delaying or preventing the onset of psychosis, substantially alter for the better the life trajectories of these individuals. Current approaches for identifying individuals at ultra-high risk for transition to psychosis within the following few years are accurate in about a third of cases. But what happens to the other two-thirds of individuals who have sought help and been identified as at risk? Lin and colleagues (2) addressed this question by following, for periods of 2–14 years, 226 help-seeking individuals identified as at ultra-high risk when they were 15–30 years of age but who did not subsequently develop psychosis. They found that 68% of these individuals experienced a nonpsychotic disorder (principally depression, anxiety, and/or substance use disorder) and only 7% did not have a diagnosable disorder either at baseline or during follow-up. These findings remind us that mental illnesses of many types have their initial appearance during adolescence or early adult life and, consequently, that reducing the lifetime burden of these disorders will require the ability to bend the trajectory of illness progression across multiple types of clinical presentations.

Long-Term Outcome of Psychiatric Treatment—Effects on the Next Generation

Robert Michels, M.D.

We published an intriguing article by Myrna Weissman and her colleagues (3) in the May 2015 issue. They started with the observation that "when a depressed mother's symptoms remit, her children's psychiatric symptoms decrease."

In this study they assessed children of depressed mothers who were participating in a clinical trial of two different antidepressant drugs or their combination (note: no psychotherapy). As expected, the mothers got better, with no difference among the three treatments. Children of mothers in one of the monotherapy groups improved in both symptoms and function, but not the children of mothers in the other two groups. Further analyses suggested that the mothers whose children improved had enhanced ability to listen and to talk to their children—i.e., they were not only less depressed, they were also better mothers.

We have long known that psychopathology runs in families, and we have recently made immense advances in understanding the genetic basis of this intergenerational transmission. However, we also know that there is an environmental basis, and for young children no environment is as important as the family, and particularly the mother.

Demonstrating that healthier mothers are associated with healthier children is important, but only the beginning. Refining the observation—only some healthier mothers, those with improved parental functioning, seem to make a difference—offers an important clue about possible mechanism. We want our treatments to do more than relieve symptoms; we would like them to enhance our patients' lives and those of their families.

The study also calls our attention to an important issue in public health and clinical psychiatric research. The burden of psychiatric illness is not only the symptoms of the patient, but also the impact on others in the patient's social network. This may not be apparent for months or years after the episode and its treatment. We should study not only short-term symptom relief, but also long-term impact on others. The greatest benefit in treating a depressed mother may be the enhanced functioning of her children years later.

What we think of, study, and promote as tertiary prevention may be even more important as primary prevention.

Linking Brain Development and Adolescent Alcohol Consumption

Daniel S. Pine, M.D.

As brain imaging methods continue to mature, this research is gradually becoming clinically relevant. Embedding imaging studies in developmentally oriented research represents one important way to increase clinical relevance. My favorite article in this year's *Journal* uses this approach to examine relationships between adolescent brain development and heavy alcohol use.

Squeglia and colleagues (4) repeatedly assessed 134 adolescents over a three-and-a-half year period, finding that 75 of these adolescents became heavy drinkers whereas the other 59 did not. The authors acquired as many as six structural magnetic resonance imaging scans over this same period, which allowed them to examine the relationship between changes in drinking patterns and the trajectory of brain development. Findings suggested that heavy-drinking adolescents exhibited an accelerated pace of gray matter attenuation and a reduced rate of white matter growth. As such, the work highlights the need to redouble our efforts to understand the many subtle ways in which heavy drinking in adolescence might impair mental, physical, and social development.

Setting the Stage for Early Intervention

A. John Rush, M.D.

How often do we hear “Do you think one of my children might also have bipolar disorder?” from a parent with bipolar

disorder? And what are we to do? There is no established practice for either identification or perhaps early treatment of these young at-risk but not yet affected persons.

In the July 2015 issue, Axelson and colleagues (5) provide important indicators that appear to be valuable in reducing the typically multiyear time between onset of bipolar I or II disorder and its recognition and treatment. Many children later diagnosed with bipolar disorder move through adolescence with their behavior already severely disrupted.

The large, longitudinal study of 6–18-year-old offspring of a parent with bipolar I or II disorder identified distinct subthreshold episodes of mania or hypomania that were highly specific to the high-risk offspring and were the “strongest predictor of progression” to full threshold manic, mixed, or hypomanic episodes in the at-risk cohort.

This finding allows clinicians to focus on a very limited number of symptoms to detect those children at risk who are likely to progress to full bipolar I or II disorder. Their assessment is brief—perhaps even doable over the telephone or with telemedicine. This approach is analogous to the management of other medical conditions with a high genetic contribution (e.g., hypercholesterolemia) in which early and regular assessments can be life-saving.

This study suggests a simple, clinically actionable recommendation: evaluate at-risk offspring during these subthreshold symptomatic periods regularly enough to intervene if needed. In addition, educating the family about these indicators would be worthwhile. Furthermore, the data reveal that these subthreshold symptoms affect 10% of the at-risk offspring by age 12, so assessments might best begin at age 8.

Food for Thought in Predicting Dementia

Susan K. Schultz, M.D.

The article by Claudia Cooper et al. (6) reminds us that patient engagement can be a powerful means of encouraging healthy behaviors that have significant potential to improve cognitive outcomes in older adults. The article presents a meta-analysis across 62 longitudinal studies of the progression from mild cognitive impairment (MCI) to a diagnosis of dementia. Risk factors examined included diabetes, hypertension, hypercholesterolemia, smoking, alcohol use, metabolic syndrome, as well as the presence of neuropsychiatric symptoms, depression, apathy, or anxiety. Additional factors examined included use of the Mediterranean diet, serum folate levels, and amount of education.

This meta-analysis touches upon perhaps the most common of nagging worries among baby boomers who are beginning to recognize age-related memory changes and are motivated to consider ways to improve their cognitive resilience. Fortunately for the many individuals in this group, this meta-analysis identified prognostic factors that are amenable to patient engagement in lifestyle practices. For example, the presence of diabetes and prediabetes was associated with the conversion of amnesic MCI to dementia. The detection of prediabetes in particular affords a window of opportunity for

exercise and dietary adjustments that may have a beneficial impact on risk for dementia. Surprisingly, this study did not find that education had an effect in predicting conversion of MCI to dementia, yet this is consistent with the idea that higher education delays the recognition of cognitive impairment and that neuropathology may be more advanced at the time it is detected.

Providing even more support for the potential power of personal lifestyle changes was the finding that the Mediterranean diet was associated with a lower likelihood of progression to dementia. Hence Cooper et al. provide us with an important “practice alert” that we can all take to heart in clinical care. Empowering patients to be involved in lifestyle changes may have profound benefits in both mental and physical health. Definitely food for thought!

Prenatal Training on Mothering Improves the Psychosocial Health of the Newborn/Child

Carol A. Tamminga, M.D.

Early childhood trauma and neglect is suspected to be a determinant of adult-onset serious mental illness, including psychosis, depression, and substance abuse. Family Spirit, a home-visit prenatal program for expectant mothers, was designed for use on Indian reservations. Barlow et al. (7) reported that it was delivered to teen expectant mothers (12–19 years old) by trained paraprofessionals, in the most disadvantaged Indian reservations in the southwest, to test the extent to which this intervention could improve the psychosocial health of both mother and child. The Family Spirit intervention was delivered by culturally accepted tribal women and taught parenting, coping skills, and healthy lifestyle interventions to the expectant mothers; it was contrasted with a treatment-as-usual program for expectant mothers. The outcomes were remarkable. The Family Spirit intervention was faithfully delivered by the culturally accepted paraprofessionals to the highly vulnerable teen mothers-to-be. The beneficial outcomes fell both to the mothers (specifically, reduced “problem behaviors,” depression, and drug use) and to the children born to these mothers (specifically, reduced internalizing and externalizing behaviors, as well as “of concern” behaviors). These benefits to mothers and children were demonstrated immediately and were maintained over the 3 years of follow-up. I value the study because it demonstrates that social and educational interventions to mothers, even in the most challenging environment, can generate measurable mental health benefits for children, benefits that portend positive, enduring mental and physical health outcomes.

From the *Residents Journal*: Response to Trauma and Prevention of PTSD

Rajiv Radhakrishnan, M.B.B.S., M.D.

The July issue of the *American Journal of Psychiatry Residents' Journal* featured a review article by Jennifer Harris (8)

on prevention of posttraumatic stress disorder (PTSD). The article outlined the factors that influence human response to trauma and discussed their relevance to the prevention of PTSD. It highlighted that PTSD is a less common outcome among the hypothesized trajectories of response to trauma, ranging from resilience and recovery to delayed dysfunction and chronic dysfunction. Harris then attempted to elucidate the factors that are thought to play a role in determining if a person would progress along a trajectory leading to greater psychopathology or one leading to resilience. The list of factors included neurobiological factors such as neuropeptide Y, brain-derived neurotrophic factor (BDNF), and corticotropin-releasing hormone (CRH); early-life experience; gender; and presence of premorbid anxiety disorder or personality disorder. Finally, the article reviewed the evidence for pharmacological and psychological interventions in the prevention of PTSD. Harris also helped create a podcast for her article (<http://on.fb.me/1L8Ksmh>). The article was well-written and informative, and it represents a successful review by a resident under the guidance of a senior researcher in the field of disaster psychiatry, Carol North. It is indeed heartening to see a senior researcher help a resident write a review article for the *Residents' Journal*. The article was also chosen by *Psychiatric Times* to feature among its “Monthly Roundup: Top 6 Psychiatry Stories in July” (<http://www.psychiatristimes.com/cultural-psychiatry/monthly-roundup-top-6-psychiatry-stories-july>).

AUTHOR AND ARTICLE INFORMATION

Address correspondence to Dr. Freedman (ajp@psych.org).

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