2018 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*.

Returning to the Doctor-Patient Alliance

Robert Freedman, M.D.

"Improving Depression Outcome by Patient-Centered Medical Management" by John Rush and Michael Thase (1) brings to a close the 175th volume of *The American Journal of Psychiatry*. We recognized the *Journal*'s 175th year with a series of articles that looked forward to the next decade with a nod to our past. The series began in January with P.F. Sullivan and the Psychiatric Genomics Consortium's "Psychiatric Genomics: An Update and an Agenda" (2). December's finale includes Benjamin G. Druss and Howard H. Goldman's perspective on integrating mental health services into the larger world of health care (3). The series thus literally builds from molecules to communities. In between, the series astounded me with its breadth of perspective on molecules, neurons, development, and psychopathology. Every article included new clinical guidance informed by fresh scientific synthesis. Anita Thapar's formulation of how molecular signatures indicate different approaches to attention-deficit disorders (4) and Eduard Vieta et al.'s interventions for youths showing early signs of bipolar disorder are examples (5). The Rush and Thase article struck me because it re-examines the fundamental issue in patient care, how doctors work collaboratively with patients. The NIMH-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, which Rush organized, was the first major clinical study that we published when I began my 13 years as Editor of the *Journal* (6). From STAR*D, Rush learned that patients often become frustrated and stop their medication prematurely when it does not seem to provide immediate help. Furthermore, for patients who did not respond immediately to pharmacotherapy, psychotherapy was the most helpful adjunctive treatment. However, the psychotherapy and pharmacotherapy were not coordinated. Instead, psychotherapy was contracted to another group at a different location, where the patient had to go and pay separately. Rush and Thase now propose a new synthesis of psychotherapy and pharmacotherapy to help patients, at a time when they are already depleted by the depression itself, overcome this barrier to treatment and possible recovery. The treatment relies on the physician's better awareness of the hurdles that patients face and a more focused effort to help patients stay the course of treatment.

In Pursuit of a Mechanistic Understanding of the Neurobiology of Suicide

David A. Lewis, M.D.

The rising suicide epidemic continues unabated in the United States; the magnitude of the problem remains unfathomable and yet is seemingly equally underappreciated by society. Multifaceted approaches are needed to address this scourge. Among these are the acquisition of a deeper understanding of the brain alterations that are associated with, and might prove to be causal of, the act of suicide. Toward this goal, Wang and colleagues probed upstream biological processes that might contribute to elevated levels of tumor necrosis factor-alpha (TNF-α), a key proinflammatory cytokine (7). TNF-α has been reported to be elevated in the brains of suicide victims, and serum or cerebrospinal TNF-α has been positively correlated with suicide attempts or ideation, respectively. Wang and colleagues replicated the finding of elevated TNF-α in the prefrontal cortex of suicide victims in two separate cohorts, although TNF-α also was elevated in people with major depressive disorder who died by other means. However, among the microRNAs that regulate TNF-α levels, only miR-19a-3p was upregulated in the prefrontal cortexes of suicide victims (regardless of the associated psychiatric diagnosis) and was unaltered in individuals with major depressive disorder who died by other means. In addition, the investigators found that both TNF-α and miR-19a-3p were elevated in peripheral blood mononuclear cells obtained from individuals with suicidal ideation. Additional studies suggested that the potential mechanistic relationship between altered miR-19a-3p and TNF-α levels in suicide is likely complex and that further investigation is needed. Furthermore, it remains to be explained how proinflammatory processes in the brain contribute to changes in neural processes that are associated with suicidal thoughts and actions. Nonetheless, the study by Wang et al. from Yogesh Dwivedi's research team provides a compelling example of a careful and rigorous research design that

resulted in findings that suggest next steps to improve our understanding of the neurobiology of suicide.

Journey of a Thousand Miles

Robert Michels, M.D.

Most treatments in psychiatry, like the rest of medicine, are born out of tradition, expert opinion, or pure theory. Some are effective, others not, but unfortunately most are less effective than we might wish. Once these treatments have been developed, they can be tested by systematic research, such as randomized clinical trials, to evaluate whether they are effective. This is important scientific work, but it does not improve the treatment, it only confirms what its advocates already believe.

Psychotherapy is at this stage in its development. A considerable amount of data demonstrate that it is effective. However, it is not effective enough. How can we make it better?

The study by Jennissen et al. (8), from Heidelberg, Germany, marks an early step in this direction. They performed a meta-analysis of 23 reports, covering a variety of conditions and therapies, that studied the correlation between insight and treatment outcome. This goes beyond whether psychotherapy works, by offering suggestions about how it might work—about what may mediate its effect on outcome. However, there is much more work yet to be done.

As the authors report, the data are correlational and do not allow for causal inferences. It has not yet been demonstrated that change in insight precedes change in outcome. Because of the small number of studies in the literature, we have not been able to determine the importance of treatment type, diagnostic category, or specific measures used—all essential before we can begin to modify the therapy to see what changes improve outcome. Only then will the research agenda make a difference to patients. This analysis is an important beginning, however. As it is said, "the journey of a thousand miles begins with a single step."

Propranolol and PTSD

Daniel S. Pine, M.D.

I am particularly excited to see articles on treatment in the *Journal*, as they communicate new findings that may one day significantly improve patient care. My favorite article in this year's *Journal* provides data from a randomized controlled trial involving patients with posttraumatic stress disorder (PTSD), a condition for which novel treatments targeting specific mechanisms are needed. In this article, Brunet and colleagues (9) use such a mechanism-based treatment. They compare the efficacy of propranolol therapy versus placebo therapy added to a series of brief memory reactivation sessions for patients with PTSD. A clinical benefit from addition of the propranolol therapy was observed.

Two features excite me about this article. First, research on propranolol's effects on memory has targeted a specific mechanism, which was discovered through both basic and clinical research. In this instance, basic and clinical researchers pursued similar ideas about the role of memory in PTSD. Thus, clinical observations on traumatic memories inspired basic science researchers, who generated the idea of using propranolol to inhibit retrieval of traumatic memories. Second, this is not the first trial of propranolol treatment for PTSD, and past findings have been inconsistent. Rather than abandoning a mechanistic area of research in the face of such inconsistencies, Brunet and colleagues continued to refine their approach and pursue this important area of translational research. It is gratifying to see this combination of basic-science informed thinking and determined clinical research begin to yield dividends.

Adjunctive Mid-Day Bright Light for Bipolar Depression: A Needed Option

A. John Rush, M.D.

Sit and colleagues (10) reported a robust symptom benefit with adjunctive 7000-lux bright light (N=23) versus 50-lux dim red light (the placebo condition) (N=23) in a 6-week randomized, double-blind trial of adults with depressed phase, bipolar I or II disorder, who were on stable concomitant medication regimens. Response was assessed with the Structured Interview Guide for the Hamilton Depression Scale with Atypical Depression Supplement (SIGH-ADS) (11). The remission rate for those treated with bright light was substantial (68.2%), as compared with the remission rate for those exposed to dim light (22.2%) (adjusted odds ratio=12.6) at weeks 5 and 6. No between-group difference in sleep quality was found. Numerically, more patients withdrew from the group exposed to dim light than from the group exposed to bright light (21.7% versus 4.3%), yet 87% of participants completed the trial.

The authors suggested that the later onset of differential effects at weeks 5 and 6 could have been due to the incremental dosing schedule: 15 minutes between noon and 2:30 p.m. in week 1, 30 minutes in week 2, 45 minutes in week 3, and 60 minutes in weeks 4 and 5—suggesting that the maximum light dosage is needed to produce a full response. Their results are consistent with another recent randomized, controlled trial (N=74) that found better response rates (78.2% versus 48.3%) with adjunctive bright light as compared with dim red light (both used in the morning) when added to stable medication regimens in patients with bipolar depression, although in that research, the participants began with the full dosage and saw earlier effects (12).

If bright light is indeed an effective adjunct to pharmacotherapy in bipolar depression (as suggested in two trials), several major clinical advantages inure. First, only a limited number of effective treatments are available for bipolar depressed phase patients (see Bobo and Shelton [13] for a review). Second, the therapeutic effect is apparently quite robust, so many patients might gain remission. The 1 hour/day treatment is modestly inconvenient, but light can apparently be used at midday (12 noon–2:30 p.m.) (10) or upon

arising (12). This therapy entails little risk of weight gain or sexual disturbances. Furthermore, bright light may be especially appropriate for adolescents, for whom multiple psychotropic medications are best avoided when possible, as well as for pregnant women or others in medically fragile states, where additional medications carry more risks. Finally, monitoring and support for treatment adherence could be easily provided through cloud-based web services.

Additional questions remain, of course. Will adjunctive bright light treatment continue to be effective over the long term? In which patients can it be stopped or reduced in dosage and when? Does effective bright light allow for simplification of medication regimens? What, if any, are the negative long-term consequences of intense midday bright light therapy in patients with bipolar disorder? Can we identify individual patients for whom bright light is best used or avoided—perhaps in those with chronobiological or other biomarkers? Isn't it time for a large definitive trial with potential biomarkers to address at least some of these questions?

Epigenetic Aging in Major Depressive Disorder

Susan K. Schultz, M.D.

Fighting aging is an increasingly common focus of public interest, considering the number of products, books, and blogs addressing this topic. The article by Laura K.M. Han and colleagues (14) offers insight into factors that account for biological aging through DNA methylation. Han et al. estimated DNA methylation age using all methylation sites in blood from a group of depressed adults and a control group. The DNA methylation ages of the subjects with depressive illness were higher than their chronological ages. Further, DNA methylation age was found to be significantly influenced by childhood trauma. This pivotal work helps us appreciate the degree to which aging is a dynamic lifelong process that is influenced continuously, beginning in early development, via epigenetic mechanisms. This finding offers perspective into how we miss opportunities to understand aging by focusing only on middle to later adulthood, when some of the more tangible health changes become apparent. The findings from Han et al. suggest that higher methylation aging is incurred in the presence of depression and that higher epigenetic aging overlaps with the mechanisms of chronological aging. These findings offer new insight into the health and mortality risks of depression. A new call for whole life care and preventive health practices may be the most powerful antiaging formula, one with foundations in real science.

Mapping Antipsychotic Drug Targets to Schizophrenia Risk Gene Networks

Carol A. Tamminga, M.D.

Rational approaches to drug development for schizophrenia are long sought and rare. So, the article by Kauppi et al. (15), "Revisiting Antipsychotic Drug Actions Through Gene Networks Associated With Schizophrenia," caught my attention. Here the authors advocate for the use of gene/protein network analysis in addressing the need for therapeutic treatments in schizophrenia. The Psychiatric Genomics Consortium's genetic analysis, which found 108 schizophrenia risk loci (16), was foundational to this article by providing a sufficient number of schizophrenia risk genes to which to apply the tools of network science (17). Kauppi et al., took two data sets, one of genes for schizophrenia developed by the Consortium (16) and the other, of the genes associated with antipsychotic drug action; they subjected these to novel computational network analyses to identify "gene-schizophrenia disease" with "gene-antipsychotic drug" interactions. This analysis found, first, a set of schizophrenia risk genes significantly more interconnected with each other than by chance; then, four genes were found that overlapped as schizophrenia risk genes and as targets for antipsychotic drugs: GRM_3, DRD_2, $CHRM_4$, and CYP_2D6. In addition, the researchers identified several molecular targets within the disease risk genes that were not connected to current antipsychotic drugs, representing potentially novel targets for these medications. These results are not yet at the stage of direct application, but rather are available for further development in identifying disease and drug targets for informative studies. The article represents a novel alternative strategy for drug discovery. The availability of large data sets makes this approach an early example of new computational strategies for drug discovery.

From *The AJP Residents' Journal*: Inspiration and Integrated Care

Oliver Glass, M.D.

The American Journal of Psychiatry Residents' Journal has evolved significantly over the last year. As Editor-in-Chief, I have expanded the editorial board and focused on inspiring trainees as they attempt to build their curricula vitae. In the next year, *The AJP Residents' Journal* editors will be looking for articles on integrated care, a topic that is vital for the sustainability of our health care system. We also recognize issues with societal impact, such as mental health among veterans and the gravely ill and celebrities who have died by suicide. It is with honor that I select "Reflections on the Spade and Bourdain Suicides" by Somya Abubucker, M.D., (18) as an article that conveys what many of us feel but may not have been able to articulate. In this article, Dr. Abubucker, this year's Culture Editor and Social Media Editor for *The AJP Residents' Journal*, calls for more research into understanding suicide risk and creating safety plans for those in need. Although some may argue that progress has been made, mental health stigma continues to linger deep in our culture. As trainees, psychiatrists, and health professionals, we must lead the effort to dismantle this stigma so that individuals who struggle with psychiatric crises can obtain immediate

support. One way to help those with mental health challenges is to provide them with adequate access to resources, such as the National Suicide Prevention Lifeline, 1-800-273-TALK (8255). Developing an integrated care model within our health system also is important. Collaborative care among specialties will allow for mental health to be interwoven within primary care, ultimately allowing for the dismantling of stigma.

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Disclosures of financial relationships of the Editors of *The American Journal of Psychiatry* appear in the April 2018 issue. Dr. Pine is serving in a personal capacity; the views expressed are his own and do not necessarily represent the views of NIH or the U.S. government.

Am J Psychiatry 2018; 175:1163–1166; doi: 10.1176/appi.ajp.2018.18091065

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