Past and Present Progress in the Pharmacologic Treatment of Schizophrenia

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Despite treatment advances over the past decades, schizophrenia remains one of the most severe psychiatric disorders that is associated with a chronic relapsing course and marked functional impairment in a substantial proportion of patients. In this article, a historical overview of the pharmacologic advances in the treatment of schizophrenia over the past 50 years is presented. This is followed by a review of the current developments in optimizing the treatment and outcomes in patients with schizophrenia. Methodological challenges, potential solutions, and areas of particular need for further research are highlighted. Although treatment goals of response, remission, and recovery have been defined more uniformly, a good "effectiveness" measure mapping onto functional outcomes is still lacking. Moreover, the field must advance in transferring measurement-based approaches from research to clinical practice. There is an ongoing debate regarding whether and which first- or second-generation antipsychotics should be used. However, especially when considering individual adverse effect profiles, the differentiation into first- and second-generation antipsychotics as unified classes cannot be upheld, and a more differentiated view and treatment selection are required. The desired, individualized treatment approach needs to consider current symptoms, comorbid conditions, past therapeutic response, and adverse effects, as well as patient choice and expectations. Acute and long-term goals and effects of medication treatment should be balanced. To date, clozapine is the only evidence-based treatment for refractory patients, and the role of antipsychotic polypharmacy and other augmentation strategies remains unclear, at best. To discover novel treatments with enhanced/broader efficacy and improved tolerability, and to enable personalized treatment, the mechanisms underlying illness development and progression, symptomatic improvement, and side effect development need to be elucidated.

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This article is part of a series honoring the 50th anniversary of the NCDEU Annual Meeting. This meeting has fostered, facilitated, documented, and disseminated a vast growth in our knowledge of clinical psychopharmacology and our ability to apply that knowledge to improving the lives of millions of people. We will try to put some of the historical development in the context of present challenges and future needs and opportunities.

EARLY BEGINNINGS AND THE ROLE OF THE EARLY CLINICAL DRUG EVALUATION UNITS

When the first meeting of the Early Clinical Drug Evaluation Units (later, the *New* Clinical Drug Evaluation Unit [NCDEU]) took place in 1959, it had been approximately 5 years since the introduction of chlorpromazine in the United States, and clinical trial methodology was in its formative stages.

In 1952, a French surgeon was exploring strategies to reduce surgical shock. He thought that antihistamines might be an effective approach. He noticed, however, that an antihistamine that he was using, chlorpromazine, had a powerful effect on mental state. A psychiatrist, Pierre Deniker, heard about these observations and decided to try chlorpromazine in some of his most difficult-to-manage patients. The results were remarkable. After some reluctance on the part of academic psychiatrists and psychologists in the United States to support testing of the drug, its value was demonstrated among patients in state institutions, and ultimately chlorpromazine was approved by the US Food and Drug Administration (FDA) in 1954. By 1964, approximately 50 million people around the world had been treated with this medication, and a revolution in the management of psychotic disorders was underway.

The somewhat serendipitous observation that chlorpromazine had pronounced "calming" activity even in individuals with psychotic signs and symptoms was one of the great advances in 20th century medicine. Although other drugs (eg, reserpine) had been used with some success to treat psychosis,[1] the safety index and overall effectiveness of chlorpromazine, and subsequently other dopamine receptor antagonists, radically changed our ability to treat schizophrenia and other psychotic disorders on a wide scale.

The pace of new discoveries regarding effective psychotropic medications in the 1950s and 1960s was staggering. At the same time, tension remained between the psychodynamic and biologic perspectives regarding the etiology and treatment of the major psychiatric illnesses. Considerable efforts were made to study the impact of psychotropic drugs, and increasingly sophisticated methodologies were brought to bear as clinical trials in medicine underwent rapid development.

In 1949, the World Health Organization published the sixth revision of the *International Statistical Classification of Diseases* (*ICD*), which for the first time included a section on

mental disorders.[2] The first official *Diagnostic and Statistical Manual of Mental Disorders* was published in 1952 by the American Psychiatric Association (APA).[3] Diagnostic criteria were not really specified for discrete disorders until the third edition of *DSM*,[4] which attempted to improve the validity and reliability of psychiatric diagnosis. This, in turn, had enormous implications for clinical practice, clinical research, and drug development.

The ECDEU, which were established by the National Institute of Mental Health (NIMH), served as unique platforms for clinical investigation. They were designed to provide stable funding for investigators studying new drugs. The Psychopharmacology Research Branch, which provided funding and guidance for these units, played a critical role in the advancement of the field.

An example of a seminal contribution by Jerry Levine, William Petrie, and Nina Schooler of NIMH, with colleagues from the Biometric Laboratory at George Washington University, was the first publication of the *ECDEU Assessment Manual for Psychopharmacology* in 1976.[5] The development and testing of assessment instruments that could be demonstrated to be both valid and reliable for the measurement of therapeutic effects on a variety of disease categories was a major advance.

A NEW ERA OF EVIDENCE-BASED PSYCHOPHARMACOLOGY AND THE ROLE OF THE NIMH PSYCHOPHARMACOLOGY SERVICE CENTER

In 1969, Donald Klein and John Davis published a seminal work entitled *Diagnosis and Drug Treatment of Psychiatric Disorders*.[6] In the introduction, they wrote,

> This simple dichotomy between medical and nonmedical practitioners does less than justice to the complicated therapeutic scene. The medical practitioners are divided largely into 2 polar camps: the analytical and psychological versus the organic and directive. The first group developed an ideology that rejects the use of organic treatments and directive methods as usually ineffective, symptomatic at best, and destructive of the growth potential of the patient by fostering pathological dependence. This stand was reinforced by the obvious ineffectiveness of most organic therapies, complicated by the addictive potential and social incapacitation often produced by sedative agents. The directive and organic group, on the other hand, emphasized short-term manipulative and symptom-relieving procedures, deriding or ignoring concern with the resolution of intrapsychic conflict and patient maturity. Unfortunately, the positive contributions of both groups were obscured by their respective biophobic and psychophobic attitudes. One might speculate that the fierce adherence of each group to its methods in the face of the remarkable lack of systematic comparative studies attests to a profound insecurity as to the value of one's procedures, dealt with by a compensatory evangelism.
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> We may be fortunate to be entering a period in which rational comparative study will become standard for therapeutic decision. Although clinical hunches and results of clinical experience are important factors in the termination of proper treatment, the findings of research studies, particularly those which are done with controlled double-blind technique, provide the behavioral scientific data for informed decision. Also important is the evidence available on the interaction of the somatic therapies with other treatment forms, such as psychological and social therapies. This book is an initial effort to organize and present such material to the psychiatric practitioner for his critical review.

With the establishment of The National Institute of Mental Health Psychopharmacology Service Center, a series of cooperative studies led by Jonathan Cole was conducted.[7] They included both private and public hospitals and initially compared chlorpromazine, fluphenazine, and thioridazine with placebo. All 3 drugs were found to be equally effective and more efficacious than placebo. A second NIMH Cooperative Study[8] compared chlorpromazine, acetophenazine, and fluphenazine. No specific drug showed a consistent pattern of superiority across the 57 dependent variables that were assessed.

By 1969, when Klein and Davis published their review,[6] they identified 126 controlled studies comparing antipsychotic drugs and placebo in which the medications were found to be more effective and 26 comparisons in which they were not. The authors also examined the role of dose adequacy and found that most of those studies that found chlorpromazine to be ineffective used very small doses, and all 23 studies that employed doses over 500 mg were positive. Similarly, in all studies, which were judged to be methodologically rigorous, the phenothiazine derivatives (and reserpine) were shown to be more effective than controls.

NEUROMOTOR SIDE EFFECT CONCERN

Shortly after the introduction of the phenothiazines, concerns about adverse neurologic effects—first "parkinsonism" and subsequently tardive dyskinesia—took on considerable saliency. Theories as to minimum effective dosage utilized subtle parkinsonism as a measure of adequate dosing.[9] However, both the frequency and potential functional consequences (including attendant stigma) associated with adverse neurologic effects became an important focus of attention.[10–12] Given the frequency of extrapyramidal symptoms (EPS) and likelihood of underdiagnosis,[13–15] debate ensued as to whether the use of prophylactic antiparkinsonian medication should be routinely recommended. At the same time, antiparkinsonian agents were associated with their own burden of adverse effects.

In the 1980s, the concern about tardive dyskinesia became even more intense with increasing medicolegal issues and the publication of 2 APA Task Force Reports.[16,17] Ultimately, prospective studies began to clarify both the incidence of and risk factors for tardive dyskinesia. The incidence was generally found to be 5% per year of cumulative antipsychotic drug

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exposure with first-generation antipsychotics.[18,19] Increasing age, particularly the postmenopausal phase in women, was associated with higher risk, as was vulnerability to early occurring extrapyramidal side effects.[20]

ANTIPSYCHOTIC DOSE FINDING AND BLOOD LEVELS IN FLUX

Phases in dosage recommendations also ensued over the coming decades with trials of very high doses[21] and trials of very low doses,[22] with, as usual, mixed results. In general, however, once blood levels of psychotropic drugs became widely available, it became apparent that very high doses provided no added value for the average patient and that measuring blood drug levels might help to some degree in explaining the heterogeneity of response.[23] Measurement of blood drug levels never really caught on in routine clinical practice, and even now they play much less of a role in research than they did in the 1980s (for reasons that are not entirely clear). The identification of dopamine as a key neurotransmitter in the mechanism of action of antipsychotic drugs and the discovery of various dopamine receptors in specific brain regions led to renewed enthusiasm about finding more "rational" pharmacologic agents and again setting the stage for further progress in understanding dosage requirements and heterogeneity of response. A number of studies emphasized the feasibility of utilizing substantially lower doses in the maintenance phase of treatment than had been commonly employed.[24,25] Interestingly, the most informative studies examining dose-response relationships in maintenance treatment and relapse prevention utilized long-acting injectable formulations. This was particularly important in eliminating the potential confound of poor or partial adherence with dosing requirements.[22] Although these studies emphasized the feasibility of utilizing lower than customary doses, they also established thresholds below which relapse rates increased substantially.

Concerns regarding dose-response (and dose-tolerability) relationships were also an important focus in evaluating comparative data between first- and second-generation antipsychotics. Although some reviews and meta-analyses had suggested that some of the apparent superiority of second- versus first-generation antipsychotics was due to unnecessarily high dosages of first-generation medications,[26] other reviews have not supported this conclusion.[27,28] It has been shown that even low doses of haloperidol, ie, 4 mg/d, in the acute treatment of chronic patients are associated with a significant risk of EPS.[29] Moreover, in 2 recent first-episode studies, haloperidol treatment of 3 mg/d was associated with significantly greater relapse rates[30] or all-cause discontinuation rates[31] than the second-generation comparators.

MAINTENANCE TREATMENT AND RELAPSE PREVENTION

In the late 1950s,[32,33] investigators began to systematically examine the consequences of controlled phenothiazine withdrawal. It became increasingly apparent that patients receiving placebo experienced significantly higher rates of rehospitalization than patients continuing to receive medication.[34]

By 1969, Klein and Davis were already recommending that "all patients who have an acute schizophrenic psychosis should be maintained on phenothiazine, possibly with an adjunctive antidepressant, indefinitely."[6(p160)] However, others did not share this view, and it took many years to establish a consensus as to the need for maintenance treatment, particularly in the early phases of a schizophrenia illness.

The increasing concern about tardive dyskinesia in the 1980s led to a reevaluation of the overall benefit-to-risk ratio of maintenance or relapse prevention treatment. There were renewed efforts to establish minimum effective dosage and/or the value of "intermittent" or "targeted" treatment, all of which were intended to reduce cumulative medication exposure, with the hope of reducing the incidence of tardive dyskinesia. These results helped to further clarify the need for continuous maintenance treatment for the average patient and confirmed a threshold of drug activity that was necessary to prevent or delay relapse.[35]

ADDRESSING NONADHERENCE

In the 1970s, long-acting injectable fluphenazine enanthate and fluphenazine decanoate were approved. Fluphenazine decanoate ultimately became the more widely used agent because of better tolerability.[36] This provided a strategy to help patients overcome the challenges of consistent medication-taking in the face of a complex illness often resulting in poor insight and impaired cognitive functioning.[37,38] Despite the promise of this approach, the use of long-acting injectable medications never became as popular in the United States as it did in many other countries. However, the current availability of more and newer agents in long-acting formulations[39] in combination with ever increasing needs to control the costs associated with relapse and rehospitalization might yet impact utilization rates.

TREATMENT-REFRACTORY ILLNESS AND CLOZAPINE

With the development and testin g of clozapine in Europe, early observations suggested a novel compound had been developed with a qualitatively different clinical profile. Most clinicians were impressed with the relative absence of drug-induced extrapyramidal effects, although some debate arose as to the incidence of akathisia. In addition, early observations indicated the potential of clozapine to have some therapeutic benefit among patients who had failed to respond to other agents. At the same time, a series of cases of agranulocytosis associated with clozapine were reported in Finland and elsewhere.[40] This led to a delay in the further development of clozapine in the United States. However, once a large clinical trial was conducted demonstrating the clear superiority of clozapine over chlorpromazine in treatment-

refractory schizophrenia patients,[41] the benefit-to-risk ratio (with the requirement for weekly blood monitoring) was felt to be sufficient to justify FDA approval with the narrow indication for treatment-resistant patients in 1990. Since then, the singular role of clozapine in treatment-refractory patients with schizophrenia has been confirmed.[42]

To some extent, clozapine served as a prototype and a stimulus for the development of other new drugs with the receptor-binding profiles that might replicate clozapine's unique clinical attributes. This created a number of challenges, particularly in various domains of drug development as well as in clinical design and methodology. It might be said that a major focus of work in the past decade has been to clarify the extent to which any, some, or all of the second-generation (sometimes referred to as *atypical*, a term that we believe has outlived its usefulness) medications are superior to any, some, or all of the first-generation antipsychotics.

In this context, a reemphasis on the study of dose-response relationships and dose equivalency between drugs has occurred,[43] as did a partial reevaluation of the public health importance of drug-induced parkinsonism and tardive dyskinesia.[44]

ATTENTION TO FIRST-EPISODE SCHIZOPHRENIA

Beginning in the mid 1980s, the field started to focus on patients with a first episode of schizophrenia.[45] The increased attention on first-episode patients seemed warranted in order to evaluate treatment outcomes that were not confounded by the effects of prior treatment, multiple relapses, and chronic illness. Studies revealed cognitive and psychosocial deficits that were present at illness onset,[46] a long duration of untreated psychosis prior to first mental health contact and treatment,[47] and increased sensitivity to medication side effects,[48] but also a better treatment response compared to more chronically ill patients.[49] These results, representing a mixture of putative pathophysiologic processes and environmental effects, were greeted with efforts to shorten the duration of untreated psychosis through outreach, which has been associated with some degree of improved outcomes.[50]

However, despite interventions during the first episode of schizophrenia, the overwhelming majority of patients was found to relapse in the subsequent years,[51] with medication discontinuation significantly increasing risk, and the achievement of at least 2 years of concurrent symptomatic and psychosocial recovery has remained as low as 15%.[52] The documented low recovery rates revitalized efforts at testing an integrated, personalized, and evidence-based psychopharmacologic and psychosocial intervention package against treatment as usual in first-episode patients in 2 parallel NIMH-funded Recovery After an Initial Schizophrenia Episode (RAISE) projects (http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml) to evaluate if the functional outcome trajectory can be modified early in the illness phase. In addition, as part of the move toward the early treatment of schizophrenia, and the response to new FDA incentives, the efficacy of antipsychotics has also been tested and validated in recent years in a series of placebo-controlled studies in adolescents with schizophrenia.[53]

THE PRODROME TO SCHIZOPHRENIA: EARLY RECOGNITION AND PREVENTION EFFORTS

Stimulated by first-episode research and the related recognition of a symptomatic, "prodromal" phase preceding the first full psychotic episode, early identification and intervention even during the prepsychotic illness phase became an area of increasing research attention beginning in the 1990s. The development of specific assessment tools and delineation of criteria for individuals considered at clinical high risk for psychosis[54,55] were followed by the examination of conversion rates in at-risk cohorts followed naturalistically. However, despite initially encouraging results concerning the predictive validity of the psychosis risk syndrome criteria, recent studies have reported declining conversion rates,[56] highlighting the need for further investigations. Throughout a series of mostly small, randomized, controlled studies, several pharmacologic and nonpharmacologic interventions, involving omega-3 fatty acids, second-generation antipsychotics, and cognitive-behavioral therapy, have been found to delay or prevent the onset of psychosis, at least as long as the active treatment was provided.[57] However, recent discussions of potentially including the psychosis risk syndrome in *DSM-V* have been met with criticism for fear of a high rate of false-positives; an overmedicalization of ill-defined and nonspecific psychopathology; insufficient time and training in clinical settings to utilize complex, research-based instruments for the identification of high-risk individuals; and the resultant risk of stigma and the unnecessary use of treatments with a potential for significant long-term side effects.[57]

COMPARATIVE EFFICACY AND EFFECTIVENESS OF FIRST-GENERATION AND SECOND-GENERATION ANTIPSYCHOTICS

With the introduction of second-generation antipsychotics, findings of lower EPS burden and tardive dyskinesia risk were coupled with expectations of superior efficacy for positive, negative, and cognitive symptoms. Initial efficacy studies seemed to confirm the superiority of second-generation antipsychotics, but the comparator consisted predominantly of haloperidol, used at moderate to high doses and often without anticholinergic cotreatment, which made early treatment discontinuation and secondary negative symptom presentations more likely in haloperidol-treated patients. Since then, a series of acute phase and longer-term studies have been completed, including large efficacy-effectiveness hybrid trials[31,58–60] that compared first- and second-generation antipsychotics. These data have been evaluated and interpreted in a number of different ways. Interpretations include that

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there is no difference between first- and second-generation antipsychotics, that second-generation antipsychotics are superior to first-generation antipsychotics, that some second-generation antipsychotics are superior to either all or some first-generation antipsychotics, in general, or in certain efficacy and/or side effect domains, or in patient subgroups that are not yet easily identified prior to choosing a specific agent. Because such a number of divergent interpretations have been offered, this indicates that blanket statements do not do justice to the complex clinical situation and database.

Taken together, the evidence seems to suggest that in refractory patients, clozapine is superior to first-generation antipsychotics[61–63] and second-generation antipsychotics (although the latter was hardly confirmed by a recent meta-analysis,[64] which was attributed to inappropriately low clozapine doses). Compared to first-generation antipsychotics, only 3 second-generation antipsychotics (amisulpride, olanzapine, and risperidone) were superior based on Positive and Negative Syndrome Scale (PANSS) score change differences,[61] but these were also the medications studied at a time when first-generation antipsychotics predominated, whereas the newer second-generation antipsychotics were tested mostly at a time of predominant second-generation antipsychotic use. While this could have introduced a cohort sampling bias, the differences between nonclozapine antipsychotics were very modest, with effect sizes as low as 0.1 to 0.3. Similarly, differences between second-generation antipsychotics studied head-to-head were either nonexistent or also marginal, favoring in some comparisons risperidone (vs quetiapine and ziprasidone) or olanzapine (vs aripiprazole, quetiapine, risperidone, and ziprasidone), with the same low effect size difference of only 0.1 to 0.3.[59–61] Moreover, the differences between second-generation antipsychotics were even more restricted when not analyzing mean total PANSS score differences, but analyzing discontinuation of medication due to inefficacy.[61] Thus, differences in design, including active or placebo control, dosing, and sponsorship,[65–67] may have a greater impact on efficacy outcomes than the actual choice of nonclozapine antipsychotics.

The CATIE [Clinical Antipsychotic Trials of Intervention Effectiveness] and CUtLASS [Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study] studies seemed to suggest that there are generally no differences between second-generation antipsychotics and first-generation antipsychotics in all-cause discontinuation, especially when analyzing quality of life[60] and patients who had switched antipsychotics.[68] However, these conclusions have been challenged on the basis of insufficient sample sizes to make noninferiority claims.[69] Moreover, in first-episode samples, all-cause discontinuation rates and relapse rates were significantly higher at 1 and 2 years, respectively, with modestly dosed haloperidol compared to the respective second-generation antipsychotic comparators.[31] Even in chronically ill samples, relapse rates were also significantly higher in first-generation antipsychotics, although haloperidol doses were higher than currently recommended.[70]

The clinical effectiveness of first-generation antipsychotics, a measure of objective and subjective outcomes encompassing symptom-based and functional effects, is challenged by increased acute[71] and chronic[72] extrapyramidal side effects and related symptoms of dysphoria, compared to second-generation (atypical) antipsychotics. Even though at chlorpromazine equivalents below 600 mg/d there was no increased EPS rate with typical versus atypical antipsychotics, at those doses, the efficacy of second-generation antipsychotics was superior.[27] Furthermore, while masking of EPS can be achieved with prophylactic anticholinergic treatment,[58] the risk of tardive dyskinesia is not reduced, but rather potentially increased,[72] and recent data suggest that anticholinergic medication load is associated with decreased efficacy of cognitive remediation treatment.[73]

Ultimately, we feel that the controversy regarding the most likely oversimplified dichotomy between first- and second-generation antipsychotics has resulted in progress, in that it stimulated the conduct of large trials and examination of effectiveness outcomes beyond symptom reduction. These trials have generated new and important data, but also highlighted methodological challenges. These challenges include the definition of clinically meaningful endpoints, the effect of baseline medication and past treatment history, the limitation of available treatments used at a more chronic illness phase, and the importance of differences in acute and long-term adverse effects. All of these data point to the need for new treatments with novel mechanisms, tailored approaches that map onto the pathophysiology of the disease process (that may vary between patients and between different illness stages), and biologic dissection of patients into meaningful subgroups that can inform a stratified or, even, individualized treatment selection.

SHIFTING ADVERSE EVENT FOCUS TO PHYSICAL HEALTH

Over the last decade and coinciding with the predominant use of second-generation antipsychotics, there has been a shift in side effect concerns from parkinsonism and tardive dyskinesia to physical health risks and outcomes.[74–76] The relevance of antipsychotic-related weight gain was highlighted by data suggesting that severely mentally ill patients die on average 25 years earlier than the general population, and that this is predominantly due to premature cardiovascular and cerebrovascular mortality,[77] both of which are related to weight gain, obesity, and associated metabolic abnormalities. Reasons for the increased prevalence of the cardiovascular risk factors, morbidity, and mortality in the mentally ill are complex, but include effects of the psychiatric illness and poor lifestyle behaviors, but also weight gain and metabolic abnormalities conferred by psychiatric treatments, particularly second-generation antipsychotics. For a while, the discussion seemed to focus on having to decide between a higher risk for EPS and tardive dyskinesia with first-generation antipsychotics and a greater risk for weight gain

and long-term cardiometabolic consequences with second-generation antipsychotics. Increasingly, however, the field has been moving to a more differentiated view, recognizing that neither second- nor first-generation antipsychotics are homogeneous classes regarding adverse effect risk. Thus, although clozapine and olanzapine, 2 second-generation antipsychotics, are among the most weight gain–producing and metabolically problematic antipsychotics, the low-potency first-generation antipsychotic chlorpromazine is also associated with considerable adverse cardiometabolic effects.[78] Furthermore, high- and mid-potency first-generation antipsychotics most likely have a similar cardiometabolic risk potential as low-risk second-generation antipsychotics, such as aripiprazole and ziprasidone, yet, in treatment-naive and first-episode patients, all antipsychotics, even those considered more neutral in chronic patients, are associated with considerable weight gain.[79–81]

As a result of the antipsychotic-related cardiometabolic effects, the traditional role of psychiatrists as health care providers who have little to do with the somatic well being of their patients has been challenged. The redefinition of the psychotropic medication prescriber and psychiatric health care provider as at least an orchestrator/facilitator of integrated medical care and as the focal point of health care monitoring in patients receiving medications with cardiometabolic impact is still in process.[82] Despite the warning of the FDA in 2003 about the diabetes risk associated with antipsychotics, which was shortly followed by monitoring guidelines for weight, blood pressure, and fasting glucose and lipids in antipsychotic-treated patients,[83] a series of recent database and audit studies confirmed a concerning low rate of metabolic monitoring that in one study was similar to the background monitoring in a nonpsychiatric control population prescribed albuterol.[84,85] In addition to insufficient monitoring, several studies have shown that mentally ill patients receive substandard medical care targeting coronary heart disease risk factors in psychiatric settings[86–88] and addressing diabetes or myocardial infarction in medical settings.[89,90] While patient nonadherence with medical appointments and interventions might contribute to this problem, the field needs to effectively address the suboptimal monitoring and management behaviors of mental and medical health care providers, as well as systems issues of fragmented care and poor access to care.

RAISING THE BAR FOR OUTCOMES

In addition to a broadened focus on physical health, outcomes other than symptomatic improvement have become standard in the field. These include more standardized approaches to measuring response, remission, and recovery.[91–94] In addition, subjective well-being[95,96] and quality of life,[54] cognition,[97–99] and psychosocial performance, including employment,[100–102] have become endpoints of interest and goals for patients, families, clinicians, and researchers. To move toward these important goals, it has become clear that the field needs to study and engage in the routine application of measurement-based psychiatry, clinical and shared decision-making, psychoeducation, and adherence management, as well as in the integration of rational psychosocial treatment elements in the often too one-sided pharmacologic treatment planning.[103]

TARGETING INDIVIDUALIZED TREATMENT

Individualized treatment based on reliable probabilities of outcome for a specific patient is an important treatment goal. Unfortunately, this goal is still largely out of reach, due to the heterogeneity of patients and treatment response, most likely related to mostly unknown genetic, structural, and functional physiologic differences between patients and within patients over time. Efforts at increasing the predictability of outcomes have included clinically driven nosologic and phenomenological approaches, but these have not really succeeded. Current approaches that do not yet have clinical applicability include the use of genetics, neuroimaging, neurocognition, and blood- or tissue-based biomarkers and sets of biomarkers, also called *biosignatures*.[104,105] Similarly, developments are underway to define biomarkers as surrogate endpoints in drug development and approval.[106]

However, there is a powerful clinical tool that uses the patients' own response pattern to predict outcomes. This intraindividual test of early response/nonresponse as a predictor of subsequent response[107,108] or of dysphoric response[109] was studied briefly in the 1980s. As much as 15 to 20 years later, these findings have been revisited and expanded upon, stimulated by analyses showing that, at least at a group level, the majority of antipsychotic response occurs within the first few weeks[110,111] and, even, days[112] after antipsychotic initiation. Building on these findings, a series of post hoc analyses[113–117] plus a recent prospective study[118] showed that nonresponse at study endpoint can be predicted with high sensitivity, specificity, and predictive power by presence of less than a minimal response equivalent to less than 20% reduction in the PANSS[119] or Brief Psychiatric Rating Scale[120] total score at 2 weeks after antipsychotic initiation. However, having identified this general response pattern, questions remain as to whether response patterns are similar in likely more heterogeneous first-episode schizophrenia samples and in treatment-refractory patients, whether a limited set of specific symptom items that could be used in clinical practice is equally valid and reliable, what one can learn from symptom trajectories at an individual patient level, and what alternative treatments are likely to be more successful after early nonresponse has been identified.

CHALLENGES, UNMET NEEDS, AND FUTURE DIRECTIONS

A number of unmet needs and challenges exist in schizophrenia. These include methodological and practical problems, such as the decreasing ability to separate

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medication effects from placebo, with resultant high rates of "failed" trials and/or the need to increase sample sizes. Unmet needs also include areas of psychopathology that are insufficiently impacted with currently available treatments, such as negative symptoms and cognitive dysfunction, as well as problems with adherence to treatment guidelines and the adoption of best clinical practices, for example by the routine adoption of measurement-based treatment strategies. More work is also needed regarding the conduct of sufficiently large or long-term comparative effectiveness studies; the identification of simple, meaningful, and measurable effectiveness outcome measures; and the best ways to translate evidence into clinical practice. All of these areas seem to be amenable to incremental steps of improvement.

However, to qualitatively change outcomes in schizophrenia, there is a need for the detection of valid biomarkers and biosignatures that map onto the underlying pathophysiology of the disease. In this context, the discovery of mechanisms and predictors of efficacy and tolerability is required to guide the rational treatment selection. Our increasing technological sophistication makes biomarker studies more feasible in an age when clinical classification might be replaced by genomic, proteomic, or metabolomic approaches, to name but a few. The resultant developments are expected to greatly facilitate the much needed discovery of mechanistically novel treatments that either work in a complementary way, enabling also rational combination treatments, or are particularly effective for specific symptom domains and readily separable subgroups of patients. The resultant new treatments will hopefully speed up or increase the magnitude of symptom reduction across all relevant domains of schizophrenia, enhance relapse prevention, and bolster efficacy for nonresponders and currently refractory patients, while reducing the likelihood of developing key adverse effects. Finally, the primary or secondary prevention of psychosis is an important goal that will depend, in part, on uncovering mechanisms underlying the susceptibility for and progression toward psychosis, so that neuroprotective and low-risk agents can be investigated in samples that can be characterized as being at true risk for psychosis in a highly reliable way.[49]

To discuss the specific agents under development for these various treatment targets is beyond the scope of this review, but compounds are being explored with a variety of putative mechanisms of action. These include metabotropic glutamate agonists, α-nicotinic receptor agonists, muscarinic agonists, histamine-3 receptor antagonists, glycine transporter inhibitors, ampakines, phosphodiesterase-10 inhibitors, D_1 agonists, D_3 antagonists, 5-HT_{2A} antagonists, and partial dopamine agonists, among others.[121–124]

SUMMARY AND CONCLUSION

In summary, building on more than 5 decades of pharmacotherapy research and clinical practice in schizophrenia, in which the ECDEU and NCDEU played a major role, the field has finally entered a phase that promises to develop and test the necessary tools that will enable more targeted and, ultimately, individualized treatment approaches. The hope is that a more detailed mechanistic understanding of the factors involved in the development, progression, and amelioration of the disease process will give rise to a number of new treatment approaches and that the focus will shift from symptomatic to disease-modifying and, ideally, curative interventions. Being in the midst of these developments, it is important to realize how far we have come, what role the prior advancements have played in our current state of knowledge, and what still needs to be accomplished to further improve the outcome of patients suffering from schizophrenia.

Drug names: albuterol (Proventil and others), aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), reserpine (Serpalan and others), risperidone (Risperdal and others), ziprasidone (Geodon).

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