Factors That Influence Treatment Success in Schizophrenia

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This article reviews the factors that influence (and typically limit) treatment success in schizophrenia. These factors can be conveniently grouped into 3 categories: treatment-related factors, patient-related factors, and environment- or system-related factors.

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TREATMENT-RELATED FACTORS THAT INFLUENCE SUCCESS

Key treatment factors, as they relate to pharmacotherapy, include *Was the right drug chosen? Was the drug administered at an adequate dose?* and *Was the drug taken for an adequate duration?* From an evidence-based medicine standpoint, data are currently not available to provide clear and unequivocal guidance to clinicians on any of these 3 issues.

Right Choice of Drug

Multiple randomized controlled trials (RCTs) have been reported, the great majority sponsored by pharmaceutical companies, which compare second-generation antipsychotics (SGAs) to first-generation antipsychotics (FGAs) or to other SGAs. The results vary across trials, but meta-analyses by the Cochrane group and other authors[1–3] support an advantage in efficacy for clozapine over FGAs. Olanzapine and risperidone appear to offer perhaps a modest advantage in efficacy over FGAs, while other atypical antipsychotics (quetiapine, ziprasidone, aripiprazole) have not demonstrated consistent superiority in efficacy to FGAs.

Meta-analytic data provide a one-size-fits-all answer that blurs clinical issues important to decision-making about choice of drug. Choice of drug must take into account not only efficacy but also the relative safety and tolerability, as well as cost, of each antipsychotic. Safety and tolerability are especially important when considering choosing an SGA, because within-class differences in efficacy are relatively modest. In addition, interindividual differences between patients are paramount. However, our understanding of these variables is limited.

Few studies provide comparator data on whether there are differences between individual SGAs and FGAs in terms of efficacy in *specific* clinical presentations such as (1) first-episode versus chronic versus treatment-resistant patients; (2) patients with prominent positive or negative symptoms; (3) patients with depression, anxiety, substance use disorder, or other comorbidity; and (4) patients with medical comorbidity.

Ideally, within-class meta-analytic comparisons should evaluate efficacy, not as a unidimensional outcome, but in terms of the differential efficacy of each drug on multidimensional end points, such as positive or negative symptoms, cognitive function, social withdrawal, and quality of life and functioning. Expert panels have also provided consensus input on first-line recommendations. An earlier panel offered treatment strategies for patients with chronic schizophrenia who present with predominantly negative symptoms (risperidone, aripiprazole, and ziprasidone and then olanzapine, quetiapine, or clozapine); for patients in whom both positive and negative symptoms are prominent (risperidone, aripiprazole, ziprasidone, and olanzapine and then quetiapine or clozapine); and for patients whose clinical picture is complicated by suicidal behavior (clozapine, followed by risperidone, olanzapine, and ziprasidone).[4]

Given the inherent limitations in the generalizability of RCTs to the complexities of clinical practice, the ongoing publication of the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[5] represents an important first step in the use of neutrally funded, multicomparator, effectiveness trial designs to

address real-world clinical practice issues. In CATIE, patients meeting DSM-IV criteria for schizophrenia (N = 1493) were randomly assigned to 18 months of double-blind, parallel-group treatment with olanzapine (7.5–30 mg/day), perphenazine (8–32 mg/day), quetiapine (200–800 mg/day), risperidone (1.5–6.0 mg/day), or ziprasidone (40–160 mg/day; this treatment group was added after 40% of enrollment was complete). Restricting the heterogeneity of the patient sample and the generalizability of the results were the following exclusions: (1) first-episode patients, (2) treatment-resistant patients, (3) patients with a serious and unstable medical condition, (4) patients with a history of adverse effects from any of the study medications, and (5) patients with schizoaffective disorders. The primary outcome was treatment discontinuation for any cause. Increasing the generalizability of the study were the inclusion of patients with comorbid substance use disorder (37%), comorbid medical illnesses (diabetes, 11%; hyperlipidemia, 14%; hypertension, 20%), and patients taking concomitant medications.

A Kaplan-Meier analysis found that treatment with olanzapine was associated with significantly longer time to discontinuation for any reason compared to quetiapine and risperidone.[5] Time to discontinuation due to lack of efficacy was significantly longer for olanzapine compared to quetiapine, risperidone, and perphenazine.[5] Finally, contrary to previous data from RCTs that have tended to find larger differences in tolerability than in efficacy, CATIE showed no significant between-drug differences in time to discontinuation due to intolerability.[5] Any between-drug differences in time to discontinuation were small compared to the large overall discontinuation rate: 74% of patients discontinued before 18 months, ranging from a low of 64% in the olanzapine group to a high of 82% in the quetiapine group.

As with efficacy, tolerability and discontinuation rate data are conflicting across studies. For example, comparative rates of treatment discontinuation (defined as > 14 days off medication) have been recently reported for a large sample (N = 2947) of patients diagnosed with schizophrenia or schizoaffective disorder who were treated in the managed care setting.[6] The hazard ratios (HRs) versus FGAs for time to treatment discontinuation found the lowest risk of discontinuation among patients treated with aripiprazole (HR = 0.60), followed by quetiapine (HR = 0.67), ziprasidone (HR = 0.74), risperidone (HR = 0.79), and olanzapine (HR = 0.83).

Role of Concomitant Medications and Polypharmacy

The use of concomitant medications frequently occurs in the treatment of schizophrenia. For example, in a 1-year naturalistic outpatient study,[7] 57% of patients had a prolonged period (> 60 days) of polypharmacy, with 43% of the total sample receiving polypharmacy for longer than 6 months. Despite the frequency of polypharmacy, RCTs that

systematically evaluate the efficacy, safety, and tolerability of combination therapy are remarkably absent.

Adequate Dose of Drug

Choosing an adequate dose is as important as choosing the right drug. Here, again, there is a relative dearth of controlled research designed to establish dose-response curves for key clinical outcomes, and (ideally) to correlate these dose-response curves with plasma levels, and, where feasible, with receptor occupancy based on positron emission tomography imaging.

Fixed-dose study designs are required to establish the relationship between dose and response. It is important to note that dose-response curves may be different for improving various outcomes (e.g., positive symptoms, negative symptoms, cognitive function). Dose-response curves may also differ in patients who are experiencing a first episode versus patients with chronic schizophrenia. Similarly, acute versus maintenance treatment may have different optimal dose requirements for preventing recurrence.

An issue that is closely related to dose response is dose equivalence. Dose equivalence among antipsychotics is important, because the great majority of patients treated for prolonged periods will switch drugs at some point (and often multiple times), due to either efficacy or tolerability issues. Knowing dose equivalence facilitates decision-making. It is also useful for clinicians to know dose equivalence in order to better judge the results of comparator RCTs. Although comparator trials are necessary, they often report conflicting results that may be attributable, at least in part, to differences in dosing regimens. For example, one study reported that olanzapine was superior (mean daily dose = 17.2 mg) to risperidone (mean daily dose = 7.2 mg),[8] while another study reported that risperidone (mean daily dose = 4.8 mg) was superior to olanzapine (mean daily dose = 12.4 mg).[9] In another recent randomized (but not blinded) effectiveness trial, aripiprazole (mean daily dose = 19.9 mg) was compared with ziprasidone (mean daily dose = 103.4 mg), risperidone (mean daily dose = 3.4 mg), quetiapine (mean daily dose = 352 mg), and olanzapine (mean daily dose = 13.9 mg). All 3 of these studies raise the issue of whether the efficacy advantage for the sponsor's drug was achieved by use of suboptimal doses of competitor drugs.[10]

The current author conducted a survey[11] of clinical psychiatrists attending a national meeting to elicit information on dose equivalence of SGAs to a daily dose of 4 mg of risperidone. The modal dose endorsed as equivalent was 15 mg for aripiprazole, 160 mg for ziprasidone, 600 mg for quetiapine, and 15 mg for olanzapine. A survey of experts[4] had previously reported dose equivalence data, also based on 4 mg of risperidone as a benchmark dose (Table 1). The expert dose equivalence estimates were similar for olanzapine (15 mg) and aripiprazole (15 mg), but experts who were surveyed gave notably lower dose

Table 1. Comparison of Daily Dosing and Estimated Dose Equivalence Across Studies and Settings[a]

Drug	Target Dose Range, PDR, 2007[13]	Current Average Prescribed Dose, IMS data,[12] 2005	CATIE Mean Dose (chronic), Lieberman et al,[5] 2001–2004	CAFE Mean Dose (first episode) Keefe,[14] 2002–2004	Expert Panel: Mean Consensus Dose Equivalent to Risperidone 4 mg, Kane et al,[4] 2002	Near Maximal Effective Dose, Based on Dose Response Data, Davis and Chen,[2] 1995–2003	Mean Dose for Hospitalized Patients, Citrome et al,[15] 2003
Perphenazine	12–24 mg	21.0 mg	20.8 mg	…	24 mg	…	…
Olanzapine	10–15 mg	15.7 mg	20.1 mg	11.7 mg	15 mg	16+ mg	22.5 mg
Risperidone	4–8 mg	3.6 mg	3.9 mg	2.4 mg	4 mg	4 mg	4.5 mg
Quetiapine	300–500 mg	420.4 mg	543.4 mg	506 mg	450 mg	150–600 mg	597.7 mg
Ziprasidone	40–160 mg	136.9 mg	112.8 mg	…	120 mg	120–160 mg	135.0 mg
Aripiprazole	10–15 mg	…	…	…	15 mg	10 mg	22.4 mg

[a]For surveys, year refers to reported (or approximated) year of survey.
Abbreviations: CAFE = Comparison of Atypicals for First-Episode Psychosis, CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, IMS = Intercontinental Medical Systems, PDR = Physicians' Desk Reference.
Symbol: … = not included.

equivalence estimates for ziprasidone (120 mg vs. 160 mg) and quetiapine (450 mg vs. 600 mg).

It is of interest to compare these 2 survey results to other published data on dosing. Davis and Chen[2] have published a meta-analysis in which they attempt to use dose-response data, available as of 2003, to determine the "near maximal effective" dose for SGAs. Table 1 summarizes their findings, as well as dosing results from other data sources. A few trends noted in Table 1 deserve comment. First, as expected, daily doses of hospitalized patients were consistently higher than doses used in primarily outpatient settings. Also as expected, doses were also consistently higher for the treatment of patients with chronic compared to first-episode schizophrenia. When the expert panel recommendations[4] are compared to the Davis and Chen meta-analysis of near-maximal doses, the results are similar, with 2 exceptions: Davis and Chen found the aripiprazole dose-response curve to asymptote at 10 mg, while the expert panel recommended use of a notably higher dose (15 mg); conversely, the expert panel recommendation for ziprasidone was on the low end (120 mg) of the meta-analytic "near maximal effective" dose identified by Davis and Chen. When mean doses in CATIE[5] are compared to current average dosing used in the community,[12] the doses of perphenazine and risperidone are very similar, while the daily doses of olanzapine and quetiapine are notably higher than community dosing and expert panel recommendations, and at the high end of maximal doses suggested by the Davis and Chen meta-analysis.[2] In contrast, CATIE dosing of ziprasidone is lower than average community dosing and expert panel recommendations and at the low end maximal doses suggested by the Davis and Chen meta-analysis.[2]

One important limitation of dose equivalence discussions is that they are predicated on the assumption that, at optimal doses, all FGAs and SGAs are equivalent in efficacy. While this may be the case, it also may not. Much more detailed information from fixed-dose studies is needed, based on head-to-head comparator trials, to determine the efficacy asymptote (noninferiority).

Adequate Duration of Treatment

As with so many decisions in the treatment of schizophrenia, data as to what constitutes an adequate duration of acute treatment based on RCTs specifically designed to address this issue are not well established.

In the absence of these types of studies, the best we can do is rely on consensus recommendations. If little or no response is observed, then experts have recommended that treatment be continued for 3 to 6 weeks; if a partial response is observed, then the recommendation is to continue treatment for 4 to 10 weeks. There is also disagreement as to whether the next step in the event of an inadequate response is to increase the dose or switch the medication. Depending on the SGA being used, 57% to 93% of an expert panel recommended that a dose increase be tried first, while 7% to 43% recommended switching medication as a first step.[7]

Reasons for switching medication include inadequate response in 1 or more efficacy parameters, as well as intolerability due to a range of adverse events, including extrapyramidal symptoms, weight gain, sedation or insomnia, anticholinergic effects, subjective dysphoria, or metabolic problems.

Two separate switch studies were recently reported in phase II of the CATIE trial. In the first ("tolerability pathway") trial,[16] patients (N = 444) who had discontinued an SGA for any reason in CATIE phase I were randomly assigned to 18 months of double-blind treatment with a different SGA, either olanzapine (mean daily dose = 20.5 mg), quetiapine (mean daily dose = 565.2 mg), risperidone (mean daily dose = 4.1 mg), or ziprasidone (mean daily dose = 115.9 mg). Discontinuation rates for any reason were high across all treatments, but were significantly lower for olanzapine (67%) and risperidone (64%) compared to quetiapine (84%) or ziprasidone (77%). Among the subgroup of patients who discontinued phase I due to lack of efficacy, olanzapine performed best in phase II, mostly due to greater improvement in the Positive and Negative Syndrome Scale (PANSS) positive

symptom and general psychopathology subscales. In contrast, the subgroup that discontinued phase I due to lack of tolerability did worse taking olanzapine in phase II (80% discontinuation rate) compared to risperidone (63% discontinuation rate). Interestingly, patients who switched to ziprasidone lost weight and improved their lipid parameters, but this did not translate into a clear advantage in terms of lower discontinuations due to tolerability.

The other phase II CATIE study was the "efficacy pathway," recommended (but not required) for patients who discontinued phase I because of lack of efficacy.[17] This phase II trial was much smaller (N = 99), and it randomly assigned patients to open-label treatment with clozapine (mean daily dose = 332.1 mg) versus double-blind treatment with olanzapine (mean daily dose = 23.4 mg), quetiapine (mean daily dose = 642.9 mg), or risperidone (mean daily dose = 4.8 mg). Discontinuation rates for all causes were lower with clozapine (56%) compared to olanzapine (71%), quetiapine (93%), and risperidone (86%). Consistent with this finding, the PANSS total score showed significant postswitch improvement at both 3 months and 6 months with clozapine (–11.7/–18.4) compared to olanzapine (–3.2/–7.7), quetiapine (+2.5/–1.3), and risperidone (+4.1/–0.3).

PATIENT-RELATED FACTORS THAT INFLUENCE SUCCESS

The 2 main categories of patient-related variables that influence treatment success are the genetic/molecular and the psychosocial. Genetic factors are just beginning to come into focus as variables that contribute to treatment response and the tolerability of treatment. Psychosocial factors consist of patients' active engagement in their own therapy and in the larger process of recovery. Noncompliance with treatment is the most prominent and intractable symptom of a disturbance in the therapeutic process.

Pharmacogenetics and Polymorphisms

Until recently, the reasons one patient achieves remission while another patient shows minimal or no response to an antipsychotic have been a mystery. Multivariate analyses provide indirect and inconsistent answers by attempting to identify clinical variables that predict differential treatment response. Advances in molecular genetics are now beginning to provide a new method for understanding the heterogeneity of individual treatment response.[18]

Lencz and colleagues[19] have recently reported a study that illustrates the potential of pharmacogenomics. They describe the first evidence that single nucleotide polymorphisms (SNPs) in the dopamine D_2 receptor gene are significantly correlated with levels of sustained response to atypical antipsychotics. Two D_2 promoter region SNPs had previously been identified: (1) a substitution of gua-

nine for adenine (G carriers vs. A/A homozygotes) and (2) a deletion (del) (vs. insertion [ins]) of cytosine at position –141C (ins/ins homozygotes vs. del carriers). In the Lencz et al. study (Figure 1), G carriers (first panel) and ins/ins homozygotes (second panel) each had significantly higher levels of sustained response. The third panel shows the influence of the combined (diplotype) status of both polymorphisms on sustained response. As can be seen, individuals who were not G carriers and who did not have the cytosine ins (the "contains Del/no G" group) had significantly lower treatment response rates than A-Ins homozygotes or G carriers (contains G): 83% vs. 52% vs. 30% (p = .002). It is important to note that the sample size was small (N = 61), and the results need replication, but the methodological strengths of the study included use of patients with first-episode schizophrenia, 79% of whom were drug-naive, and a rigorous assessment of treatment response. In vitro studies suggest that these promoter region polymorphisms may alter gene expression, resulting in changes in D_2 receptor densities.[20]

Another example of pharmacogenomic dissection of response is the 5-HT$_{2A}$ receptor gene. This gene has a His452Tyr mutation that has been found, on meta-analysis,[21] to predict nonresponse to clozapine. Individuals who were homozygous for the His452Tyr variant had a 5.6 odds ratio for nonresponse.

The potential value of pharmacogenetics is not limited to characterizing genetic variations that predict differential efficacy; it may also help predict safety and tolerability. In a recent study by Ellingrod et al.,[22] weight gain was significantly predicted by the presence of 5-HT$_{2C}$–750 C/T polymorphism. Another example of the potential value of pharmacogenetics is a technology designed to identify patients at higher risk for poor tolerability by analyzing variations in 2 key CYP genes, *CYP2D6* and *CYP2C19*.[23] Risperidone, aripiprazole, haloperidol, and perphenazine have clinically relevant *CYP2D6* metabolism. Approximately 7% of Caucasians have a *CYP2D6* genotype (slow metabolizers), while up to 29% of individuals of North African or Middle Eastern descent are considered ultrarapid metabolizers. There is evidence that *CYP2D6* slow metabolizers have poorer tolerability, with higher discontinuation rates.[24]

Patient Variables and Noncompliance

Pharmacotherapy of patients diagnosed with schizophrenia occurs within the broader context of the long process of recovery. An expert consensus panel, sponsored by the Substance Abuse & Mental Health Services Administration (SAMHSA), has enumerated 10 key components of recovery that characterize the process[25]: *self-direction*, *responsibility*, and *empowerment* (emphasizing patients' responsibility to actively collaborate in their own treatment); *individualized* and *holistic* (emphasizing the importance of adapting the treatment process to the individual needs of

Figure 1. *D2D2* Promoter Region Variation as a Predictor of Sustained Response to Antipsychotic Medication[a]
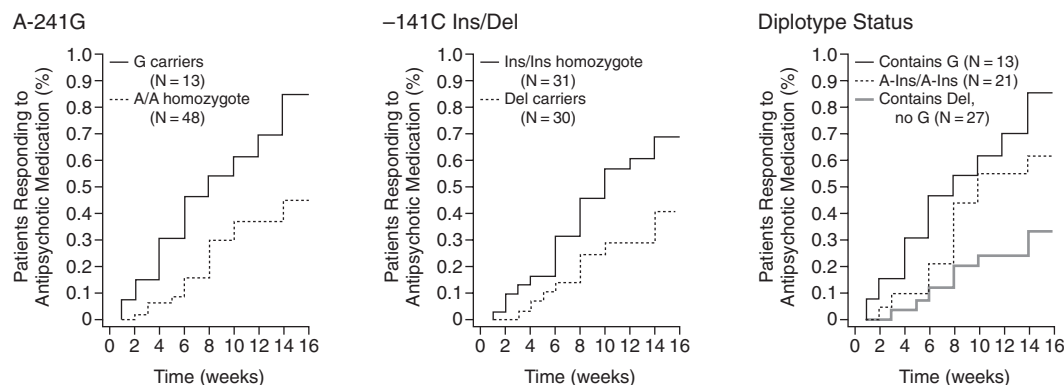
[a]Reprinted with permission from Lencz et al.[19]
Abbreviations: Del = deletion, Ins = insertion.

each patient, and treating the whole patient); *nonlinear* (emphasizing that setbacks are an inevitable part of progress); *strengths-based* and *peer-support* (emphasizing the importance in the treatment process of identifying and building on strengths within the larger, mutually supportive context of social networks); *respect* (emphasizing the importance of self-acceptance, and eliminating discrimination and stigma); and *hope* (emphasizing the importance of hope as a catalyst of the recovery process).

The consensus recovery goals are difficult to achieve in today's healthcare system. Noncompliance with medication is the most frequent symptom of a breakdown in the recovery process; it is estimated to occur at some point in the long-term treatment of schizophrenia in up to 75% of patients.[26,27] In phase I of the CATIE study, 35% of the randomly assigned patients discontinued their assigned study medication and quit the study altogether.[15] Noncompliance is associated with higher rates of emergency room visits and hospitalizations among schizophrenia patients.[28,29]

A large body of research—of highly variable methodological quality—has identified various risk factors for noncompliance. These include perceptions and beliefs about the illness, ranging up to full lack of insight, substance abuse comorbidity, poor therapeutic alliance, subjective effects of the medication, and lack of family support of treatment. Table 2 summarizes the results of one regression analysis,[30] which found higher risk of noncompliance among patients with negative attitudes toward treatment, men (table shows data for women), poor insight (table shows data for high insight), and lack of career involvement (table shows favorable effect of high career involvement). Previous studies have also reported favorable effects on compliance using compliance therapy, which combines psychoeducation with cognitive therapy techniques.[31,32]

A range of interventions has been proposed to address the issue of treatment noncompliance. These include the

Table 2. Predictors of Compliance in Schizophrenia[a]

Predictor	Odds Ratio (95% CI)
Attitude to treatment (DAI)	1.36 (1.09 to 1.70)
Symptoms (PANSS)	0.95 (0.89 to 1.00)*
Baseline suboptimal compliance	11.89 (0.73 to 193)*
Baseline compliance	29.59 (1.08 to 812)
Sex	0.01 (0.00 to 0.30)
Compliance therapy	0.17 (0.01 to 2.51)*
Insight score (SAI)	0.84 (0.56 to 1.25)*
Career involvement	0.001 (0.00 to 0.10)
NART score	0.93 (0.80 to 1.08)*

[a]Data from O'Donnell et al.[30]
*p > .05.
Abbreviations: DAI = Drug Attitude Inventory, NART = National Adult Reading Test, PANSS = Positive and Negative Syndrome Scale, SAI = Schedule for Assessment of Insight.

use of long-acting injectable antipsychotics, use of electronic pillboxes or other electronic reminders, as well as behavioral reinforcement programs and skills and cognitive adaptive training. The problem of noncompliance is complex, and it requires a multifactorial approach (Table 3)[33] that attempts to instill in the patient and his or her family or support group the key components of recovery itemized in the SAMHSA consensus statement.[25]

THE HEALTHCARE ENVIRONMENT AND SYSTEMS ISSUES THAT INFLUENCE TREATMENT SUCCESS

The SAMHSA statement on recovery grows out of a perspective that views recovery as not just an *outcome* (e.g., relief of psychotic symptoms, return to full functioning) but also as a *process* whose hallmarks are an increased sense of personal responsibility and empowerment, goal orientation, and hopefulness about the future. As noted above, treatment must be placed in a broader psychosocial and systems context in order to optimize the possibility of treatment success. However, psychosocial

Table 3. Recommendations of Expert Consensus Guidelines on Improving Compliance[a]

Pharmacologic	Psychological	Programmatic
Base choice of medication on the side effect profile most acceptable to the patient	Family education and support	Concurrent treatment of substance abuse
Consider using a long-acting depot antipsychotic, particularly if the patient has lack of insight into the need for medication	Patient education and support	Provide assertive community treatment services
Monitor symptoms and side effects	Motivation interviewing (eg, helping the patient realize that attaining personal goals requires compliance with treatment)	Continuity of primary clinician across treatment modalities (eg, inpatient, outpatient, and residential programs)
Monitor medication (eg, direct observation, weekly pill box)	Introduce new interventions gradually according to the level of clinical recovery and cognitive impairment	Provide a depot medication clinic
	Time interventions based on patient's preference and sense of urgency	Provide more intensive services (eg, case management, day hospital)
		Supervised residential services

[a]Data from McEvoy et al.[33]

interventions must be subjected to the same evidence-based standards as drug therapy. The Patient Outcomes Research Team has undertaken a series of treatment reviews[34,35] that have identified a list of evidence-based interventions and services. These include illness management skills,[36] assertive community treatment,[37] supported employment,[38] family psychoeducation,[39] and integrated treatments for mental illness and substance abuse.[40]

Emerging data suggest that integrating drug treatment with an evidence-based psychosocial intervention optimizes treatment outcome. Unfortunately, state-by-state support for such programs is meager. In fact, a recent state-by-state review of mental health services for the seriously mentally ill conducted by the National Alliance for the Mentally Ill is cause for concern.[41] Though there was great variability in the quality of services provided, no state received a grade of A, and 5 states received a grade of B. The report confirms the characterization by the New Freedom Commission on Mental Health that the U.S. mental health system designed to serve the severely mentally ill is a fragmented "system in shambles."[42]

CONCLUSIONS

More than 50 years into the modern era, the treatment of schizophrenia remains very much a work-in-progress. The most progress has been made in identifying effective new tools—new drugs, new psychosocial treatments, new understanding of the ingredients needed to optimize treatment success.

Some progress has been made in effectively using these tools integrating drug and psychosocial treatments within the context of a supportive mental health service environment. However, unless further progress is made on these fronts, true treatment success will remain hard to achieve.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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