

At Issue: Translating Research Into Practice: The Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations

by Anthony F. Lehman, Donald M. Steinwachs,
and the Co-Investigators of the PORT Project

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Abstract

Beginning in 1992, the Agency for Health Care Policy and Research and the National Institute of Mental Health funded the Schizophrenia Patient Outcomes Research Team (PORT) to develop and disseminate recommendations for the treatment of schizophrenia based on existing scientific evidence. These Treatment Recommendations, presented here in final form for the first time, are based on exhaustive reviews of the treatment outcomes literature (previously published in *Schizophrenia Bulletin*, Vol. 21, No. 4, 1995) and focus on those treatments for which there is substantial evidence of efficacy. The recommendations address antipsychotic agents, adjunctive pharmacotherapies, electroconvulsive therapy, psychological interventions, family interventions, vocational rehabilitation, and assertive community treatment/intensive case management. Support for each recommendation is referenced to the previous PORT literature reviews, and the recommendations are rated according to the level of supporting evidence. The PORT Treatment Recommendations provide a basis for moving toward "evidence-based" practice for schizophrenia and identify both the strengths and limitations in our current knowledge base.

Key words: Mental health services, quality of care.

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In 1992 the Agency for Health Care Policy and Research (AHCPR) and the National Institute of Mental Health established a Patient Outcomes Research Team (PORT) for Schizophrenia at the University of Maryland School of Medicine and the Johns Hopkins University School of Public Health. This PORT combines the expertise of three major research centers at two universities: the Center for Research on Services for Severe Mental Illness (Johns Hopkins University and the University of Maryland), the University of Maryland Center for Mental Health Services Research, and the Maryland Psychiatric Research Center (at the University of Maryland). The prime objective of the PORT is to develop recommendations for the treatment of persons with schizophrenia based on a synthesis of the best scientific evidence, with the ultimate goal of improving the quality and cost-effectiveness of care for persons with this diagnosis.

The PORT Treatment Recommendations are statements about the care of persons with schizophrenia based on substantial scientific evidence. They begin with the assumption that an accurate diagnosis of schizophrenia has been made. They also recognize that treatment for an individual will depend on a variety of factors other than a diagnosis of schizophrenia, such as the presence of other psychiatric and medical conditions, personal and social circumstances, and individual variations. By nature of the fact that the Treatment Recommendations are based on scientific studies, they reflect what is known from well-controlled research. However, this requirement that recommendations be based on substantial scientific evidence means they are silent about or may appear to understate the importance of other aspects of treatment that have not been evaluated adequately. Therefore, there are many

Reprint requests should be sent to Dr. A.F. Lehman, Dept. of Psychiatry, University of Maryland School of Medicine, 645 West Redwood St., Baltimore, MD 21201.

more recommendations about pharmacotherapies than about psychosocial treatments. This does not mean that psychosocial treatments are less important than medications, but reflects the fact that we know much less about which psychosocial treatments are helpful. Future research may shed light on these other aspects of care that are often viewed by practitioners, consumers, and families as vitally important, but for which we lack adequate scientific evidence for efficacy and effectiveness at the present time. Even with these limitations in mind, it is hoped that the PORT Treatment Recommendations will be used to enhance the treatment currently being offered to persons with schizophrenia.

The PORT Treatment Recommendations are organized according to categories of interventions, consistent with the framework of the recently completed review of the treatment literature by the PORT—see *Schizophrenia Bulletin*, Vol. 21, No. 4, 1995. The intervention categories are (1) antipsychotic medications; (2) adjunctive pharmacotherapies for anxiety, depression, and aggression/hostility; (3) electroconvulsive therapy; (4) psychological interventions; (5) family interventions; (6) vocational rehabilitation; and (7) assertive community treatment/assertive case management. For each recommendation, a brief rationale and annotations to the above referenced issue of *Schizophrenia Bulletin* are provided. These earlier literature reviews offer extensive bibliographies for the interested reader.

The level of evidence for each recommendation is also provided. In writing the recommendations, the PORT investigators adopted the criteria on levels of evidence used for development of the AH CPR Depression Guidelines, as follows:

Level A: Good research-based evidence, with some expert opinion, to support the recommendation

Level B: Fair research-based evidence, with substantial expert opinion, to support the recommendation

Level C: Recommendation based primarily on expert opinion, with minimal research-based evidence, but significant clinical experience

We sent initial drafts of these recommendations to experts for review. The experts were asked to rate their level of agreement with each recommendation based on their knowledge of the literature and to provide citations of studies that would argue for revision of the recommendations. Recommendations were modified based on this feedback only if supporting data from published research were provided; that is, opinion alone was not considered adequate to modify a recommendation.

Treatment Recommendations

Pharmacotherapies: Treatment of Acute Symptom Episodes.

Recommendation 1. Antipsychotic medications, other than clozapine, should be used as the first-line treatment to reduce psychotic symptoms for persons experiencing an acute symptom episode of schizophrenia.

Rationale. Over 100 randomized double-blind studies consistently support the efficacy of antipsychotic medications relative to placebo in the reduction of the acute positive symptoms (hallucinations, delusions, thought disorganization, bizarre behavior) of schizophrenia. Approximately 50 to 80 percent of persons will improve significantly with this treatment compared with about 5 to 45 percent on placebo. (Review references: Dixon et al. 1995, p. 568; Umbricht and Kane 1995, p. 603; Level of evidence: A)

Recommendation 2. The dosage of antipsychotic medication for an acute symptom episode should be in the range of 300–1,000 chlorpromazine (CPZ) equivalents per day for a minimum of 6 weeks. Reasons for dosages outside this range should be justified. The minimum effective dose should be used. (Cross-reference tables of CPZ dose equivalents of various antipsychotic agents are included in tables 1–3.)

Rationale. Randomized clinical trials have consistently found that acute positive symptoms in most persons respond to a daily dose of an antipsychotic medication between 300 and 1,000 CPZ equivalents administered for a minimum of 6 weeks. The risk of suboptimal response increases substantially below this range, and there is little evidence of further benefit above this range. Higher doses also carry an increased burden of side effects. (Review reference: Dixon et al. 1995, p. 569; Level of evidence: A)

Recommendation 3. Persons experiencing their first acute symptom episode should be treated with an antipsychotic medication other than clozapine, but dosages should remain in the lower end of the range mentioned in Recommendation 2 (300–500 mg CPZ equivalents per day).

Rationale. Recent studies indicate that persons experiencing their first episode of acute symptoms of schizophrenia respond as well or better to antipsychotic medications in terms of symptom reduction than persons experiencing a recurrent episode. They may also respond to somewhat lower doses. Although “watchful waiting” is an alternative approach raised by concerns about medication side effects, this option is mitigated by concerns that persistent psychosis may complicate the subsequent course of illness. (Review reference: Dixon et al. 1995, p. 574; Level of evidence: B)

Table 1. Chlorpromazine (CPZ) equivalencies and PORT recommended dosing of antipsychotic medications

Medication	CPZ equivalence ¹	CPZ-equivalence multiplier ²	PORT recommended total daily dose range (mg/day)	
			Acute therapy	Maintenance therapy
Chlorpromazine	100	1	300–1000	300–600
Triflupromazine	25	4	75–250	75–150
Mesoridazine	50	2	150–400 ³	150–300
Thioridazine	100	1	300–800 ³	300–600
Acetophenazine	20	5	60–200	60–120
Fluphenazine HCl	2	50	6–20	6–12
Perphenazine	10	10	30–100	30–60
Prochlorperazine	15	6	50–150	50–100
Trifluoperazine	5	20	15–50	15–30
Chlorprothixene	100	1	300–1000	300–600
Thiothixene	5	20	15–50	15–30
Haloperidol	2	50	6–20	6–12
Loxapine	10	10	30–100	30–60
Molindone	10	10	30–100	30–60
Clozapine	50	2	200–600	200–800
Risperidone	1	100	4–10	4–10

Note.—PORT = Patient Outcomes Research Team. HCl = hydrochloride. Adapted from Zito 1994 and Kane 1996.

¹Approximate dose equivalent to 100 mg of chlorpromazine (relative potency); may not be the same at lower versus higher doses.

²This number multiplied by the dose of antipsychotic medication results in the chlorpromazine-equivalent dose.

³To avoid the risk of retinopathy, doses of 400 mg (mesoridazine) and 800 mg (thioridazine) should not be exceeded.

Table 2. Chlorpromazine (CPZ) equivalencies and dosing of fluphenazine decanoate

Decanoate dosing schedule												
Q every week			Q every 2 weeks			Q every 3 weeks			Q every 4 weeks			
FPZ-DEC (mg)	Oral FPZ HCl (mg)	CPZ-EQ (mg)	FPZ-DEC (mg)	Oral FPZ HCl (mg)	CPZ-EQ (mg)	FPZ-DEC (mg)	Oral FPZ HCl (mg)	CPZ-EQ (mg)	FPZ-DEC (mg)	Oral FPZ HCl (mg)	CPZ-EQ (mg)	
6.25 (.25 cc)	10	500	6.25 (.25 cc)	5	250	6.25 (.25 cc)	3.3	165	6.25 (.25 cc)	2.5	125	
12.5 (.50 cc)	20	1000	12.5 (.50 cc)	10	500	12.5 (.50 cc)	6.6	333	12.5 (.50 cc)	5.0	250	
18.75 (.75 cc)	30	1500	18.75 (.75 cc)	15	750	18.75 (.75 cc)	10.0	500	18.75 (.75 cc)	7.5	375	
25 (1.0 cc)	40	2000	25 (1.0 cc)	20	1000	25 (1.0 cc)	13.3	665	25 (1.0 cc)	10.0	500	
37.5 (1.50 cc)	60	3000	37.5 (1.5 cc)	30	1500	37.5 (1.50 cc)	20.0	1000	37.5 (1.5 cc)	15.0	750	
50 (2.0 cc)	80	4000	50 (2.0 cc)	40	2000	50 (2.0 cc)	26.3	1315	50 (2.0 cc)	20.0	1000	

Note.—Q = quantity. Fluphenazine decanoate (FPZ-DEC) doses are converted to daily oral fluphenazine hydrochloride (oral FPZ HCl) doses and to estimated daily chlorpromazine-equivalent (CPZ-EQ) doses. Decanoate conversions are based on an empirical rule suggested by Kane (25 mg every 3 weeks of decanoate is equivalent to 665 CPZ-EQ per day). These are theoretically determined values and should be interpreted as approximations only. Therefore, comparisons of daily CPZ-EQ doses derived from these values with Patient Outcomes Research Team (PORT)-recommended oral dosing ranges should not be made. However, decanoate doses below the bold line are NOT recommended. Adapted from Zito 1994 and Kane 1996.

Recommendation 4. Massive loading doses of antipsychotic medication, referred to as the practice of “rapid neuroleptization,” should not be used.

Rationale. Rapid loading doses of antipsychotic medications have shown no general advantage over more moderate dosing approaches (see Recommendation 2).

Table 3. Chlorpromazine (CPZ) equivalencies and dosing of haloperidol decanoate

HPL-DEC	Q every month	HPL Q every day	CPZ-EQ
50 mg	(1.0 cc)	5 mg	250 mg
100 mg	(2.0 cc)	10 mg	500 mg
150 mg	(2.5 cc)	15 mg	750 mg
200 mg	(3.0 cc)	20 mg	1000 mg

Note.—Q = quantity. Haloperidol decanoate (HPL-DEC) doses are converted to daily oral haloperidol (HPL) doses and to estimated daily chlorpromazine-equivalent (CPZ-EQ) doses. Decanoate conversions are based on the following rule: 5 mg oral HPL per day is equivalent to 50 mg HPL-DEC every month. These are theoretically determined values and should be interpreted as approximations only. Therefore, comparisons of daily CPZ-EQ doses derived from these values with Patient Outcomes Research Team (PORT)-recommended oral dosing ranges should not be made. Adapted from Zito 1994 and Kane 1996.

They also carry a significant side-effect burden. Rapid initiation of antipsychotic treatment is important at the onset of an exacerbation, but not a rapid loading dose. (Review reference: Dixon et al. 1995, p. 569; Level of evidence: A)

Recommendation 5. Since studies have found no superior efficacy of any antipsychotic medication over another in the treatment of positive symptoms, except for clozapine in treatment-refractory patients, choice of antipsychotic medication should be made on the basis of patient acceptability, prior individual drug response, individual side-effect profile, and long-term treatment planning.

Rationale. As above, studies have found no superior efficacy of any of the antipsychotic medications relative to each other in the treatment of positive symptoms. (Review reference: Dixon et al. 1995, p. 573; Level of evidence: A for equivalent efficacy; C for other factors affecting medication choice)

Recommendation 6. Monitoring of plasma levels of antipsychotic medications should be limited to the following circumstances: (1) when patients fail to respond to what is usually an adequate dose; (2) when it is difficult for the clinician to discriminate drug side effects—particularly akathisia or akinesia—from symptoms of schizophrenia such as agitation or negative symptoms (a high blood level might be associated with increased adverse effects); (3) when antipsychotic drugs are combined with other drugs that may affect their pharmacokinetics; (4) in the very young, the elderly, and the medically compromised in whom the pharmacokinetics may be significantly altered; and (5) when noncompliance is suspected. Plasma levels are most useful when using haloperidol, which has only one active metabolite.

Rationale. In general, there is at best a moderate correspondence between plasma drug level and clinical response to antipsychotic medications. Studies suggest an

inverted-U or therapeutic window response curve such that persons with moderate plasma levels of haloperidol show a better clinical response than those with low or high levels. The upper end of this therapeutic window is often defined by side effects. Inadequate clinical response to apparently adequate dosages of antipsychotic medications warrants assessment of plasma levels to rule out unusual or altered drug metabolism or noncompliance. (Review references: Baldessarini et al. 1990; Kane and Marder 1993; Level of evidence: B)

Recommendation 7. Prophylactic use of anti-Parkinson agents to reduce the incidence of extrapyramidal side effects (EPS) should be determined on a case-by-case basis, taking into account patient and physician preferences, prior individual history of EPS, and other risk factors for both EPS and anticholinergic side effects. The effectiveness of and continued need for anti-Parkinson agents should be assessed in an ongoing fashion.

Rationale. Although the data are clear that anti-Parkinson agents are effective in reducing or eliminating the EPS of antipsychotic medications, experts disagree about the advisability of using these agents prophylactically. The controversy arises in weighing the risks of EPS against those of the side effects of anti-Parkinson agents. Prophylaxis may be especially important among persons with a prior history of noncompliance or drug discontinuation related to EPS and among persons for whom even mild EPS may lead to drug aversion (e.g., among patients with paranoia or somatic delusions). Avoidance of anticholinergic effects may be especially important in the elderly and in individuals with a history of anticholinergic crises. (Review references: Rifkin and Siris 1987; Davis et al. 1989; Level of evidence: B)

Pharmacotherapies: Maintenance Pharmacotherapy.

Recommendation 8. Persons who experience acute symptom relief with an antipsychotic medication should continue to receive this medication for at least 1 year subsequent to symptom stabilization to reduce the risk of relapse or worsening of positive symptoms.

Rationale. More than 30 clinical trials have confirmed that maintenance therapy with an antipsychotic medication after an initial positive response during an acute symptom episode significantly reduces the risk of symptom relapse during the first year after the acute symptom episode. On average, persons on maintenance therapy experienced symptom relapse over a followup year at a rate of about 20 to 25 percent compared with about 55 percent for those on placebo. The value of maintenance therapy beyond the first year has not been studied extensively. (Review reference: Dixon et al. 1995, pp. 569–570; Level of evidence: A)

Recommendation 9. The maintenance dosage should be in the range of 300 to 600 CPZ equivalents (oral or depot) per day. If the initial dosage to relieve an acute symptom episode exceeds this range, efforts should be made to reduce the dosage gradually to this range, such as a 10 percent reduction in dosage every 6 weeks until either early signs of relapse begin to emerge or until the lower level of this recommended range is achieved (see Recommendation 2). The new maintenance dosage should be at the last level at which symptoms were well controlled. Dosages in excess of 600 CPZ equivalents per day should be avoided unless symptom control and patient comfort are clearly superior at these higher dosages. The lowest effective dose should be used.

Rationale. Maintenance therapy trials have found that maintenance doses below 300 mg CPZ equivalents per day carry an increased risk of relapse, although a substantial proportion of persons (up to 50%) can be maintained successfully at these lower doses, warranting a gradual and carefully monitored effort to reduce dosage over time. There is no evidence that maintenance doses above 600 mg CPZ equivalents per day confer any additional advantage in general. (Review reference: Dixon et al. 1995, pp. 570–572; Level of evidence: A)

Recommendation 10. Reassessment of the dosage level or the need for maintenance antipsychotic therapy should be ongoing. Patients who have had only one episode of positive symptoms before initiation of antipsychotic therapy and who have experienced *no* positive symptoms during the year of maintenance therapy should be given a trial period off medication, assuming they are aware of the potential risk of relapse and agree to this plan. For patients with more than one prior episode who have experienced good symptom control on the medication during the preceding year, maintenance therapy should be continued unless unacceptable side effects or some other contraindications to antipsychotic treatment have developed. If the maintenance dosage has been high (>600 CPZ equivalents) during the past year, attempts to lower the dosage as described in Recommendation 9 should be considered. Reasons for not attempting to lower dosage should be clearly indicated, such as patient preference in the face of concerns about symptom relapse or life stressors that militate against attempts to lower medications.

Rationale. Clinical trials of maintenance antipsychotic therapy have generally not followed patients in maintenance therapy beyond 1 year, and thus evidence regarding long-term maintenance is lacking (see also rationale for Recommendation 8). (Review references: Kissling 1992; Dixon et al. 1995, pp. 570–571; Level of evidence: C)

Recommendation 11. Targeted, intermittent dosage maintenance strategies should not be used routinely in lieu of continuous dosage regimens because of the increased risk of symptom worsening or relapse. These strategies may be considered for patients who refuse maintenance or for whom some other contraindication to maintenance therapy exists, such as side-effect sensitivity.

Rationale. The relatively few studies of targeted, intermittent dose strategies suggest that the relapse rate is higher than for continuous maintenance therapy. Therefore, this approach is recommended only for the circumstances identified above. (Review reference: Dixon et al. 1995, pp. 570–571; Level of evidence: B)

Recommendation 12. Depot antipsychotic maintenance therapy should be strongly considered for persons who have difficulty complying with oral medication or who prefer the depot regimen. Depot therapy may be used as a first-option maintenance strategy.

Rationale. Controlled trials have produced inconsistent results with regard to whether depot medication reduces the risk of relapse in comparison with oral medication. However, the design of these studies, which by definition include persons willing to accept medication in a clinical trial, may bias against any advantage of depot medication. Further, the duration of these studies has been inadequate to demonstrate a strong advantage for depot medication. In persons for whom compliance is a problem, depot medication offers clear advantages if it is accepted by the patient. If acceptable to the patient, depot medication is just as appropriate as oral medication as the first-line maintenance therapy strategy. (Review reference: Dixon et al. 1995, p. 573; Level of evidence: B)

Pharmacotherapies: New Antipsychotic Medications.¹

Recommendation 13. A trial of clozapine should be offered to patients with schizophrenia or schizoaffective disorder whose positive symptoms do not robustly respond to adequate trials of two different classes of antipsychotic medications. Exceptions include patients who cannot receive clozapine due to a history of blood dyscrasia or cardiac arrhythmia. Lack of response to previous antipsychotic trials is defined by persistent symptoms after two 6-week trials of up to 1,000 CPZ equivalents of antipsychotic agents from two different chemical

¹As of the writing of these recommendations (September 1996), additional antipsychotic agents were expected to reach the market within the next 1 to 2 years. These agents include olanzapine, quetiapine, sertindole, and ziprasidone. No recommendations specific to these newer compounds are included because the level of data on them is more limited than for clozapine and risperidone. Until proven otherwise, the use of these newer compounds, when marketed, should follow the recommendations for antipsychotic agents other than clozapine.

classes (e.g., phenothiazines and butyrophenones). An adequate clozapine trial should last at least 3 months at a dosage from 300 to 800 mg per day. Dosages should reflect the lowest possible effective dose. If patients do not respond, a blood level should be obtained and dosages slowly increased to 800 mg to the extent that side effects are tolerated. If effective, clozapine should be continued as maintenance therapy.

Rationale. Controlled clinical trials have found that clozapine produces significant clinical improvement in at least 30 percent of patients who fail to achieve an adequate response to or cannot tolerate conventional antipsychotic medications. It should be considered only after other antipsychotic medications prove inadequate because of its low but significant risk of agranulocytosis, complexity of management (weekly white cell count reports), and cost. The level of evidence for the differential effectiveness of clozapine among outpatients is limited by the low number of studies of outpatients. (Review reference: Buchanan 1995, pp. 580–584; Level of evidence: A for inpatients; B for outpatients)

Recommendation 14. A trial of clozapine should be offered to patients with schizophrenia or schizoaffective disorder who have repeatedly displayed violent behavior and persistent psychotic symptoms that have not been responsive to trials of at least two different types of antipsychotic medications (as defined in Recommendation 13).

Rationale. Randomized clinical trials, as well as nonrandomized studies, suggest that clozapine significantly reduces hostility among treatment-refractory patients. It should only be considered after other antipsychotic medications prove inadequate. (Review reference: Buchanan 1995, p. 582; Level of evidence: B)

Recommendation 15. A trial of clozapine should be offered to patients who require antipsychotic therapy, but who experience intolerable side effects to other antipsychotic agents, including severe or very distressing tardive dyskinesia, persistent dystonia, and neuroleptic malignant syndrome.

Rationale. A limited body of evidence suggests that clozapine causes substantially less tardive dyskinesia than antipsychotic medications, although there are reports of cases in which tardive dyskinesia has worsened on clozapine. For the patient with severe tardive dyskinesia for whom ongoing treatment with another antipsychotic agent poses a substantial risk of continuation or further progression of the movement disorder, but for whom antipsychotic therapy is essential to prevent serious relapse, a trial with clozapine is indicated. (Review reference: Buchanan 1995, p. 587; Level of evidence: B)

Recommendation 16. Persons who achieve an adequate reduction in positive symptoms on conventional

antipsychotic medications, but who have significant EPS that do not respond adequately to anti-Parkinson agents, should be offered a trial of risperidone. An adequate risperidone trial for this purpose should last from 6 to 12 weeks at a dosage from 4 to 10 mg per day. Dosages should reflect the lowest possible effective dose. Per Recommendation 1, risperidone also can be used as a first-line medication.

Rationale. In clinical trials, risperidone has been found to be at least as effective as other antipsychotic medications in reducing the positive symptoms of schizophrenia. Its major potential advantage over other antipsychotic medications is that it produces fewer EPS at the lower end of its effective dose range (4–10 mg per day). Therefore, for patients on the older antipsychotic agents and in whom EPS is a significant problem, risperidone offers an alternative. (Review reference: Umbricht and Kane 1995, pp. 602–604; Level of evidence: B)

Pharmacotherapies: Adjunctive Pharmacotherapies.

Recommendation 17. Persons who experience persistent and clinically significant, associated symptoms of anxiety, depression, or hostility, despite an adequate reduction in positive symptoms with antipsychotic therapy, should receive a trial of adjunctive pharmacotherapy. A trial of a benzodiazepine or propranolol is merited for persistent anxiety. An antidepressant trial should be considered for persistent depression. Adjunctive therapy with lithium, a benzodiazepine, or carbamazepine should be considered for persistent hostility or maniclike symptoms. The reasons for the absence of such trials for appropriate patients should be documented. Certain adjunctive medications should be avoided in patients currently receiving clozapine to avoid synergistic side effects; for example, respiratory depression with benzodiazepines and bone marrow suppression with carbamazepine.

Rationale. Anxiety and tension may respond to treatment with adjunctive benzodiazepines, although a few studies reported a waning effect of these agents, perhaps due to tolerance, after a few weeks of treatment. Disruptive, dangerous, or assaultive behavior may be modified by the addition of benzodiazepines or carbamazepine to an antipsychotic regimen. Evidence of the usefulness of benzodiazepines for this indication comes from open or retrospective studies, and no double-blind studies have thus far addressed its efficacy. Similarly, these behaviors are cited as potentially responsive to adjunctive carbamazepine, although most evidence is from open studies, with only one positive double-blind study. Excitement and irritability (often classified as “affective symptoms”) seem to benefit from adjunctive lithium treatment, with a small amount of evidence that

benzodiazepines and carbamazepine also might be useful. Antidepressants seem to benefit patients who have episodic signs and symptoms of depressive illness in addition to schizophrenia, if they are administered in phases of illness other than the active, psychotic exacerbation phase. Antidepressants can be efficacious without exacerbating psychotic symptoms when used adjunctively with antipsychotics. Most studies of adjunctive treatments for schizophrenia were done with patients who had chronic schizophrenia and who were often designated as treatment refractory. Little is known about the efficacy of adjunctive agents for first-episode schizophrenia, for patients experiencing acute episodes of psychosis, or for stable patients receiving maintenance antipsychotic therapy. Little is known about the long-term effectiveness of adjunctive agents. (Review reference: Johns and Thompson 1995, pp. 612–613; Level of evidence: B)

Recommendation 18. Persons who experience persistent and clinically significant positive symptoms despite adequate antipsychotic therapy, including trials with the newer antipsychotics (clozapine or risperidone), should receive a trial of adjunctive pharmacotherapy as described in Recommendation 17.

Rationale. No adjunctive agent has demonstrated clear and consistent benefit in a majority of persons with schizophrenia. However, the most promising agents are the benzodiazepines (which may be useful in as many as 50% of patients with schizophrenia), lithium, and carbamazepine (which may be of mild or modest value to treatment-nonresponsive patients). Very little evidence supports a role for adjunctive propranolol. Valproate, calcium channel blockers, antidepressants, clonidine, and dopaminergic agents have no demonstrated use in terms of global improvement, although they may be useful for individual symptom complexes. Positive symptoms may improve when benzodiazepines, carbamazepine, lithium, or propranolol are added to antipsychotics. Adjunctive benzodiazepines produced significant improvement of positive symptoms in about half the double-blind studies that addressed this question. Adjunctive carbamazepine produced significant improvement in only a fraction of double-blind studies. Adjunctive lithium seems to alleviate, to some degree, positive symptoms in a subgroup of patients. Finally, adjunctive propranolol produces only slim evidence of a therapeutic effect on positive symptoms in a minority of double-blind studies. (Review reference: Johns and Thompson 1995, pp. 611–612; Level of evidence: C)

Electroconvulsive Therapy (ETC).

Recommendation 19. Patients who have not responded to recommended antipsychotic therapy should

be considered for a trial of ECT alone or in combination with an antipsychotic if (a) the person has been ill for less than 1 year or, if ill for more than 1 year, is in the early phase of an acute exacerbation or (b) affective or catatonic symptoms are predominant.

Rationale. There are scientifically sound studies that show that ECT reduces acute symptoms in schizophrenia. Some authors dispute this finding, however, with several pointing to the problem of affective symptoms in schizophrenia and the diagnostic confounding of schizophrenia with affective disorders. The majority of authors indicate that a secondary role is most appropriate, and there is a general consensus that the effects of ECT on schizophrenia are short lived. A few studies with minimal data show continued improvement at followup of several years when ECT is followed by maintenance antipsychotic therapy. Catatonic schizophrenia and schizoaffective disorder seem to be most responsive to ECT, and in general the affective symptoms respond selectively to it. (Review reference: Johns and Thompson 1995, pp. 610–611; Level of evidence: B)

Recommendation 20. The dosage of ECT (i.e., number of treatments) used to treat patients with schizophrenia should be comparable to that used for patients with affective disorders (about 12 treatments).

Rationale. Three controlled studies found definite improvement after 12 or fewer treatments, and another study indicates that the average number of treatments needed for improvement is 13.6. (Review reference: Johns and Thompson 1995, pp. 610–611; Level of evidence: B)

Recommendation 21. Regressive forms of ECT are *not* recommended for persons with schizophrenia.

Rationale. Most reviewers indicate that selected patients with severe and chronic schizophrenia may benefit from modified ECT, but others indicate that the procedure is “drastic,” “experimental,” and “controversial.” (Review reference: Johns and Thompson 1995, pp. 610–611; Level of evidence: C)

Psychological Treatments.

Recommendation 22. Individual and group psychotherapies adhering to a psychodynamic model (defined as therapies that use interpretation of unconscious material and focus on transference and regression) should *not* be used in the treatment of persons with schizophrenia.

Rationale. The scientific data on this issue are quite limited. However, there is no evidence in support of the superiority of psychoanalytic therapy to other forms of therapy, and there is a consensus that psychotherapy that promotes regression and psychotic transference can be harmful to persons with schizophrenia. This risk, com-

bined with the high cost and lack of evidence of any benefit, argues strongly against the use of psychoanalytic therapy, even in combination with effective pharmacotherapy. (Review reference: Scott and Dixon 1995*b*, p. 623; Level of evidence: C)

Recommendation 23. Individual and group therapies employing well-specified combinations of support, education, and behavioral and cognitive skills training approaches designed to address the specific deficits of persons with schizophrenia should be offered over time to improve functioning and enhance other targeted problems, such as medication noncompliance.

Rationale. Although the scientific data for this recommendation are limited and flawed, controlled studies have found some additional benefit when a supportive form of psychotherapy is added to pharmacotherapy for persons with schizophrenia. The most effective forms and doses of these therapies and their modes of action remain unknown. (Review reference: Scott and Dixon 1995*b*, pp. 623–627; Level of evidence: B)

Family Treatments.

Recommendation 24. Patients who have ongoing contact with their families should be offered a family psychosocial intervention that spans at least 9 months and provides a combination of education about the illness, family support, crisis intervention, and problem-solving skills training. Such interventions should also be offered to non-family caregivers.

Rationale. Randomized clinical trials have repeatedly demonstrated that family interventions that provide some combination of illness education, support, problem-solving training, and crisis intervention, in combination with appropriate pharmacotherapy, reduce 1-year relapse rates from a 40 to 53 percent range to a 2 to 23 percent range. (Review reference: Dixon and Lehman 1995, p. 639; Level of evidence: A)

Recommendation 25. Family interventions should not be restricted to patients whose families are identified as having high levels of “expressed emotion” (criticism, hostility, overinvolvement).

Rationale. Although the earlier controlled trials of family psychoeducation programs focused on the variable of family expressed emotion as a mediator of the impact of this intervention on outcomes, more recent studies have found that these interventions offer substantial benefit to patients and families regardless of the level of expressed emotion. (Review reference: Dixon and Lehman 1995, p. 639; Level of evidence: B)

Recommendation 26. Family therapies based on the premise that family dysfunction is the etiology of the patient’s schizophrenic disorder should *not* be used.

Rationale. Research has failed to substantiate hypothesized causal links between family dysfunction and the etiology of schizophrenia. Therefore, therapies specifically designed from this premise are not empirically founded. Although there has been little or no randomized, controlled research on the impact of family therapies arising from this orientation, experts in the field have expressed strong caution against the use of these techniques. The presumption that family interaction causes schizophrenia, especially as an alternative to biological risk factors, has led to serious disruption in clinician/family trust without any evidence of therapeutic effectiveness. The repudiation of the theoretical premise of these therapies, the lack of empirical studies, and the strong clinical opinion raising concerns about the potential harm caused by these approaches lead to this recommendation. (Review reference: Dixon and Lehman 1995, p. 631; Level of evidence: C)

Vocational Rehabilitation.

Recommendation 27. Persons with schizophrenia who have *any* of the following characteristics should be offered vocational services. The person (a) identifies competitive employment as a personal goal, (b) has a history of prior competitive employment, (c) has a minimal history of psychiatric hospitalization, and (d) is judged on the basis of a formal vocational assessment to have good work skills.

Rationale. Controlled studies of vocational rehabilitation interventions for persons with schizophrenia have not shown consistent or significant impacts on outcomes other than those directly related to involvement in the rehabilitation program (e.g., increased involvement in sheltered work). However, these studies have been flawed by the failure to control for individual characteristics that may alter a person’s vocational potential. They have identified subgroups of recipients post hoc who benefited from the interventions. The above characteristics have been found to be predictive of better vocational outcomes in persons with schizophrenia, and therefore persons with these characteristics should be offered such services. (Review reference: Lehman 1995, pp. 647–653; Level of evidence: C)

Recommendation 28. The range of vocational services available in a service system for persons with schizophrenia living in the community who meet the criteria defined in Recommendation 27 should include (a) prevocational training, (b) transitional employment, (c) supported employment, and (d) vocational counseling and education services (job clubs, rehabilitation counseling, postemployment services).

Rationale. Recent controlled studies have reported significantly improved vocational outcomes for the sup-

ported employment model, which emphasizes rapid placement in a real job setting and strong support from a job coach or other employment specialist to adapt to and sustain the job. Therefore, unless ongoing research fails to substantiate these early findings, supported employment should definitely be available to persons meeting the aforementioned criteria. Scientific data supporting the effectiveness of the other forms of vocational services mentioned above are lacking, but some persons who are good candidates for supported employment may benefit from the addition of these services as well, so they are mentioned in the recommendation. (Review reference: Lehman 1995, pp. 647–653; Level of evidence: B)

Service Systems.

Recommendation 29. Systems of care serving persons with schizophrenia who are high service users should include assertive case management (ACM) and assertive community treatment (ACT) programs.

Rationale. Persons with disabling schizophrenia who are at high risk for discontinuation of treatment or for repeated crises require an array of clinical, rehabilitation, and social services to address their needs. Coordination, integration, and continuity of services among providers over time can be substantially enhanced through ACM and ACT. Randomized trials have demonstrated consistently the effectiveness of these programs in reducing inpatient use among such high-risk patients. Several studies also support improvements in clinical and social outcomes. These studies suggest that both ACT and ACM are superior to conventional case management for high-risk cases. (Review reference: Scott and Dixon 1995a, pp. 659–664; Level of evidence: A)

Recommendation 30. Assertive community treatment programs should be targeted to individuals at high risk for repeated rehospitalizations or who have been difficult to retain in active treatment with more traditional types of services.

Rationale. The original ACT studies reporting efficacy for these approaches targeted these high-risk persons. The efficacy of either model with lower risk patient groups has not been established. The high cost of ACT therefore warrants careful targeting for cost-effectiveness. (Review reference: Scott and Dixon 1995a, pp. 659–664; Level of evidence: B)

Discussion

The PORT Treatment Recommendations represent a concerted and systematic effort to develop guidelines about the treatment of persons with schizophrenia distilled nar-

rowly from available scientific evidence. As such, they reflect both the strengths and limitations of this knowledge base. Such recommendations are useful from at least two major perspectives.

First, they form a basis for disseminating current knowledge into practice. The Treatment Recommendations provide focal points or benchmarks for asking whether current practices measure up to what is known to be helpful based on the best scientific evidence available. Such questions about the quality of care should be asked by treatment practitioners, patients, families, service system planners, and health care payers. Are we providing care based on the best knowledge available? These recommendations can challenge practitioners and service systems to do better and can challenge patients and families to expect better services. The recommendations are recommendations, not mandates, because individual patient needs vary considerably from the average. However, the Treatment Recommendations should stimulate close examination of practices at both the aggregate and the individual patient levels to ensure that treatments are offered in the most effective manner.

Second, they serve to highlight what we do not know. Not all of the gaps in our knowledge about treatment can be filled by evidence developed in clinical trials. Clinical wisdom can and should be accumulated and shared directly from practical experience. But there are many aspects of treatment for schizophrenia that need careful, ongoing scientific scrutiny to ensure that, whenever possible, objective evidence of effectiveness is the basis for practice. It should be good news that treatment recommendations such as those presented here will be outdated in the not too distant future and that new knowledge will require their modification, as well as the addition of new recommendations. In short, we should practice what we know today while we are continually learning to change practices for tomorrow.

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The Authors

Anthony F. Lehman, M.D., Principal Investigator of the Schizophrenia Patient Outcomes Research Team, is Professor of Psychiatry, University of Maryland School of Medicine and Co-Director of the Center for Mental Health Services Research, University of Maryland, Baltimore, MD. Donald M. Steinwachs, Ph.D., Co-Principal Investigator, is Professor of Health Policy and Management and Chair of the Department of Health Policy and Management, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD. Co-Investigators at the Center for Mental Health Services Research, University of Maryland School of Medicine include Lisa B. Dixon, M.D., M.P.H.; Howard H. Goldman, M.D., Ph.D.; Fred Osher, M.D.; Leticia Postrado, Ph.D.; Jack E. Scott, Sc.D.; and James W. Thompson, M.D. Co-Investigators from the Department of Health Policy and Management, The Johns Hopkins University School of Hygiene and Public Health include Maureen Fahey, M.A.; Pamela Fischer, Ph.D.; Judith Ann Kasper, Ph.D.; Alan Lyles, Sc.D.; and Elizabeth Ann Skinner, M.S.W. Co-Investigators from the Maryland Psychiatric Research Center include Robert Buchanan, M.D.; William T. Carpenter, Jr., M.D.; and Jerome Levine, M.D. The Co-Investigator from the RAND Corporation is Elizabeth Ann McGlynn, Ph.D. The Co-Investigator from the Department of Veterans Affairs Northeast Program Evaluation Center and Yale University is Robert Rosenheck, M.D. The Co-Investigator from the University of Maryland School of Pharmacy is Julie Zito, Ph.D.