

The Schizophrenia Patient Outcomes Research Team (PORT): Updated Treatment Recommendations 2009

Julie Kreyenbuhl^{1–3}, Robert W. Buchanan⁴,
Faith B. Dickerson⁵, and Lisa B. Dixon^{2,3}

²Division of Services Research, Department of Psychiatry, University of Maryland School of Medicine, 737 West Lombard Street, 5th Floor, Baltimore, MD 21201; ³VA Capitol Health care Network (VISN 5) Mental Illness Research, Education, and Clinical Center, Baltimore, MD; ⁴Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD; ⁵Sheppard Pratt Health System, Baltimore, MD

The Schizophrenia Patient Outcomes Research Team (PORT) project has played a significant role in the development and dissemination of evidence-based practices for schizophrenia. In contrast to other clinical guidelines, the Schizophrenia PORT Treatment Recommendations, initially published in 1998 and first revised in 2003, are based primarily on empirical data. Over the last 5 years, research on psychopharmacologic and psychosocial treatments for schizophrenia has continued to evolve, warranting an update of the PORT recommendations. In consultation with expert advisors, 2 Evidence Review Groups (ERGs) identified 41 treatment areas for review and conducted electronic literature searches to identify all clinical studies published since the last PORT literature review. The ERGs also reviewed studies preceding 2002 in areas not covered by previous PORT reviews, including smoking cessation, substance abuse, and weight loss. The ERGs reviewed over 600 studies and synthesized the research evidence, producing recommendations for those treatments for which the evidence was sufficiently strong to merit recommendation status. For those treatments lacking empirical support, the ERGs produced parallel summary statements. An Expert Panel consisting of 39 schizophrenia researchers, clinicians, and consumers attended a conference in November 2008 in which consensus was reached on the state of the evidence for each of the treatment areas reviewed. The methods and outcomes of the update process are presented here and resulted in recommendations for 16 psychopharmacologic and 8 psychosocial treatments for schizophrenia. Another 13 psychopharmacologic and 4 psychosocial treatments had insufficient evidence to support a recommenda-

tion, representing significant unmet needs in important treatment domains.

Key words: evidence-based practices/psychopharmacologic treatments/psychosocial interventions

Introduction

In 1992, the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality [AHRQ]) and the National Institute of Mental Health (NIMH) funded the Schizophrenia Patient Outcomes Research Team (PORT) Study. The Schizophrenia PORT was 1 of 14 Patient Outcomes Research Teams created in the late 80s and early 90s in response to concerns raised about the appropriateness of care being delivered for several common medical and psychiatric conditions, including schizophrenia. To improve the quality of medical care for these disorders, the PORT program sought to reduce variations in care by promoting the adoption of treatments supported by strong scientific evidence or “evidence-based practices.” To achieve this goal, the various PORTs synthesized the clinical evidence pertaining to many common medical conditions and produced treatment recommendations and other types of evidence-based clinical guidelines to be disseminated to both consumers and clinicians.

As a part of the initial Schizophrenia PORT project, investigators conducted systematic reviews of the literature to identify evidence-based practices for the care of persons with schizophrenia, from which the first Schizophrenia PORT treatment recommendations were developed and published in 1998¹ and subsequently updated in 2003.² The PORT recommendations are readily distinguishable from other clinical guidelines and algorithms for schizophrenia because only those treatments for which there is substantial scientific evidence achieve recommendation status. Although expert opinion is sought to reach consensus on the interpretation of the evidence base for a particular treatment, there are no PORT treatment recommendations based solely on expert opinion, as is the case with other efforts designed to specify best practices for schizophrenia (eg, the American Psychiatric

¹To whom correspondence should be addressed; tel: 410-605-7466, fax: 410-605-7739, e-mail: jkreyenb@psych.umaryland.edu.

Association [APA] Practice Guideline for the Treatment of Patients with Schizophrenia,³ the Texas Medication Algorithm Project [TMAP⁴]). By remaining silent on a number of aspects of care for schizophrenia for which empirical support is currently lacking, the PORT is known for being relatively conservative. However, unlike TMAP, the PORT includes recommendations for adjunctive psychopharmacologic treatments as well as for antipsychotic medications, and also includes recommendations for psychosocial interventions, which are important treatments that augment gains from medication therapies. Also, in contrast to the APA Practice Guideline and the algorithms developed by TMAP, the PORT provides clear-cut and concise statements of recommendations for best practices. As such, PORT recommendations have been applied to evaluate the quality of care provided to people with schizophrenia in a variety of treatment settings.⁵⁻⁹

Since the previous PORT update 5 years ago, research on technologies for treating persons with schizophrenia has continued to quickly evolve. Most notably, the findings of 2 large pragmatic clinical trials on the comparative effectiveness of first-generation and second-generation antipsychotic medications, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)¹⁰ and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS),¹¹ have been published. In addition, the literature on both psychopharmacologic and psychosocial interventions for neurocognitive impairments, co-occurring psychiatric and medical conditions, and treatments for individuals experiencing a recent onset of psychosis has expanded considerably. As new treatments for schizophrenia become available, new studies are completed, and new outcomes (eg, remission and recovery) are identified, it is imperative to update treatment recommendations to accommodate the ever growing and shifting evidence base. Treatment recommendations for schizophrenia must also be regularly updated to ensure that efforts to improve quality of care reflect current empirical knowledge. This article presents the methods used to produce the second update of the Schizophrenia PORT Psychopharmacological and Psychosocial Treatment Recommendations, which are included together here. The syntheses of the evidence for the 29 psychopharmacology and 12 psychosocial treatment areas reviewed for this update are included in separate papers¹²⁻¹³ and in supplemental online material in this issue.

Methods

A primary goal of this update was to review the results of new studies of schizophrenia treatments published since the last literature survey in 2002 to determine if modifications in the extant PORT treatment recommendations were warranted. We also sought to evaluate the research evidence for a number of promising areas of treatment to

determine whether the evidence was sufficient to support the development of new treatment recommendations. To identify critical new evidence, we adopted a comprehensive approach that involved conducting systematic reviews of the schizophrenia treatment literature in consultation with experts from relevant disciplines. The literature reviews were performed by 2 Evidence Review Groups (ERGs), one focusing on psychopharmacologic treatments and the other focusing on psychosocial treatments for schizophrenia. The ERGs were comprised of 16 faculty members from the University of Maryland Schools of Medicine and Pharmacy who have both clinical expertise and experience in conducting research on treatments for schizophrenia. Four residents in psychiatry and 2 postdoctoral fellows in psychology also participated on the ERGs as a component of their training.

The work of both ERGs was accomplished in consultation with Advisory Boards of recognized experts in the fields of psychopharmacologic and psychosocial interventions for schizophrenia. The Advisory Boards served a number of purposes, including helping to determine the treatment areas to be reviewed and participating in the debate over whether the evidence was sufficient for a recommendation, and if so, what the recommendation should entail. Together the ERGs and their respective Advisory Boards selected 41 treatment areas for review, which included areas of treatment addressed in the extant PORT recommendations as well as areas reviewed in previous PORT updates that had insufficient evidence at that time to support a recommendation but for which evidence had continued to accumulate (eg, interventions for negative symptoms and cognitive impairments). Also reviewed were several emerging treatment areas, including peer-delivered services, psychosocial treatments for recent-onset schizophrenia, cognitive remediation, and repetitive transcranial magnetic stimulation (rTMS). Whereas previous PORT reviews focused on treatment domains directly related to the symptoms and outcomes of schizophrenia, a new addition to this PORT effort included reviews of the literature on treatments for several co-occurring medical and psychiatric conditions that are highly prevalent and considered to be vital components of recovery-oriented treatment. These important treatment areas included psychopharmacologic and psychosocial interventions for alcohol and substance abuse, weight management, and smoking cessation. As with past PORT reviews, the ERGs did not evaluate aspects of care that meet basic human needs (eg, housing) or the benefits of having the mutual support of peers or establishing trusting relationships with providers. Each of these areas is vitally important to recovery-oriented care but is generally not amenable to randomized experiments and, thus, does not meet PORT criteria for review. Also, because the Schizophrenia PORT identifies evidence-based practices for the treatment of schizophrenia, we did not review interventions for treating prodromal

symptoms or for treating persons at high risk for an initial episode of psychosis.

To identify candidate studies for review, the ERGs first conducted extensive electronic literature searches of MEDLINE, Psychlit, and the Cochrane Library using as search terms the names of treatments or treatment methods and schizophrenia. To augment this approach, the ERGs also identified relevant primary studies by reviewing the bibliographies of systematic review articles and through consultation with the Advisory Boards. For treatment areas considered in previous PORT efforts, the time period of review was January 2002 through March 2008; studies published prior to January 2002 were only reviewed if they had not been included in previous PORT reviews. For newly reviewed areas of treatment, we searched the literature as far back as required to capture all studies that met review criteria. For all areas, we only reviewed studies published after March 2008 that were likely to significantly alter the evaluation of the evidence. We restricted our reviews to English language publications.

After reviewing abstracts of candidate studies, the ERGs then selected for more in-depth review and abstraction all randomized controlled trials for which at least 50% of participants had a schizophrenia spectrum disorder diagnosis, ie, schizophrenia, schizoaffective disorder, or schizophreniform disorder. The few exceptions to these criteria were case reports or case series that were reviewed for outcomes of psychopharmacologic treatments that constitute rare adverse events, eg, neuroleptic malignant syndrome (NMS). Also, the majority of controlled studies of psychosocial interventions for substance use disorders and peer-delivered services include populations reflective of those who receive the treatments in clinical practice. Therefore, the Psychosocial ERG reviewed studies of these services that included samples comprised of less than half of individuals with schizophrenia spectrum disorders. In all, the ERGs reviewed and abstracted 424 studies of psychopharmacologic and other somatic treatments and 175 studies of psychosocial interventions for schizophrenia.

In the case of the extant PORT treatment recommendations, the selected articles were reviewed for their potential to importantly modify these recommendations. In the case of new treatments or outcomes, there were 2 possible review results. First, the reviewed evidence could meet criteria for sufficient evidence to merit a treatment recommendation by ERG consensus. In general, the ERGs considered sufficient evidence to be at least 3 well-designed randomized controlled studies performed by independent investigator groups that concluded that the treatment is effective in promoting a desired outcome. We only deviated from this criterion in one instance, in which the conduct of multiple randomized controlled trials is logistically and ethically infeasible and involves an uncommon treatment outcome (use of clozapine for re-

ducing suicidal behaviors). In the case of pharmacologic treatments, only those treatments with at least one non-industry-sponsored investigation were considered for recommendation status because of the potential biases inherent in studies in which a company's financial interests are linked to study outcomes. Recommendation statements include a description of the treatment, the population for which the treatment is indicated, and the outcomes of the treatment. The ERGs also produced accompanying syntheses of the evidence base supporting each treatment recommendation.

Alternatively, the evidence could be judged to be not sufficient to merit a treatment recommendation, in which case a summary statement was written that described the treatment and its indication along with a summary of the evidence and the important gaps in knowledge that precluded treatment recommendation status. The ERGs also produced evidence syntheses explaining the ways in which the research fell short of permitting a recommendation. It should be noted that treatment areas for which the evidence is judged to be insufficient to support a treatment recommendation are not proscriptions against using a particular treatment, ie, they are not "negative recommendations." The PORT simply remains silent with respect to these areas of treatment for schizophrenia, many of which hold future promise but for which empirical support is currently lacking.

Next, the ERGs posted on a dedicated Web site draft versions of the updated treatment recommendations, summary statements, and accompanying evidence summaries for review by the Schizophrenia PORT Expert Panel. Along with the aforementioned members of the Advisory Boards, the Expert Panel consisted of 39 schizophrenia researchers, clinicians, and consumers, including 23 psychiatrists, 15 PhDs in psychology or related fields, and 1 individual with an MPP degree. For those treatment areas in which Expert Panel members indicated they had sufficient expertise, they provided feedback on the content and wording of the draft recommendations and summary statements via the Web site. Also, for this update, we implemented a new method by which Expert Panel members rated the strength of the body of evidence for each treatment area reviewed. However, because we experienced considerable difficulty in using and interpreting the new ratings, we are not reporting them here. Instead, we provide a full description of the expert rating process we attempted to implement and the challenges we experienced in the online supplementary material that accompanies this article.

At a 1-day conference held in Baltimore, MD, in November 2008, the feedback provided by the Expert Panel was aggregated and used to stimulate discussion in order to achieve consensus about the interpretation of the evidence base and treatment recommendation status for each treatment area reviewed by the ERGs. This contrasts with other guideline efforts in which the Expert

Panel suggests what should be recommended in treatment areas where the evidence is lacking. During the conference, the Expert Panel provided suggestions regarding the addition of studies to the evidence syntheses as well as suggestions for editing of the text of the recommendations and summary statements. With regard to potential conflicts of interest, prior to the conference we asked all members of the ERGs and Expert Panel to disclose any financial interests they had during the prior 24 months in commercial interests producing health care goods or services. Dr Anthony Lehman, principal investigator of the first PORT project and the last update, reviewed all participants' disclosures in detail, and a summary of all disclosures was provided to conference participants. Using the extensive feedback from the expert consensus conference, the ERGs revised the treatment recommendations and summary statements and distributed the revisions to the Expert Panel for a final round of comments in February 2009.

The resulting final versions of the 16 Psychopharmacological and 8 Psychosocial Treatment Recommendations are presented below and in the 2 companion papers¹²⁻¹³, which also include the detailed summaries of the evidence for each recommendation. The summary statements and associated evidence summaries for the 13 psychopharmacological treatments and 4 psychosocial treatments for which the evidence is currently insufficient to support a treatment recommendation are included in the supplementary online material associated with the 2 companion articles.

Updated Schizophrenia PORT Treatment Recommendations: Psychopharmacological Treatment Recommendations

Treatment of Acute Positive Symptoms in Treatment-Responsive People With Schizophrenia: Acute Antipsychotic Treatment Medication

Recommendation. In people with treatment-responsive, multiepisode schizophrenia who are experiencing an acute exacerbation of their illness, antipsychotic medications, other than clozapine, should be used as the first line of treatment to reduce positive psychotic symptoms. The initial choice of antipsychotic medication or the decision to switch to a new antipsychotic should be made on the basis of individual preference, prior treatment response, and side effect experience; adherence history; relevant medical history, and risk factors; individual medication side effect profile; and long-term treatment planning.

Treatment of Acute Positive Symptoms in Treatment-Responsive People With Schizophrenia: Acute Antipsychotic Medication Dose

Recommendation. In people with treatment-responsive, multiepisode schizophrenia who are experiencing an acute

exacerbation of their illness, the daily dosage of first-generation antipsychotic medications should be in the range of 300–1000 chlorpromazine (CPZ) equivalents. The daily dosage of second-generation antipsychotic medications for an acute symptom episode should be: aripiprazole: 10–30mg*; olanzapine: 10–20 mg*; paliperidone: 3–15 mg; quetiapine: 300–750 mg*; risperidone: 2–8 mg; and ziprasidone: 80–160 mg*. Treatment trials should be at least 2 weeks, with an upper limit of 6 weeks to observe optimal response. (*, There is insufficient evidence to determine the upper effective dose limit. The quoted upper dose is the FDA-approved upper dose.)

Treatment of Acute Positive Symptoms in People With First-Episode Schizophrenia: Antipsychotic Medication Choice

Recommendation. Antipsychotic medications, other than clozapine and olanzapine, are recommended as first-line treatment for persons with schizophrenia experiencing their first acute positive symptom episode.

Treatment of Acute Positive Symptoms in Treatment-Responsive People With Schizophrenia: Antipsychotic Medication Dose

Recommendation. People with first-episode schizophrenia exhibit increased treatment responsiveness and an increased sensitivity to adverse effects compared with people with multiepisode schizophrenia. Therefore, antipsychotic treatment should be started with doses lower than those recommended for multiepisode patients (first-generation antipsychotics: 300–500 mg CPZ equivalents; risperidone and olanzapine: lower half of recommended dosage range for multiepisode patients). An important exception is with quetiapine, which often requires titration to 500–600 mg/day. The therapeutic efficacy of low-dose aripiprazole or ziprasidone has not been evaluated in people with first-episode schizophrenia.

Maintenance Pharmacotherapy in Treatment-Responsive People With Schizophrenia: Maintenance Antipsychotic Medication Treatment

Recommendation. People with treatment-responsive, multiepisode schizophrenia who experience acute and sustained symptom relief with an antipsychotic medication should be offered continued antipsychotic treatment in order to maintain symptom relief and to reduce the risk of relapse or worsening of positive symptoms.

Maintenance Pharmacotherapy in Treatment-Responsive People With Schizophrenia: Maintenance Antipsychotic Medication Dose

Recommendation. In people with treatment-responsive, multiepisode schizophrenia who experience acute and sustained symptom relief with an antipsychotic

medication, the maintenance dosage for first-generation antipsychotics should be in the range of 300–600 CPZ equivalents per day. The maintenance dosage for aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone should be the dose found to be effective for reducing positive psychotic symptoms in the acute phase of treatment.

Maintenance Pharmacotherapy in Treatment-Responsive People With Schizophrenia: Long-Acting Antipsychotic Medication Maintenance Treatment

Recommendation. Long-acting injectable (LAI) antipsychotic medication should be offered as an alternative to oral antipsychotic medication for the maintenance treatment of schizophrenia when the LAI formulation is preferred to oral preparations. The recommended dosage range for fluphenazine decanoate is 6.25–25 mg administered every 2 weeks and for haloperidol decanoate is 50–200 mg administered every 4 weeks, although alternative dosages and administration intervals equivalent to the recommended dosage ranges may also be used. The recommended dosage range for risperidone long-acting injection is 25–75 mg administered every 2 weeks.

Maintenance Pharmacotherapy in Treatment-Responsive People With Schizophrenia: Targeted, Intermittent Antipsychotic Medication Maintenance Strategies

Recommendation. Targeted, intermittent antipsychotic maintenance strategies should not be used routinely in lieu of continuous maintenance treatment regimens due to the increased risk of symptom worsening and relapse.

Clozapine for the Treatment of Residual Symptoms: Clozapine for Positive Symptoms in Treatment-Resistant People With Schizophrenia

Recommendation. Clozapine should be offered to people with schizophrenia who continue to experience persistent and clinically significant positive symptoms after 2 adequate trials of other antipsychotic agents. A trial of clozapine should last at least 8 weeks at a dosage from 300 to 800 mg/day.

Clozapine for the Treatment of Residual Symptoms: Monitoring Clozapine Plasma Levels

Recommendation. If a person treated with clozapine has failed to demonstrate an adequate response, then a clozapine level should be obtained to ascertain whether the clozapine level is above 350 ng/ml. If the blood level is less than 350 ng/ml, then the dosage should be increased, to the extent that side effects are tolerated, to achieve a blood level above 350 ng/ml.

Clozapine for the Treatment of Residual Symptoms: Clozapine for Hostility

Recommendation. A trial of clozapine should be offered to people with schizophrenia who present with persistent symptoms of hostility and/or display persistent violent behaviors.

Clozapine for the Treatment of Residual Symptoms: Clozapine for Suicidality

Recommendation. A trial of clozapine should be considered for people with schizophrenia who exhibit marked and persistent suicidal thoughts or behaviors.

Other Psychopharmacological Recommendations: Prophylactic Antiparkinson Medications

Recommendation. In people treated with first-generation antipsychotics, prophylactic use of antiparkinson agents to reduce the incidence of extrapyramidal side effects should be determined on a case by case basis, taking into account individual preferences, prior history of extrapyramidal side effects, characteristics of the antipsychotic medication prescribed, and other risk factors for both extrapyramidal side effects and anticholinergic side effects. The use of prophylactic antiparkinson agents in people treated with second-generation antipsychotics is not warranted.

Other Psychopharmacological Recommendations: Medication for the Treatment of Acute Agitation in Schizophrenia

Recommendation. An oral or intramuscular (IM) antipsychotic medication, alone or in combination with a rapid acting benzodiazepine, should be used in the pharmacological treatment of acute agitation in people with schizophrenia. If possible, the route of antipsychotic administration should correspond to the preference of the individual.

Other Psychopharmacological Recommendations: Intervention for Smoking Cessation in Schizophrenia

Recommendation. People with schizophrenia who want to quit or reduce cigarette smoking should be offered treatment with bupropion SR 150 mg twice daily for 10–12 weeks, with or without nicotine replacement therapy, to achieve short-term abstinence. This pharmacological treatment should be accompanied by a smoking cessation education or support group, although the current evidence base is insufficient to recommend a particular psychosocial approach.

Other Psychopharmacological Recommendations: rTMS for the Treatment of Schizophrenia

Recommendation. Low-frequency (1 Hz) rTMS, over the left temporoparietal cortex, is recommended for

the acute treatment of auditory hallucinations that have not responded to adequate antipsychotic therapy.

Updated Schizophrenia PORT Treatment Recommendations: Psychosocial Treatment Recommendations

Assertive Community Treatment

Recommendation. Systems of care serving persons with schizophrenia should include a program of assertive community treatment. This intervention should be provided to individuals who are at risk for repeated hospitalizations or have recent homelessness. The key elements of assertive community treatment include a multidisciplinary team including a medication prescriber, a shared caseload among team members, direct service provision by team members, a high frequency of patient contact, low patient to staff ratios, and outreach to patients in the community. Assertive Community Treatment has been found to significantly reduce hospitalizations and homelessness among individuals with schizophrenia.

Supported Employment

Recommendation. Any person with schizophrenia who has the goal of employment should be offered supported employment to assist them in both obtaining and maintaining competitive employment. The key elements of supported employment include individually tailored job development, rapid job search, the availability of ongoing job supports, and the integration of vocational and mental health services.

Skills Training

Recommendation. Individuals with schizophrenia who have deficits in skills that are needed for everyday activities should be offered skills training in order to improve social interactions, independent living, and other outcomes that have clear relevance to community functioning. Skills training programs vary widely in content but typically include a focus on interpersonal skills and share several key elements, including behaviorally based instruction, role modeling, rehearsal, corrective feedback, and positive reinforcement. Skills training provided in clinic-based settings should be supplemented with strategies for ensuring adequate practice in applying skills in an individual's day-to-day environment.

Cognitive Behavioral Therapy

Recommendation. Persons with schizophrenia who have persistent psychotic symptoms while receiving adequate pharmacotherapy should be offered adjunctive cognitive behaviorally oriented psychotherapy to reduce the severity of symptoms. The therapy may be provided in either a group or an individual format and should be

approximately 4–9 months in duration. The key elements of this intervention include the collaborative identification of target problems or symptoms and the development of specific cognitive and behavioral strategies to cope with these problems or symptoms.

Token Economy Interventions

Recommendation. Systems of care that deliver long-term inpatient or residential care should provide a behavioral intervention based on social learning principles for patients in these settings in order to improve their personal hygiene, social interactions, and other adaptive behaviors. The key elements of this intervention, often referred to as a token economy, are contingent positive reinforcement for clearly defined target behaviors, an individualized treatment approach, and the avoidance of punishing consequences. The intervention should be delivered in the context of a safe treatment environment that provides patient access to basic amenities, evidence-based pharmacological treatment, and the full range of other recommended psychosocial interventions.

Family-Based Services

Recommendation. Persons with schizophrenia who have ongoing contact with their families, including relatives and significant others, should be offered a family intervention that lasts at least 6–9 months. Interventions that last 6–9 months have been found to significantly reduce rates of relapse and rehospitalization. Though not as consistently observed, research has found other benefits for patients and families, such as increased medication adherence, reduced psychiatric symptoms, and reduced levels of perceived stress for patients. Family members have also been found to have lower levels of burden and distress and improved family relationships. Key elements of effective family interventions include illness education, crisis intervention, emotional support, and training in how to cope with illness symptoms and related problems. The selection of a family intervention should be guided by collaborative decision making among the patient, family, and clinician. In addition, a family intervention that is shorter than 6 months, but that is at least 4 sessions in length, should be offered to persons with schizophrenia who have ongoing contact with their families, including relatives and significant others, and for whom a longer intervention is not feasible or acceptable. Characteristics of the briefer interventions include education, training, and support. Possible benefits for patients include reduced psychiatric symptoms, improved treatment adherence, improved functional and vocational status, and greater satisfaction with treatment. Positive family outcomes include reduced family burden and increased satisfaction with family relationships.

Psychosocial Interventions for Alcohol and Substance Use Disorders

Recommendation. Persons with schizophrenia and a comorbid alcohol or drug use disorder should be offered substance abuse treatment. The key elements of treatment for alcohol or drug use disorders for persons with schizophrenia include motivational enhancement and behavioral strategies that focus on engagement in treatment, coping skills training, relapse prevention training, and its delivery in a service model that is integrated with mental health care. The duration of the recommended substance abuse treatment cannot be specified at this time; both brief (1–6 meetings) and more extended (10 or more meetings) interventions have been found to be helpful in reducing substance use and improving psychiatric symptoms and functioning.

Psychosocial Interventions for Weight Management

Recommendation. Individuals with schizophrenia who are overweight (body mass index 25.0–29.9) or obese (body mass index greater than or equal to 30.0) should be offered a psychosocial weight loss intervention that is at least 3 months in duration to promote weight loss. The key elements of psychosocial interventions for weight loss include psychoeducation focused on nutritional counseling, caloric expenditure, and portion control; behavioral self-management including motivational enhancement; goal setting; regular weigh-ins; self-monitoring of daily food and activity levels; and dietary and physical activity modifications.

Discussion

Evidence-based medicine involves the integration of the best available evidence for the treatment of a health condition with clinical expertise and patient values.¹⁴ Over the past 15 years, the Schizophrenia PORT has played a vital role in promoting evidence-based care for schizophrenia by synthesizing the treatment research literature for use by patients and their families in making informed treatment choices in collaboration with their mental health providers. This latest update of the PORT recommendations has identified 24 treatment areas that have strong empirical evidence for improving outcomes and which should comprise the basic menu of treatments and services available to all people with schizophrenia. Consistent with the paradigm shift in schizophrenia treatment from a focus on long-term disability to one focused on optimism and recovery, the ultimate goal of the Schizophrenia PORT has been to increase the use of evidence-based treatments in order to optimize outcomes by reducing illness symptoms and the disability and burden associated with the illness.

In evaluating the validity of evidence-based guidelines over time, Shekelle and colleagues¹⁵ found that after 5 years, half of the guidelines published by the AHRQ needed to be updated, and thus, we undertook this, the second PORT update, 5 years following the first update. Our searches of the treatment literature yielded almost 600 studies that required in-depth review, the majority of which substantiated the evidence base for the extant PORT recommendations. It is encouraging that new research continues to support the effectiveness of several well-established evidence-based practices for schizophrenia, including antipsychotic medications (and clozapine in particular), assertive community treatment, and interventions for families, which primarily target the core symptoms of the disorder.

Although treatments that address the key psychiatric symptoms of schizophrenia are vital components of care, in recent years, considerable attention has been directed toward the overall poor health status of individuals with schizophrenia. Concerns have been raised about the disproportionately high rates of obesity, diabetes, and cardiovascular disease as well as significantly reduced life expectancy in individuals with schizophrenia.¹⁶ Because of the deleterious effects of cigarette smoking and overweight, in particular, on the health status of these patients, research on interventions for smoking cessation and antipsychotic-induced weight gain has expanded considerably over the past 5 years and were, thus, included in this review. The ERGs and Expert Panel found that the evidence was sufficient to support new treatment recommendations in both these areas, representing a significant contribution of this latest PORT update. Although clinicians and patients should be justifiably optimistic about the potential benefits of these treatments, such enthusiasm must also be tempered by clinical realities. Sustained abstinence from cigarette smoking and maintenance of clinically significant weight loss have been notoriously difficult for individuals with schizophrenia to achieve. This is borne out in the research we reviewed, which shows replicated findings with statistically significant, but relatively modest, smoking quit rates and amounts of weight lost. As most of the supporting studies in these areas were of relatively short duration, the extent to which more intensive treatment with these interventions leads to greater improvements is not known, but merits continued investigation to inform future iterations of treatment guidelines such as the PORT. It is hoped that designation of these treatments, along with psychosocial interventions for co-occurring substance use disorders, as evidence-based practices recommended by the PORT will increase awareness of several high prevalence and life-threatening conditions that contribute significantly to poor outcomes and disability in individuals with schizophrenia.

Other new developments in this PORT update include the deletion of 3 previous recommendations for the

psychopharmacologic management of schizophrenia. For 2 of these areas, the evidence base consisted primarily of case reports and other nonexperimental study designs that did not meet criteria for inclusion in the PORT review. Therefore, the recommendation to use clozapine in individuals who had previously experienced NMS, tardive dystonia, or tardive dyskinesia and the recommendation around obtaining antipsychotic plasma levels were eliminated. Further, although antidepressant medications are widely prescribed for individuals with schizophrenia, the evidence base supporting the effectiveness of these medications is limited primarily to studies of older antidepressants in combination with first-generation antipsychotic medications. Because the few randomized controlled trials examining the effects of newer, more widely prescribed antidepressants (eg, selective serotonin reuptake inhibitors) in individuals receiving second-generation antipsychotic medications have been largely negative, this recommendation was also removed. Although the research evidence is currently insufficient to support a PORT recommendation in this area, the absence of a recommendation is not a proscription against the use of antidepressants or any other approach to ameliorating depressive or other symptoms in affected individuals. Rather, patients and clinicians should exercise due caution when employing treatments where the benefits are less certain and should promptly discontinue such treatments if no benefits are observed. Of note, this PORT review revealed a surprising lack of robust empirical investigation of other widely prescribed adjunctive psychopharmacologic treatments (eg, mood stabilizers, benzodiazepines), underscoring the need for continued research on the safety and efficacy of polypharmacy in individuals with schizophrenia.

As mentioned, with very few exceptions, the vast majority of the studies we reviewed for this update were randomized controlled trials, reflecting the PORT's continuing mission of identifying treatments supported by the most robust empirical research evidence. By definition, treatment areas where research utilizing experimental study designs is not feasible are not addressed by the PORT, as mentioned in the "Methods" section of this article. The PORT is also silent on treatment areas where research findings are suggestive of benefits but in the opinion of experts cannot be elevated to recommendation status because of limitations of the available evidence (eg, cognitive remediation, switching antipsychotics for weight loss, [newer] antidepressants for depressive or negative symptoms). There are also some areas of treatment for schizophrenia where adequate research is available but for which the results suggest existing treatment options are ineffective (eg, antipsychotic medications for improving cognition). By remaining silent on these treatments, the PORT has risked being viewed as overly conservative and even indifferent to major areas of unmet treatment need for schizophrenia. As

a major addition to this PORT effort, the ERGs prepared parallel summary statements and evidence syntheses for those treatments for which the evidence is currently insufficient to support a recommendation. This information is provided in the online supplementary material referenced in the 2 companion articles in this issue (Buchanan et al and Dixon et al). The summary statements and accompanying evidence syntheses are analogous in format to that of the treatment recommendations and were similarly critiqued by the PORT Expert Panel. By calling comparable attention to areas of unmet treatment need for schizophrenia, we hope that researchers and funding agencies will use this information to inform future efforts to expand the evidence base in areas where few, if any, treatment options currently exist.

Although this PORT review confirms that a number of evidence-based treatments for schizophrenia do have sound empirical support, it is worth noting that the clinical results of such treatments are often incomplete for individual patients. These treatments do not "cure" schizophrenia or fully ameliorate symptoms and problems for the majority of affected individuals; such objectives remain for future generations of research. These limitations of PORT recommended treatments stem from several causes. A critical issue is that many of the recommended treatments have modest effect sizes. Further, there is the inherent tension between the internal and external validity of randomized controlled trials upon which the PORT and other evidence-based guidelines are based. Although strides in effectiveness research for schizophrenia treatments have certainly been made over the past 5 years, eg, with the completion of the CATIE and CUtLASS studies, it remains logistically and fiscally difficult to conduct research in the "real world" where people with schizophrenia typically present with a complex array of clinical problems and symptoms. Psychosocial treatment studies may include more "typical" patients, but the training needs and expertise required to carry out psychosocial interventions with high fidelity limit the effectiveness of these models. As such, more research is needed to better understand which individuals respond most favorably to treatments with demonstrated efficacy. More research is also needed to understand how evidence-based psychopharmacological and psychosocial treatments should best be combined or sequenced to optimize outcomes for individual patients, another aspect of treatment planning upon which the PORT is unable to comment.

As a major contribution of the Schizophrenia PORT project to both science and service over the past 15 years, the straightforward format of the treatment recommendations has enabled researchers and policy makers to use them as a foundation to devise quality of care indicators.⁵⁻⁹ Unfortunately, several studies have drawn attention to continuing deficiencies in the quality of medication prescribing and lack of access to most

evidence-based psychosocial interventions in clinical practice, lending support to concerns that, despite the availability of evidence-based guidelines, the quality of schizophrenia treatment may not be improving.¹⁷ Although the efforts of the PORT and others to synthesize the research literature to identify effective treatments for schizophrenia are a necessary prerequisite to implementation of evidence-based practices, they are certainly not sufficient. Research in implementation science indicates that passive dissemination of clinical guidelines alone, such as publication in a peer-reviewed journal as has been the tradition with the PORT, is generally insufficient for effecting successful implementation and improving patient outcomes.¹⁸ While widespread dissemination of the treatment recommendations and implementation of evidence-based practices remains beyond the scope of the Schizophrenia PORT project, some progress has been made, including implementation and evaluation of the TMAP algorithm for psychopharmacologic treatments and the National Implementing Evidence-Based Practices project for several psychosocial interventions.¹⁷ We hope these implementation efforts will continue and expand with this latest update of the Schizophrenia PORT treatment recommendations.

As the clinical treatment literature continues to evolve and expand, so have approaches to developing and updating clinical guidelines and treatment recommendations.^{19–21} However, it should be noted that the PORT ERGs did not provide the panel with assessments of the quality of the research design of each study comprising the evidence base, a procedure commonly employed when clinical practice guidelines are developed and updated using studies characterized by a combination of experimental and nonexperimental designs. Given the PORT's reliance on randomized controlled trials, we did not adopt this approach because the likelihood of our detecting any substantive differences in quality across the trials using one of the widely available, but relatively generic, quality rating scales was quite low.²² It was beyond the scope of the PORT project to develop and validate individual quality rating scales tailored to each of the 41 different treatment areas we reviewed.

Overall appraisal of the PORT's third set of treatment recommendations underlines both the movement forward of research on schizophrenia treatments as well as the frustratingly slow pace of knowledge acquisition in this field. While we reviewed over 600 studies for this update and identified 24 evidence-based practices, including 7 newly recommended treatments, we do not see dramatic breakthrough psychosocial treatments or medications. Further, not all people with schizophrenia have full access to these treatments, and when available, their application is sometimes incomplete and many produce only modest effects. Thus, our recommendations issue

a challenge both for continued treatment and implementation research.

Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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