

## The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements

Robert W. Buchanan<sup>1,2</sup>, Julie Kreyenbuhl<sup>3,4</sup>,  
Deanna L. Kelly<sup>2</sup>, Jason M. Noel<sup>5</sup>, Douglas L. Boggs<sup>2</sup>,  
Bernard A. Fischer<sup>2</sup>, Seth Himelhoch<sup>3</sup>, Beverly Fang<sup>6</sup>,  
Eunice Peterson<sup>6</sup>, Patrick R. Aquino<sup>6</sup>, and William Keller<sup>6</sup>

<sup>2</sup>Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, PO Box 21247, Baltimore, MD 21228; <sup>3</sup>Division of Services Research, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD; <sup>4</sup>VA Capitol Healthcare Network (VISN 5) Mental Illness Research, Education, and Clinical Center, Baltimore, MD; <sup>5</sup>Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, MD; <sup>6</sup>Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD

**In light of the large number of studies published since the 2004 update of Schizophrenia Patient Outcomes Research Team psychopharmacological treatment recommendations, we conducted an extensive literature review to determine whether the current psychopharmacological treatment recommendations required revision and whether there was sufficient evidence to warrant new treatment recommendations for prespecified outcomes of interest. We reviewed over 400 articles, which resulted in 16 treatment recommendations: the revision of 11 previous treatment recommendations and 5 new treatment recommendations. Three previous treatment recommendations were eliminated. There were 13 interventions and/or outcomes for which there was insufficient evidence for a treatment recommendation, and a statement was written to summarize the current level of evidence and identify important gaps in our knowledge that need to be addressed. In general, there was considerable consensus among the Psychopharmacology Evidence Review Group and the expert consultants. Two major areas of contention concerned whether there was sufficient evidence to recommend specific dosage ranges for the acute and maintenance treatment of first-episode and multi-episode schizophrenia and to endorse the practice of switching antipsychotics for the treatment of antipsychotic-related weight gain. Finally, there con-**

**tinue to be major gaps in our knowledge, including limited information on (1) the use of adjunctive pharmacological agents for the treatment of persistent positive symptoms or other symptom domains of psychopathology, including anxiety, cognitive impairments, depressive symptoms, and persistent negative symptoms and (2) the treatment of co-occurring substance or medical disorders that occur frequently in individuals with schizophrenia.**

*Key words:* acute treatment/antipsychotic medications/clozapine/first-episode schizophrenia/maintenance treatment/side effects

### Introduction

The Schizophrenia Patient Outcomes Research Team (PORT) psychopharmacological treatment recommendations provide a comprehensive summary of current evidence-based pharmacological treatment practices. There have been 2 previous sets of pharmacological treatment recommendations.<sup>1,2</sup> These recommendations have served to guide the development of algorithms<sup>3,4</sup> and guidelines<sup>5</sup> for the treatment of schizophrenia.

Since the last update of the PORT psychopharmacological treatment recommendations,<sup>2</sup> there have been over 600 studies published on the pharmacological treatment of schizophrenia. These have included a series of publications from 3 large pragmatic studies: the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),<sup>6</sup> the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS),<sup>7</sup> and the European First-Episode Schizophrenia Trial (EUFEST).<sup>8</sup> The CATIE and CUtLASS studies represent the 2 largest, non-industry sponsored comparisons of first-generation antipsychotic (FGA) medications and second-generation antipsychotic (SGA) medications in people with multi-episode schizophrenia, whereas EUFEST compared haloperidol to multiple SGAs in people with first-episode schizophrenia. In addition, there have been a series of new studies that have examined antipsychotic monotherapy and adjunctive strategies for the treatment of a number of symptom and behavioral outcomes, including cognitive impairments, negative symptoms, and

<sup>1</sup>To whom correspondence should be addressed; tel: 410-402-7876, fax: 410-402-7198, e-mail: rwbuchanan@mprc.umaryland.edu.

co-occurring medical and substance misuse disorders. The number of publications in these areas warrants the evaluation of the pharmacological treatment of these outcomes. Finally, although not a pharmacological intervention, there have been a number of studies that have evaluated the potential efficacy of repetitive transcranial magnetic stimulation (rTMS) for the treatment of refractory auditory hallucinations.

In the current PORT update, we evaluated published studies to determine whether the current PORT psychopharmacological treatment recommendations required revision and whether there was sufficient evidence to warrant new treatment recommendations for prespecified outcomes of interest.

## Methods

The Schizophrenia PORT Psychopharmacology Evidence Review Group (ERG) was comprised of University of Maryland Baltimore faculty with expertise in the pharmacological treatment of schizophrenia. The Psychopharmacology ERG was charged with 2 tasks: (1) to review new evidence related to the extant PORT psychopharmacological treatment recommendations and (2) in consultation with the Psychopharmacology Advisory Board, to identify new outcomes or interventions to review for the purpose of determining whether a treatment recommendation was warranted for the outcome or intervention. These outcomes and interventions included but were not limited to antidepressants, antipsychotic polypharmacy, cognition, electroconvulsive therapy (ECT), negative symptoms, rTMS, smoking cessation, and quality of life.

On a quarterly basis, the Psychopharmacology ERG conducted electronic MEDLINE literature searches, using as search terms “schizophrenia” and the names of individual antidepressants, antiepileptics, antipsychotics, benzodiazepines, and lithium; schizophrenia; and clinical trial as search terms. Other search terms included specific topic areas, such as treatment of cognition, extrapyramidal side effects, first-episode schizophrenia, negative symptoms, prolactin-related side effects, quality of life, tardive dyskinesia (TD), and weight gain. All searches were limited to English language, clinical trial, and schizophrenia and to medications with U.S. Food and Drug Administration approval.

The time period for the literature search was January 2002 through March 2008. In addition, if appropriate for the evaluation of an intervention or outcome, we included articles published prior to January 2002, if the area had not previously undergone a PORT review. We did not re-review articles published prior to January 2002, if they had been reviewed in one of the previous PORT treatment recommendation publications. If a relevant article was published after March 2008 and would significantly alter the PORT evaluation of the evidence,

then the article was included in the reviewed evidence base.

Each Psychopharmacology ERG member was assigned one or more antipsychotic medication and designated topic areas to review, with 2 ERG members assigned to each antipsychotic medication to ensure that all relevant articles were identified and included in the review. At the quarterly Psychopharmacology ERG meetings, the members would present the article abstracts from their literature search. If the study was a randomized controlled trial (RCT), and at least 50% of the participants had a schizophrenia spectrum disorder diagnosis, that is, schizophrenia, schizoaffective disorder, or schizophreniform disorder, then the article was selected for further review. The majority of studies were double-blind RCTs, with the following major exceptions: one of the CATIE phase 2 studies,<sup>9</sup> the CUtLASS study,<sup>7</sup> and EUFEST.<sup>8</sup> In the CATIE phase 2E study, the clozapine arm was open labeled<sup>9</sup>; in the CUtLASS study, participants were randomly assigned to open-label antipsychotic treatment, with clinical raters blind to treatment assignment<sup>7</sup>; and in the EUFEST study, participants were randomly assigned to open-label antipsychotic treatment and the majority of clinical ratings were not blinded to treatment assignment.<sup>8</sup> In addition, we would also allow case reports or case series, if the outcome was a rare event, eg, neuroleptic malignant syndrome (NMS).

In the case of the extant PORT pharmacological treatment recommendations, the selected articles were reviewed for their potential to importantly modify these recommendations. In the case of new interventions or outcomes, there were 2 possible review results. First, the reviewed evidence could meet criteria for sufficient evidence to merit a treatment recommendation (see Kreyenbuhl *et al.*,<sup>10</sup> this issue, for a description of these criteria). Alternatively, the evidence could be judged to be insufficient to merit a treatment recommendation, in which case a summary statement was written that described the intervention, the indication for the intervention, and provided a summary of the evidence and the important gaps in knowledge that precluded treatment recommendation status. The draft treatment recommendations and summary statements were then reviewed by the external advisory board (see Kreyenbuhl *et al.*,<sup>10</sup> this issue, for a description of this process) and their comments were incorporated into revisions, which were re-reviewed by the external advisory board, and then final versions were produced.

## Treatment Recommendations

There are 16 treatment recommendations. The treatment recommendations are grouped either by intervention or outcome. The presentation of each treatment recommendation follows the same format: the title of the treatment

recommendation, the full recommendation, the expert rating of the treatment recommendation, and the evidence summary for the recommendation.

### Treatment of Acute Positive Symptoms in Treatment-Responsive People With Schizophrenia

#### *Acute Antipsychotic Treatment*

**Recommendation.** In people with treatment-responsive, multi-episode 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 medication 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.

**Evidence Summary.** Since the last PORT update, there have been several new studies comparing SGAs to placebo for the treatment of acute positive symptoms. The majority are registration studies sponsored by the pharmaceutical industry.<sup>11-15</sup> These studies continue to support the efficacy of antipsychotic medications for positive symptoms in treatment-responsive people with multi-episode schizophrenia.

The primary question of interest remains whether SGAs compared with FGAs should be preferentially used for this indication. Two new pragmatic clinical trials have been completed, which partially address this issue: the CATIE study<sup>6</sup> and the CUtLASS study.<sup>7</sup> In both these studies, the sample included participants who were experiencing an acute exacerbation of their illness, as well as individuals who were changing their medications because of inadequate response to or intolerable side effects from prior antipsychotic treatment. However, neither study separately analyzed these subsamples of participants. In the CATIE study, risperidone, olanzapine, quetiapine, and ziprasidone were compared with the FGA: perphenazine. In the CUtLASS study, antipsychotic medications were classified into FGA and SGA groups and were compared by group. In the CATIE study, participants randomized to olanzapine had a significantly longer time to discontinuation than those who received risperidone, quetiapine, ziprasidone, and perphenazine, though the differences between olanzapine and ziprasidone and olanzapine and perphenazine were no longer significant after correction for multiple comparisons. There was no significant difference among olanzapine, risperidone, and perphenazine on Positive and Negative Syndrome Scale (PANSS) total score. In the CUtLASS study, there were no significant FGA vs SGA group differences for PANSS total score or the positive or negative syndrome subscale scores. These studies suggest that there are limited

positive symptom efficacy differences, except for possibly olanzapine, between FGAs and SGAs. There continues to be no data to support a change to a SGA for those people who experience adequate symptom control and minimal side effects with an FGA.

The other major considerations in the choice of antipsychotic medication are individual and treatment-related factors that may influence treatment outcomes. In the context of whether SGAs should be preferentially used to treat schizophrenia, the question revolves around the relative side effect risks of FGAs and specific SGAs. There are 4 major side effects to consider when choosing among the first- and second-generation agents: (1) extrapyramidal symptoms (EPS), including TD, (2) weight gain and associated metabolic effects, (3) prolactin elevation and associated sexual side effects, and (4) QTc prolongation. The relative risk for EPS among FGAs and SGAs is high-potency FGAs > mid-potency FGAs = risperidone > low-potency FGAs > olanzapine = ziprasidone > quetiapine > clozapine. There is currently insufficient comparative data among the different FGAs and SGAs to rank aripiprazole (see “Prophylactic Antiparkinson Medications” Treatment Recommendation in the Other Psychopharmacological Recommendations section for further details). The relative risk for causing TD is FGAs > SGAs > clozapine (see “Antipsychotic Choice and Treatments for Tardive Dyskinesia” Summary Statement in the Supplementary Material for further details).

Select SGAs are more likely to cause weight gain and metabolic abnormalities than most FGAs or other SGAs. In particular, olanzapine and clozapine are more likely to cause weight gain, glucose elevation, and lipid abnormalities than other SGAs and medium- and high-potency FGAs.<sup>16,17</sup> The relative metabolic risk of these SGAs vs low-potency FGAs, such as chlorpromazine and thioridazine, has not been directly assessed, but these agents are known to have a higher relative metabolic risk than medium- or high-potency FGAs. Risperidone and quetiapine have an intermediate risk for weight gain and glucose elevation.<sup>6,16,17</sup> There is less information available for paliperidone on all these measures, although weight gain appears similar to risperidone. Quetiapine has an intermediate risk for lipid elevation, whereas risperidone has a low risk for lipid elevations.<sup>6,16,17</sup> In contrast, aripiprazole and ziprasidone have low risk for weight gain and other metabolic side effects.<sup>6,16,17</sup> In summary, the relative risk for weight gain among antipsychotic medications is clozapine = olanzapine > low-potency FGA medications > risperidone = paliperidone = quetiapine > medium-potency FGA medications > high-potency antipsychotic medications = molindone = aripiprazole = ziprasidone (see “Pharmacological Prevention and Treatment of Antipsychotic-Associated Weight Gain in Schizophrenia Summary Statement” section in the Supplementary Material for further details). The relative

**Table 1.** Recommended Oral Antipsychotic Dosage Ranges for the Treatment of Schizophrenia

Medication (First-Generation Antipsychotic Medications)	CPZ <sup>a</sup>	PORT Recommended Dosage Range	
		Acute Therapy (mg/day)	Maintenance Therapy (mg/day)
<b>Phenothiazines</b>			
Fluphenazine HCl	2	6–20	6–12
Trifluoperazine	5	15–50	15–30
Perphenazine	10	12–64	12–40
Chlorpromazine	100	300–1000	300–600
Thioridazine	100	300–800	300–600
<b>Butyrophenone</b>			
Haloperidol	2	6–20	6–12
<b>Others</b>			
Thiothixene	5	15–50	15–30
Molindone	10	30–150	30–100
Loxapine	10	30–100	30–60

*Note:* CPZ, chlorpromazine equivalent; PORT, Schizophrenia Patient Outcomes Research Team.

<sup>a</sup>Approximate dose equivalent to 100 mg of chlorpromazine (relative potency); may not be the same at lower vs higher doses. CPZ doses are not relevant to the second-generation antipsychotics and, therefore, are not provided for these agents.

risk for prolactin elevation and sexual side effects is risperidone = paliperidone > FGA medications > olanzapine > ziprasidone > quetiapine = clozapine > aripiprazole (see “Antipsychotic-Induced Prolactin Elevations, Hormonal Side Effects and Sexual Dysfunction” Summary Statement in the Supplementary Material for further details). Finally, the relative risk for QTc prolongation is thioridazine > ziprasidone > quetiapine = risperidone = olanzapine = haloperidol ≥ clozapine.<sup>18–21</sup> Aripiprazole,<sup>22–24</sup> fluphenazine,<sup>25</sup> and chlorpromazine<sup>25,26</sup> do not appreciably prolong the QTc interval. Clozapine may increase the QTc interval, but the effect is dose dependent<sup>27</sup> and is equivalent to olanzapine and haloperidol.<sup>28</sup> However, one study found that clozapine did not increase the QTc interval.<sup>29</sup>

In light of the comparable efficacy and variable risk of side effects among the different FGAs and SGAs, a straightforward recommendation for preferential use of SGAs over FGAs for first-line treatment of acute positive symptoms is not currently warranted. Rather, the initial choice of antipsychotic medication or the decision to switch to a new antipsychotic medication should be made through shared decision making between the physician and the person with schizophrenia based on 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.

### Acute Antipsychotic Medication Dose

**Recommendation.** In people with treatment-responsive, multi-episode schizophrenia who are experiencing an acute exacerbation of their illness, the daily dosage of FGA medications should be in the range of 300–1000 chlorpromazine equivalents (CPZ) (see table 1). The daily dosage of SGA medications for an acute symptom episode should be aripiprazole: 10–30 mg\*, 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.).

**Evidence Summary.** Since the 2004 PORT recommendations, no new information has emerged to warrant a change in the recommended FGA dosage range for treatment of acute positive symptom episodes.<sup>2</sup>

The recommended dosage ranges for aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone reflect those demonstrated to be safe and efficacious in pivotal clinical trials.<sup>2</sup> There are currently no new data to support the safety and efficacy of aripiprazole, olanzapine, quetiapine, or ziprasidone dosages above the aforementioned upper limits.

Paliperidone received FDA approval in 2006. The recommended dosage range is based on registration studies.<sup>12–14</sup>

In general, because the incidence of side effects increases with the use of doses at the upper end of the recommended range, the lowest effective dose should be used to treat the acute episode. There is no absolute proscription against the use of doses outside the recommended range, but reasons for such use should be documented.

### Treatment of Acute Positive Symptoms in People With First-Episode Schizophrenia

#### *Antipsychotic Choice for First-Episode Schizophrenia*

**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.

**Evidence Summary.** In first-episode psychosis, early treatment with antipsychotic drugs is associated with significant symptom reduction, and the results of several studies suggest that there are no significant short-term efficacy differences between FGAs and SGAs. RCTs comparing haloperidol and SGAs have demonstrated equivalent improvements in psychopathology scores and 12-week response rates.<sup>30–32</sup> In an 8-week study of people with early-onset schizophrenia and related spectrum disorders (aged 8–19 years), there were no significant

differences among molindone, risperidone, and olanzapine in response rates or symptom reduction.<sup>33</sup> Finally, in a study comparing chlorpromazine and clozapine in antipsychotic-naïve people with first-episode schizophrenia, in the 12-week intention to treat analyses, there were no significant group differences in Brief Psychiatric Rating Scale (BPRS) total or Clinical Global Impression-Severity (CGI-S) scores.<sup>34</sup> In the 12-week observed cases analyses, clozapine was superior to chlorpromazine on BPRS total and CGI-S scores. In neither analysis was there a significant group difference for positive symptoms. Clozapine treatment was associated with significantly greater improvements in negative symptom scores.

There is some evidence to suggest that SGAs compared with FGAs may show greater long-term benefits. In a 2-year study of haloperidol and olanzapine, Green and colleagues<sup>35</sup> observed superior remission rates and treatment retention with olanzapine. After 2 years, 23.4% of participants in the olanzapine group remained on treatment compared with 12.1% of haloperidol-treated participants. In a long-term study comparing risperidone and haloperidol, there was a significantly longer median time to relapse in the risperidone group (466 vs 205 days).<sup>32</sup> However, overall treatment retention and rates of clinical improvement were similar between the 2 groups. In contrast, the 1-year interim analysis of another long-term study of individuals with first-episode schizophrenia randomized to risperidone or low-dose haloperidol failed to replicate the findings from Schooler and colleagues.<sup>36</sup> In this latter study, there were no significant group differences in relapse, rehospitalization, or other measures of clinical worsening.

The EUFEST, a large, open-labeled, 1-year randomized trial, showed that treatment discontinuation was greatest for haloperidol compared with participants receiving any of 4 SGAs.<sup>8</sup> Clinical Global Impression scores and Global Assessment of Functioning scores were also superior for the SGA group compared with haloperidol, but there were no group differences in PANSS total scores or the Calgary Depression Scale (CDS) and quality of life scores.

Finally, in the chlorpromazine vs clozapine first-episode schizophrenia study,<sup>34</sup> the 52-week data analyses showed no differences in any of the symptom outcome measures. There were no significant differences in the proportion of participants who met a priori remission criteria, though participants randomized to clozapine met remission criteria significantly faster than those randomized to chlorpromazine. In light of the negligible group differences in efficacy and the adverse side effect profile of clozapine, these results do not warrant elevating clozapine to a first-line treatment of people with first-episode schizophrenia.

No clinically meaningful differences in efficacy have been observed among SGAs in the treatment of first-episode patients. In studies comparing multiple

SGAs, there have been no differences in overall symptom scores and response rates among treatment groups.<sup>8,37,38</sup>

Significant differences in adverse effects, including drug-induced movement disorders and metabolic side effects, have been observed between and among FGAs and SGAs and should be considered in shared decision making around selection of initial antipsychotic treatment (see “Acute Antipsychotic Treatment” Treatment Recommendation in the Treatment of Acute Positive Symptoms in Treatment-Responsive People with Schizophrenia section for further details). Olanzapine treatment has consistently been shown to have the highest liability for weight gain when compared with most other FGAs and SGAs. In a 4-month, single-blind comparison,<sup>37</sup> olanzapine was associated with significantly greater increases in body weight and body mass index than risperidone. In a head-to-head comparison with quetiapine and risperidone, olanzapine was associated with up to 2 times the increase in weight at 12 and 52 weeks.<sup>38</sup> In the Sikich and colleagues<sup>33</sup> study, olanzapine was associated with significant increases in weight, fasting insulin, cholesterol, and low-density lipoprotein cholesterol compared with risperidone and molindone, whereas risperidone was associated with significantly greater weight gain than molindone. In the absence of any evidence of significantly enhanced therapeutic benefits, the association of olanzapine with significant metabolic risks suggests that olanzapine should not be considered as a first-line treatment for individuals experiencing their first episode of schizophrenia.

Although not systematically evaluated in first-episode schizophrenia, there are other significant risks associated with many of the FGAs, especially when used in moderate-to-high doses. Low-potency FGAs, such as thioridazine and chlorpromazine, are associated with adverse effects such as cardiac arrhythmias, hepatotoxicity, metabolic abnormalities, orthostasis, sedation, skin and retinal pigmentation, and weight gain. High-potency FGAs, including haloperidol and fluphenazine, carry significant risks of motor symptoms, including acute dystonia and akathisia, and TD, which can be irreversible. All these risks should be taken into consideration when deciding whether to use FGAs in people with first-episode schizophrenia.

The available data have several limitations. Haloperidol is still the most frequently used FGA comparator. Because people with first-episode schizophrenia show a high degree of sensitivity to the motor side effects of high-potency FGAs, the use of non-high-potency comparators may produce different results. The long-term advantages of risperidone and olanzapine compared with haloperidol observed in some, but not all studies, may be partially due to this differential sensitivity to motor side effects. Ziprasidone and aripiprazole have no available published randomized, double-blind data on their use in first-episode schizophrenia. Finally, it

also remains to be seen whether the use of long-acting injectable (LAI) preparations of FGAs or risperidone offer additional benefits or disadvantages in the first-episode population.

### *Antipsychotic Medication Dose for First-Episode Schizophrenia*

**Recommendation.** People with first-episode schizophrenia exhibit increased treatment responsiveness and an increased sensitivity to adverse effects compared with people with multi-episode schizophrenia. Therefore, antipsychotic treatment should be started with doses lower than those recommended for people with multi-episode schizophrenia (FGA medications: 300–500 mg CPZ equivalents per day; risperidone and olanzapine: lower half of recommended dosage range for multi-episode 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.

**Evidence Summary.** The use of lowest effective doses is especially important in people with first-episode schizophrenia in order to establish treatment acceptance and reduce the severity of adverse effects. Most recently published studies assessing antipsychotic efficacy in people with first-episode schizophrenia have been specifically designed to evaluate the efficacy of lower doses. In these studies, the mean modal risperidone dosages ranged from 2.4 to 4 mg/day,<sup>30,32,37,38</sup> and the mean modal daily olanzapine dosages ranged from 9.1 to 12.6 mg/day.<sup>8,31,35,38</sup> These risperidone and olanzapine dose ranges were found to be effective and represent the lower end of the dose range for multi-episode people with schizophrenia (see “Maintenance Antipsychotic Medication Dose” Treatment Recommendation in the Maintenance Pharmacotherapy in Treatment-Responsive People with Schizophrenia section for further details).

In contrast, the extant evidence suggests that quetiapine cannot be effectively used in doses lower than what are used in people with multi-episode schizophrenia. In the McEvoy and colleagues study, the mean modal dose of quetiapine was 506 mg, with similar efficacy to the comparator treatments.<sup>38</sup> A similar result was observed in the open-label EUFEST study,<sup>8</sup> in which the mean dose of quetiapine was 498.6 mg/day; a dose that was associated with comparable treatment retention and overall psychopathology scores to the other treatment groups. These mean doses are almost exactly the same as the mean quetiapine dose in the CATIE study.<sup>6</sup>

There have been several new studies that have documented the efficacy of low-dose haloperidol in this population. In a 6-week, randomized controlled study comparing haloperidol 2 mg/day to haloperidol 8 mg/day in first-episode psychosis, Oosthuizen and col-

leagues reported no between-group differences in overall psychopathology score and clinician global impression improvement scores, whereas the 2-mg/day group showed significantly lower parkinsonism adverse effect scores than the 8-mg/day group.<sup>39</sup> In double-blind studies, in which haloperidol was compared with SGAs, mean haloperidol dosages ranged from 2.9 to 4.8 mg/day.<sup>31,32,35</sup> These lower doses of haloperidol produced comparable symptom amelioration and tolerability to SGAs, but haloperidol was associated with inferior treatment retention in some<sup>31,35</sup> but not all<sup>32</sup> studies.

The lack of adequately controlled data with ziprasidone and aripiprazole precludes the determination of whether the recommendation to use doses in the lower half of the recommend dose range for multi-episode people with schizophrenia applies to these agents.

### **Maintenance Pharmacotherapy in Treatment-Responsive People With Schizophrenia**

#### *Maintenance Antipsychotic Medication Treatment*

**Recommendation.** People with treatment-responsive, multi-episode 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.

**Evidence Summary.** Since the last PORT review, 5 studies have examined the comparative efficacy of an SGA and placebo for the prevention of relapse in schizophrenia.<sup>40–44</sup> These studies have documented the superior efficacy of aripiprazole, olanzapine, paliperidone, quetiapine, and ziprasidone compared with placebo for preventing relapse.

Since the last PORT review, several studies have addressed the comparative efficacy of FGAs and SGAs for maintenance treatment.<sup>6,7,36,45–49</sup> Two of these studies compared the long-term efficacy of risperidone and haloperidol for preventing psychotic relapse. In contrast to an earlier study by Csernansky and colleagues,<sup>50</sup> these studies did not find a significant benefit of risperidone for preventing relapse.<sup>36,45</sup> Two studies compared the long-term efficacy of olanzapine to haloperidol. In a 12-month study of people who were currently hospitalized or had been hospitalized within the last 2 years, Rosenheck and colleagues<sup>46</sup> failed to find any symptom or retention differences between the 2 drugs. In contrast, Kongsakon et al<sup>47</sup> found an advantage for olanzapine on overall symptom improvement but not for positive symptoms. The difference between the 2 studies may be related to the use of prophylactic anticholinergic agents in the study by Rosenheck et al but not in the industry-sponsored study of Kongsakon and colleagues. The

lack of prophylactic anticholinergics may also have contributed to the observed group differences in the risperidone studies by Csernansky et al and Schooler et al.

The CATIE study was comprised of multiple phases, which compared the effectiveness of an FGA, perphenazine, to olanzapine, quetiapine, risperidone, and ziprasidone and the comparative effectiveness among the different SGAs.<sup>6,48,49</sup> In the CATIE phase 1 study,<sup>6</sup> olanzapine had a significantly longer time to discontinuation than risperidone, quetiapine, ziprasidone, and perphenazine, though the differences between olanzapine and ziprasidone and olanzapine and perphenazine were no longer significant after correction for multiple comparisons. There was no significant difference among olanzapine, risperidone, and perphenazine on PANSS total score. In the CATIE phase 1B study,<sup>49</sup> the time to discontinuation for participants randomized to olanzapine or quetiapine was significantly longer than that for participants randomized to risperidone. However, there were no significant symptom differences among the 3 groups. In the phase 2T study,<sup>48</sup> participants who had discontinued their phase 1 study drug because of lack of efficacy or intolerability were randomized to olanzapine, quetiapine, risperidone, or ziprasidone. The time to discontinuation for participants randomized to olanzapine or risperidone was significantly longer than that for people randomized to quetiapine or ziprasidone. The 3 studies taken together suggest that there may be some benefit of olanzapine compared with the other SGAs for time to discontinuation and to quetiapine and ziprasidone for symptom amelioration. The potential therapeutic advantage of olanzapine has to be balanced by side effect considerations (see Acute “Antipsychotic Treatment” Treatment Recommendation in the Treatment of Acute Positive Symptoms in Treatment-Responsive People with Schizophrenia section for further details).

In the CUtLASS study, there were no significant FGA vs SGA group differences for PANSS total score or the positive or negative syndrome subscale scores.<sup>7</sup> In contrast to the CATIE study, response differences for specific agents were not examined.

In summary, studies published since the last PORT review continue to confirm that maintenance therapy with an FGA or SGA reduces the risk of symptom relapse during the first to second year following an acute symptom episode. Although, several studies suggest that SGAs may be more effective than FGAs for preventing relapse, there is not sufficient information to recommend SGAs for this indication.

#### *Maintenance Antipsychotic Medication Dose*

**Recommendation.** In people with treatment-responsive, multi-episode schizophrenia who experience acute and sustained symptom relief with an antipsychotic medication, the maintenance dosage for FGA medications

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.

**Evidence Summary.** Since the last PORT review<sup>2</sup>, no new evidence has emerged to warrant a change in the recommended dosage range or dosage reduction strategies during maintenance treatment with FGAs. In contrast to previously reviewed maintenance studies with FGAs,<sup>1,2</sup> maintenance studies with SGAs have not adequately examined whether the dose used to treat acute positive symptom exacerbations is required for maintenance treatment.

In general, because the incidence of side effects increases with the use of doses at the higher end of the recommended range, the lowest effective dose should be used for maintenance treatment. However, there is no absolute proscription against the use of doses outside the recommended range, but reasons for such use should be documented.

#### *Long-Acting Antipsychotic Medication Maintenance Treatment*

**Recommendation.** 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.

**Evidence Summary.** LAI formulations of antipsychotic medications provide a convenient alternative to taking multiple daily oral doses of antipsychotic medications. LAI formulations are available for 2 FGA agents (fluphenazine and haloperidol) and 1 SGA agent (risperidone). Previous reviews and a recent study comparing rates of symptom exacerbation and side effects across 4 fixed doses of haloperidol decanoate support our recommendation of administering 50–200 mg of this medication once monthly.<sup>1,51,52</sup> In the study by Kane and colleagues,<sup>52</sup> rates of symptom exacerbation were significantly higher for participants randomized to monthly administration of 25 mg (60%) of haloperidol decanoate compared with those who received 50 (25%), 100 (23%), or 200 (15%). There were no differences in adverse effects, including EPS, among participants receiving the 3 higher doses of haloperidol decanoate. The previous PORT reviews<sup>1,51</sup> and the commentary by Kane and colleague<sup>52</sup>

on the fluphenazine decanoate literature also support the recommendation of administering 6.25–25 mg of this agent every 2 weeks. The administration of equivalent doses at different time intervals than those recommended is acceptable when clinically appropriate.

In 2003, the LAI formulation of risperidone, risperidone microspheres, became available in the United States. Three double-blind, randomized, controlled trials of risperidone microspheres, all of which were industry sponsored, have examined the efficacy and safety of this formulation. In a 12-week study, fixed risperidone microspheres doses of 25, 50, and 75 mg were compared with placebo in individuals with schizophrenia.<sup>53</sup> All doses were more effective than placebo, though the findings must be interpreted in the context of very high rates of attrition across all study groups (51%–68%). In a second 12-week study, Chue and colleagues<sup>54</sup> demonstrated that risperidone microspheres, in doses ranging from 25 to 75 mg every 2 weeks, did not exhibit inferior efficacy compared with daily doses of oral risperidone ranging from 2 to 6 mg. In a 52-week trial, Simpson and colleagues found that risperidone microspheres doses of 25 and 50 mg administered every 2 weeks exhibited comparable efficacy with respect to time to relapse.<sup>55</sup> The risperidone microspheres doses did not differ on secondary efficacy outcomes and were similar on all neurological and metabolic safety measures except prolactin elevation, which was more pronounced in the 50-mg group.

There remain significant gaps in the evidence base for all these agents. In particular, there are no new long-term, randomized, controlled trials investigating whether FGA or SGA LAI antipsychotic medications reduce the risk of relapse in comparison to oral antipsychotic agents, although 2 such studies of LAI risperidone are currently underway. There are also no data to support the use of LAI antipsychotic agents compared with oral antipsychotic medications as first-line treatments for schizophrenia or studies demonstrating that use of LAI agents improves long-term adherence to treatment. Finally, comparative studies of the efficacy and safety of LAI formulations of FGAs vs LAI risperidone have not been conducted. Therefore, the current evidence is insufficient to recommend a specific LAI antipsychotic agent over another.

#### *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.

**Evidence Summary.** In efforts to limit the risks of medication adverse effects and to offset the risks of unsuper-

vised treatment discontinuation, a strategy of targeted intermittent treatment has been suggested for select people with first-episode and multi-episode schizophrenia who can be monitored closely during drug withdrawal and who do not experience symptom worsening during medication tapering.

Since the last PORT review, in a study involving both first-episode and multi-episode individuals with schizophrenia, Gaebel and colleagues conducted a post hoc reanalysis to compare the use of maintenance antipsychotic treatment to 2 intermittent treatment protocols.<sup>56</sup> Participants were randomized to receive maintenance antipsychotic treatment (MT), intermittent treatment to be reinitiated upon emergence of prodromal symptoms (PI), or intermittent treatment to be reinitiated upon experiencing a “full relapse” (CI). In a completer analysis of participants with first-episode schizophrenia, the differences in relapse rates did not achieve statistical significance (MT: 38%; PI: 42%; CI: 67%). The comparable relapse rate between the PI and MT groups suggests that if people can be monitored closely and the first signs of clinical exacerbation detected, then an intermittent treatment strategy can be used in select people with recent-onset schizophrenia.

In multi-episode schizophrenia, the MT group (20%) had a statistically significant relapse rate advantage compared with both the PI (71%) and CI (78%) conditions.<sup>56</sup> In addition, significant differences in rehospitalization rates were noted for participants randomized to the MT group (24%) compared with the PI (45%) and the CI (52%) groups. These findings are consistent with previous investigations in multi-episode people with schizophrenia.<sup>2</sup>

There have been 2 studies that have examined drug discontinuation in first- or early-episode people with schizophrenia. Gitlin and colleagues<sup>57</sup> enrolled people with recent-onset schizophrenia in a placebo-controlled crossover trial of fluphenazine decanoate. Study participants had their medication withdrawn under clinical supervision. Within the 18-month follow-up period, 96% of participants experienced an exacerbation of psychotic symptoms or a relapse. Among individuals experiencing an exacerbation or relapse, the median time to exacerbation or relapse was 245 days. Wunderink and colleagues<sup>58</sup> carried out a study in which after 6 months of successful treatment, remitted first-episode participants were randomized to either a medication maintenance strategy or a medication discontinuation strategy. Participants randomized to the medication discontinuation group were significantly more likely to relapse (43% vs 21%). Only 20% of participants who were randomized to the discontinuation strategy were relapse free for a median period of 15 months.

Although Gaebel and colleagues<sup>56</sup> failed to find a statistical difference between maintenance and targeted treatment strategies in first-episode people with



schizophrenia, the high rate of symptom exacerbation or relapse in the 2 drug discontinuation studies<sup>57,58</sup> suggests that these strategies should be considered only for people with schizophrenia who refuse continuous maintenance treatment or for whom some other contraindication to continuous maintenance treatment exists, such as extreme side effect sensitivity.

### 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.

**Evidence Summary.** Since the last PORT review, 12 new studies have compared clozapine with other antipsychotic medications for the treatment of positive symptoms. The available empirical evidence continues to support the use of clozapine in people who have not responded to adequate treatment with FGAs.<sup>1,2</sup>

There is new evidence to suggest that clozapine is more effective than other SGAs in people who have failed to adequately respond to either an FGA or SGA.<sup>9,59</sup> The CATIE phase 2E study compared clozapine (open label), olanzapine, risperidone, and quetiapine.<sup>9</sup> Clozapine had a longer time to all-cause discontinuation than olanzapine, quetiapine, and risperidone, with the comparison between clozapine and quetiapine and clozapine and risperidone statistically significant. Clozapine had a significantly longer time to discontinuation due to lack of efficacy than all 3 drugs. Clozapine produced greater improvements in PANSS total and positive syndrome subscale scores, with the difference in PANSS total scores significant for clozapine vs quetiapine and risperidone but not olanzapine. In the CUtLASS 2 trial, open-label clozapine was compared with a group of other SGAs, including olanzapine, quetiapine, and risperidone, and produced significantly greater reductions in the PANSS total score than these other agents.<sup>59</sup>

**Other Second Generation Antipsychotic Medications.** Since the last PORT review, several studies have addressed the question of whether other SGAs may also exhibit superior efficacy in people who have failed to adequately respond to previous trials of FGAs or SGAs. In addition to the CATIE and CUtLASS studies described above, which failed to demonstrate the superior efficacy of olanzapine, quetiapine, and risperidone, there have been 6 studies that have compared the use of olanzapine with clozapine,<sup>60–65</sup> with 3 studies comparing high-dose olanzapine with clozapine<sup>59,63,64</sup> and 2 studies conducted in children and adolescents.<sup>61,64</sup> In the 4 studies conducted in adult populations, 3

of the 4 studies reported a numerical advantage for clozapine on total and positive symptom scores, but the group difference did not reach statistical significance.<sup>60–62,65</sup> The lack of statistical group differences has led to the claim that olanzapine was non-inferior to clozapine for positive symptoms in treatment-resistant schizophrenia.<sup>61,62,65</sup> However, these studies have several methodological problems, including the use of low clozapine doses,<sup>61,62</sup> small sample sizes,<sup>60,65</sup> the inclusion of participants who were treatment intolerant to prior medications rather than treatment resistant, which would tend to minimize potential group differences,<sup>61,62</sup> and the failure to include an FGA comparator arm.<sup>60–62,65</sup>

Two studies evaluated olanzapine and clozapine in children or adolescents with treatment-resistant schizophrenia.<sup>63,64</sup> In the study by Shaw and colleague,<sup>63</sup> clozapine produced a marked reduction in total and positive symptoms, whereas participants treated with olanzapine had essentially no change in total symptoms and a worsening of positive symptoms. The group differences were not statistically significant, probably, because of the relatively small sample sizes. In the study by Kumra and colleague, participants treated with clozapine were significantly more likely to meet response criteria, but there were no significant group differences in total or positive symptoms.<sup>64</sup>

In summary, clozapine continues to be the treatment of choice for people who have failed to adequately respond to previous antipsychotic treatment. Several studies have compared clozapine with olanzapine, but various methodological problems with these studies undermine interpretations of “non-inferiority” of olanzapine to clozapine, and prior direct tests of olanzapine vs haloperidol in people with treatment-resistant schizophrenia found little benefit of either agent.<sup>60,66</sup> There are no studies examining the use of aripiprazole, paliperidone, or ziprasidone for use in treatment-resistant schizophrenia.

#### *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.

**Evidence Summary.** Five studies have evaluated the relationship between clozapine blood levels and therapeutic response. All 5 studies showed increased positive symptom response to be associated with higher clozapine blood levels. Two studies showed that treatment response was related to clozapine levels above 350 ng/ml<sup>67,68</sup> and one study<sup>69</sup> showed that treatment response was related to clozapine levels above 370 ng/ml. In the study by Potkin and colleagues,<sup>70</sup> treatment response was related to clozapine levels above 420 ng/ml. These 4 studies all adjusted

clozapine dose to therapeutic response or had a fixed clozapine dose and then measured clozapine blood levels. VanderZwaag and colleagues<sup>71</sup> found that a clozapine blood level of 250 ng/ml distinguished responders from non-responders. No response rate difference was found between clozapine blood levels above 250 ng/ml or clozapine blood levels above 350 ng/ml, but each of these clozapine blood levels was superior to clozapine blood levels below 250 ng/ml. In this study, the clozapine blood levels were monitored and then the clozapine dose was adjusted to achieve the desired clozapine blood level.

The 5 studies were of varying duration, yet each study had a similar percentage of responders to clozapine when clozapine blood levels were above the threshold value. The comparable response rates suggest that study duration did not confound the observed dose-response results.

In summary, the evidence suggests that clozapine levels above 350 ng/ml are associated with improved clozapine treatment response. The VanderZwaag and colleagues<sup>71</sup> study is the only study that found clozapine levels lower than 350 ng/ml to be associated with treatment response, but this study had a 2 or 3 times per day dosing regimen for clozapine, which may have led to lower clozapine blood levels. VanderZwaag and colleagues suggest that if clozapine is dosed once daily, then the clozapine blood level should be above 350 ng/ml.

### *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.

**Evidence Summary.** There is substantial evidence to support the use of clozapine in people with schizophrenia who display persistent violent behaviors.<sup>2</sup> A recent 12-week double-blind study compared clozapine, olanzapine, and haloperidol for reducing physical assaults and other aggressive behaviors in physically assaultive people with schizophrenia or schizoaffective disorder. They found that clozapine was superior to both olanzapine and haloperidol in reducing the number and severity of physical assaults and reducing overall aggression.<sup>72</sup> In a secondary analysis of chronically ill people with schizophrenia, Volavka and colleagues<sup>73</sup> reported that clozapine compared with olanzapine, risperidone, or haloperidol was more effective for reducing aggressive behavior and for improving measures of hostility.<sup>74</sup> However, clozapine only separated from oral haloperidol after excluding the first 24 weeks of data.<sup>75</sup> In a treatment-resistant sample, clozapine compared with olanzapine was found to produce significant improvement in BPRS activation items, and there was a trend for improvement in hostility and aggression.<sup>60</sup>

The evidence that SGAs other than clozapine can reduce violent behaviors is suggestive, but inconclusive,

and most studies did not evaluate aggression or hostility as the primary end point. The only randomized controlled study designed to include participants with aggression and to examine aggression or hostility with an SGA other than clozapine found olanzapine to be superior to haloperidol but not as effective as clozapine.<sup>72</sup> The CATIE trial failed to find any differences in recorded acts of violence in people receiving SGA vs FGA agents, with the exception of significantly less violence in the perphenazine group compared with those on quetiapine.<sup>75</sup> Finally, 2 RCTs failed to find any differences between risperidone and haloperidol on BPRS hostility ratings at 1<sup>36</sup> and 2 years.<sup>45</sup>

There are limited data demonstrating improvements in BPRS or PANSS hostility ratings from RCTs for non-clozapine SGAs relative to placebo. The populations studied were not selected for hostile or aggressive behaviors, were observed over shorter periods of time, and measurements other than hostility symptom rating scales were not employed. Nonetheless, quetiapine,<sup>43,76</sup> paliperidone,<sup>13</sup> and aripiprazole<sup>77</sup> all have demonstrated improvements in hostility relative to placebo.

Recent studies continue to support the efficacy of clozapine for persistent aggressive and hostile behaviors in people with schizophrenia, including those who do not meet formal criteria for treatment-resistant schizophrenia. There continues to be limited data on the effectiveness of FGAs or SGAs, other than clozapine, for the treatment of hostility.

### *Clozapine for Suicidality*

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

**Evidence Summary.** There is evidence to suggest that clozapine is associated with reduced suicide rates in people with schizophrenia. Most of the observational and retrospective studies have included only people with treatment-resistant schizophrenia.<sup>78-84</sup> In an international, randomized, single-blind study of people with schizophrenia considered at high risk for suicide, of whom only 27% were considered treatment resistant, participants randomized to clozapine showed significantly less suicidal behavior over 2 years than those randomized to olanzapine.<sup>85</sup> A more recent meta-analysis of 6 studies<sup>86</sup> confirmed these findings and reported that clozapine treatment was associated with a 3-fold overall reduction in the risk of suicidal behaviors compared with other antipsychotic medications.

## **Other Psychopharmacological Recommendations**

### *Prophylactic Antiparkinson Medications*

**Recommendation.** In people treated with FGA medications, 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 SGA medications is not warranted.

**Evidence Summary.** Since the last PORT review,<sup>2</sup> multiple studies have continued to document very low-to-low rates of extrapyramidal side effects with SGAs in multi-episode schizophrenia. In the CATIE study, among the participants treated with an SGA, the percentage of participants with Simpson-Angus Scale (SAS) total scores  $\geq 1$  ranged from 4% to 8%, with no significant group differences in treatment-emergent EPS among the various SGAs.<sup>6</sup>

Epidemiological studies have shown lower rates of anticholinergic prescriptions for people with schizophrenia taking SGAs compared with those taking FGAs,<sup>87,88</sup> though the use of anticholinergic agents may vary among the SGAs. People with schizophrenia receiving risperidone were 1.43 times more likely to receive anticholinergics compared with people on olanzapine.<sup>87</sup> In addition, Park and colleagues found a 20% decrease in the co-prescription of anticholinergics in people with schizophrenia switched from an FGA to olanzapine, whereas there was no change in anticholinergic prescriptions for those switched from an FGA to risperidone.<sup>88</sup> In the CATIE study, there was a statistically significant difference in the use of anticholinergics, with those randomized to risperidone most likely and those randomized to quetiapine least likely to receive them.<sup>89</sup>

The delineation of the relative risk of EPS among FGAs and between FGAs and SGAs is complicated by factors such as dosing. In a meta-analysis, Leucht and colleagues<sup>90</sup> found the relative risk of EPS of SGAs vs haloperidol differed depending on whether the haloperidol dose was greater or less than 12 mg. However, regardless of dose, haloperidol had a higher relative risk of EPS compared with SGAs than did low-potency FGAs.<sup>90</sup> In addition, the CATIE study found that the mid-potency agent perphenazine was no different from olanzapine, quetiapine, risperidone, or ziprasidone in treatment-emergent EPS.<sup>6,89</sup> Randomized, double-blind, head-to-head comparisons of EPS risk in FGAs are rare.

There is some evidence to suggest that people experiencing their first episode of schizophrenia may be more sensitive to EPS than people with multi-episode schizophrenia. Several studies have used low-dose haloperidol in first-episode populations (mean/mean modal dose range 2.9–4.4 mg/day) and found that antiparkinson medications were required in about 50% of participants.<sup>8,31,32</sup> People with first-episode schizophrenia

may also be more sensitive to risperidone. Schooler et al<sup>32</sup> found that 42% of participants randomized to risperidone required anticholinergics. However, the CAFÉ study reported that only 16% of participants had a rating  $> 1$  on one or more SAS items, and the percentage of participants requiring anticholinergics ranged from 4 to 11%.<sup>38</sup> There were no significant EPS differences among the olanzapine, quetiapine, and risperidone arms.<sup>38</sup> In the EUFEST study, rates of parkinsonism ranged from 6% to 16% in participants randomized to olanzapine, quetiapine, and ziprasidone.<sup>8</sup>

In summary, there is evidence for differences among antipsychotic agents in the risk for developing EPS. From greatest to least risk for EPS, a general ranking is high-potency FGAs  $>$  mid-potency FGAs = risperidone  $>$  low-potency FGAs  $>$  olanzapine, ziprasidone  $>$  quetiapine  $>$  clozapine. There is currently insufficient evidence to rank aripiprazole nor to further refine the ranking of FGAs.

#### *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.

**Evidence Summary.** Agitation is defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised*<sup>91</sup> as excessive motor activation with concurrent inner tension and is commonly observed in acutely psychotic people with schizophrenia.<sup>92</sup> If untreated, either behaviorally or with medications, agitation can escalate to behavioral dyscontrol and aggression toward others, self, or the environment.<sup>93</sup> Although positive symptoms can contribute to agitation, they are discrete dimensions of the illness and should not be confused with each other.

Several fundamental questions need to be addressed when developing a recommendation for the treatment of agitation: (1) does a specific medication (either antipsychotic or benzodiazepine) show superior efficacy in the treatment of agitation?; (2) does the combination of an antipsychotic medication and a benzodiazepine have increased efficacy over either agent alone?; and 3) are IM formulations more effective than oral formulations?

Benzodiazepines are commonly used to treat agitation,<sup>94–96</sup> with lorazepam being the most commonly used benzodiazepine due to its predictable and rapid absorption, no active metabolites, and no hepatic metabolism.<sup>97</sup> Salzman and colleagues<sup>98</sup> found that lorazepam was as effective as haloperidol in the treatment of

agitation but caused fewer EPS. Battaglia and colleagues<sup>99</sup> found that either lorazepam or haloperidol were beneficial in the treatment of agitation, although the combination was the most effective. However, in these studies of agitation, none of the study samples have included at least 50% participants with schizophrenia, which precludes a specific recommendation about the use of benzodiazepines for agitation in schizophrenia. More recent studies have specifically evaluated the treatment of agitation in people with schizophrenia, but the focus of these studies has been treatment with SGAs. In these studies, benzodiazepines were used frequently as a rescue or safety medication.<sup>100–106</sup> This use of benzodiazepines provides indirect support for their use in acute agitation, but until studies are conducted that directly compare IM or oral benzodiazepine therapy with SGA therapy for acute agitation in schizophrenia, there is not sufficient evidence to support a treatment recommendation for the use of benzodiazepines as the primary treatment of acute agitation, even though this may be a common clinical practice.

Aripiprazole, olanzapine, and ziprasidone have been evaluated for the treatment of acute agitation in schizophrenia. The IM formulations of these drugs have been consistently demonstrated to exhibit superior efficacy compared with placebo or the low-dose active comparator medication.<sup>100–106</sup> There are no studies that have compared 2 or more of these agents with each other. Therefore, we cannot recommend a specific IM SGA to be preferentially used for acute agitation. A comparison across 4 studies showed IM haloperidol to be equally effective as IM aripiprazole and olanzapine but with a higher incidence of EPS.<sup>105,107</sup> Ziprasidone has not been compared with an active comparator. Because EPS occurs at a greater rate with IM haloperidol, pre-treatment or concurrent treatment with an anticholinergic or benzodiazepine may be warranted, although this has not been systematically evaluated.

Superiority of a specific oral antipsychotic medication has also not been established for the treatment of acute agitation. Studies with oral aripiprazole<sup>108</sup> and oral olanzapine<sup>109</sup> found that both are equally effective as oral haloperidol for the acute treatment or prevention of agitation. Higher doses of olanzapine (40 mg/day) may be more effective than olanzapine 20 mg/day for the acute treatment of agitation.<sup>110</sup> Studies comparing the oral vs the IM formulation of an antipsychotic agent for the treatment of agitation have not been conducted. Either preparation may be beneficial for acute agitation and individual preference should be considered when possible.<sup>111</sup>

#### *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 (NRT), 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.

**Evidence Summary.** There have been 6 blinded RCTs of bupropion SR 150 mg twice daily to enhance smoking cessation in schizophrenia with one study reporting a 2-year follow-up in a separate publication. Three studies added bupropion SR or placebo to a 9- to 12-week cognitive-behavioral or supportive smoking cessation group.<sup>112–114</sup> Those randomized to bupropion SR had lower expired carbon monoxide (CO) and serum cotinine (when measured) as well as higher abstinence rates vs the placebo groups during and at the end of these studies (end of study abstinence rates of 11% vs 0%, 16% vs 0%, and 50% vs 12.5% for Evins and colleagues<sup>112,114</sup> and George and colleagues,<sup>113</sup> respectively). One study used a crossover design with 9 people on bupropion SR (dose not reported) or placebo for 3 weeks with a 1-week washout period.<sup>115</sup> While on bupropion SR, individuals exhibited a trend toward decreased expired CO and urine cotinine, which was reversed when on placebo. However, there were no significant group differences on these measures.

Two studies have examined the effect of adding bupropion vs placebo to NRT. In the first study, all participants received the nicotine patch with a standardized downward titration over the course of the study.<sup>116</sup> Nicotine gum was available, as needed, for cravings. Individuals who received bupropion SR + NRT had significantly lower expired CO levels compared with those receiving placebo + NRT. Of interest, abstinence rates significantly favored bupropion SR + NRT at week 8, but after the nicotine patch was titrated down, previously abstinent individuals restarted smoking and the abstinence rates between the arms were identical by the end of the study. In the second study, George and colleagues<sup>117</sup> found 28% of the participants who received bupropion SR + transdermal nicotine patch were continuously abstinent from the quit date to the end of the 10-week study compared with 3% of those receiving placebo + NRT. In the 6-month follow-up, 14% of the bupropion SR + NRT group was still abstinent compared with none of the placebo + NRT participants. The comparative efficacy of bupropion SR + NRT to bupropion SR has not been directly evaluated, so the extent to which the addition of NRT enhances treatment response is not known.

The long-term benefits of short-term treatment with bupropion SR have only been examined in 2 studies. At 6 months, George and colleagues<sup>113</sup> found only modest numerical differences in sustained abstinence between those randomized to bupropion SR vs placebo (ie 3/16 abstinent in the bupropion SR group vs 1/16 in the placebo group. In contrast, Evins and colleagues<sup>118</sup> followed participants for

2 years and observed that those receiving bupropion SR had maintained the decreased CO seen in the trial. However, participants randomized to placebo had lowered their expired CO to match the bupropion SR group.<sup>118</sup> Participants in both study groups had received other smoking cessation treatments in the intervening years.

All the long-term bupropion SR studies examined the comparative efficacy of bupropion SR in the context of a standard psychosocial intervention. Evins and colleagues<sup>112,114,116</sup> provided all participants with a cognitive-behavioral smoking cessation program that was adapted for people with schizophrenia from materials developed by the American Heart Association and the American Lung Association and included education, motivational enhancement, problem solving, relapse prevention, and behavioral goal setting. George and colleagues<sup>113,117</sup> provided all participants with 10 weekly psychosocial smoking cessation groups; these groups included motivational enhancement therapy, education, social skills training, and relapse prevention training. These studies suggest that a concurrent psychosocial intervention may be necessary to observe the clinical benefit of bupropion SR but were not designed to directly assess whether a psychosocial intervention is required nor do they provide information on the most effective psychosocial interventions to treat smoking cessation in schizophrenia. Unfortunately, there are no studies that have compared bupropion SR with and without a psychosocial intervention. However, 3 randomized trials have examined psychosocial interventions as the primary treatment modality for smoking cessation in schizophrenia. In light of the potentially critical role of psychosocial interventions for the efficacy of bupropion SR, we include a review of these studies.

George and colleagues<sup>119</sup> randomly assigned people with schizophrenia or schizoaffective disorder to 10 weekly sessions of either a specialized smoking cessation program developed for smokers with schizophrenia (motivational enhancement, relapse prevention, social skills training, and psychoeducation) or to a standard American Lung Association program. All participants also received NRT. The controlled phase of the study lasted 12 weeks, and participants were followed up for an additional 6 months. The groups did not differ in smoking abstinence at end point or expired CO levels. There was a trend for the experimental group to report a greater rate of continuous abstinence in the last 4 weeks of treatment (32.1%) relative to the comparison group (23.5%). There was a significant difference in smoking abstinence rates at 6 months favoring the comparison group (10.7% in experimental group vs 17.6% in comparison group).

Chen and colleagues<sup>120</sup> compared an experimental smoking cessation program (the American Lung Association 7-step Program) to a control group (assessment only). Participants were assessed at the end of 8 weeks of treatment and at an 8-week posttreatment assessment,

with “quit” defined as “no smoking in the last 7 days.” The experimental group showed an 8% quit rate in the week following the end of the program vs 0% in control group. Eight weeks later, 16% of experimental group had quit smoking vs 0% in control group.

Baker and colleagues<sup>121</sup> compared an 8-session behavioral/motivational enhancement intervention + NRT with routine care. Outcomes were assessed at 3-, 6-, and 12-months posttreatment. There were no differences between the conditions in continuous or point prevalence abstinence rates at all time points. There was a significant group difference in smoking reduction at 3 months, with 43.5% of the experimental group reduced their smoking by at least 50% relative to baseline as compared with 16.6% of the comparison group. This difference was maintained at the 12-month follow-up. In the completer analyses, participants randomized to the experimental group were significantly more likely to have improved on all outcome variables at 3 months, were more likely to be abstinent (point prevalence) at the 6- and 12-month assessments, and to have reduced their smoking by at least 50%. In addition, at 3 months, 84% of the treatment group (compared with 29.8% of the comparison group) reported use of NRT. Rates of use of NRT converged at the 12-month assessment.

In summary, the literature suggests that people with schizophrenia can benefit from both pharmacological and psychosocial interventions for smoking cessation. The data from several well-designed RCTs suggest that bupropion SR, with or without NRT, can be a helpful tool for establishing short-term abstinence within the context of a supportive environment. The long-term benefit of this intervention is unclear. The few studies that have examined the efficacy of psychosocial interventions support their benefit when combined with psychopharmacologic treatment but do not provide sufficient data to delineate the key components of the interventions.

#### *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.

**Evidence Summary.** Twelve sham-controlled studies have examined the efficacy of low-frequency (1 Hz) rTMS applied to the left temporoparietal cortex for the treatment of auditory hallucinations that have not responded to adequate antipsychotic treatment (ie, refractory auditory hallucinations). A meta-analysis of 10 of the 12 studies found a significant advantage of active rTMS treatment vs sham treatment for the acute treatment of refractory auditory hallucinations (Cohen  $d = 0.76$ ).<sup>122</sup> There was significant heterogeneity among the studies, which was primarily driven by a single study that had multiple pauses during the stimulation

session.<sup>123</sup> After exclusion of this study, the difference between active and sham rTMS increased (Cohen  $d = 0.88$ ). In the 2 studies not included in the meta-analysis, one had insufficient data to calculate an effect size<sup>124</sup> and the other had not yet been published.<sup>125</sup> Rosa and colleagues treated 11 people with schizophrenia on clozapine with refractory auditory hallucinations over 10 days with low frequency rTMS or sham treatment. No significant difference was seen between treatments. These latter 2 studies suggest that the effect size may be lower than suggested in the meta-analysis, but the small sample sizes would most likely not negate the conclusions of the meta-analysis. Moreover, a second meta-analysis reached the same conclusion that low-frequency rTMS is effective in the acute treatment of refractory auditory hallucinations.<sup>126</sup>

Four studies have examined the persistence of the rTMS effect on auditory hallucinations.<sup>125,127–129</sup> After 4 days of rTMS treatment, Chibbaro and colleagues<sup>127</sup> showed a significant change in positive symptoms that lasted 8 weeks. Poulet and colleagues<sup>129</sup> treated people for 5 days and found after 8 weeks half of the rTMS participants continued to have a >20% decrease in auditory hallucinations. None of those randomized to sham treatment responded to treatment. Rosa and colleagues did not find a significant group difference between active and sham rTMS treatment over time, but those receiving rTMS continued to show improvement in symptoms 4 weeks after treatment had stopped, whereas sham-treated participants did not continue to improve.<sup>129</sup> Hoffman and colleagues<sup>128</sup> reported that the mean survivorship interval for the 45 persons receiving either masked or unmasked active rTMS was 13 weeks post-trial. Non-survivorship was defined as a return of hallucination severity to 80% of pretrial levels, increase in antipsychotic drug dose, or change in antipsychotic drug. These studies suggest that the therapeutic effects of rTMS may persist for up to 8–12 weeks.

Several cases have been published examining the effect of rTMS maintenance treatment for refractory auditory hallucinations.<sup>130–134</sup> However, there are no long-term controlled studies of rTMS for refractory hallucinations.

In light of the current evidence for efficacy and the low risk of adverse effects, rTMS should be offered as an acute treatment option for auditory hallucinations that have not responded to an adequate trial of antipsychotic therapy. Future studies will need to be conducted to determine if maintenance rTMS treatment should be instituted for people who respond to initial treatment and the long-term efficacy of this intervention.

### Summary Statements

There were 13 interventions or outcomes for which there was insufficient evidence to warrant a treatment recommendation. A summary of the intervention or outcome,

the evidence to date and future areas of investigation are presented for each of these areas. The summaries are grouped either by intervention or outcome. A more detailed presentation of the available evidence for the intervention is presented in the online supplemental materials. The absence of a treatment recommendation should not be construed as a proscription against the particular practice. Rather, the interventions may be potentially beneficial, but at the time of the PORT review, the evidence did not reach the level to warrant the designation of an evidence-based practice.

### Adjunctive Treatment Strategies

#### *Antipsychotic Polypharmacy*

**Summary Statement.** Many individuals with schizophrenia have an incomplete symptom response to antipsychotic monotherapy. The use of combinations of antipsychotic medications (antipsychotic polypharmacy) has become an increasingly common treatment approach for people who have failed to adequately respond to previous antipsychotic treatment. The majority of studies of combinations of antipsychotic medications have examined the efficacy and safety of a single combination: clozapine and risperidone. These studies have failed to document sufficient efficacy and safety of this combination to support a recommendation in people with treatment-resistant schizophrenia.

#### *Anticonvulsants and Lithium for Treatment-Resistant Positive Symptoms*

**Summary Statement.** A substantial proportion of people with schizophrenia treated with antipsychotic medications continue to exhibit residual positive symptoms. Lithium and anticonvulsants are used extensively to augment antipsychotic treatment of these symptoms. However, few studies have been conducted to formally evaluate the efficacy of these approaches. Of the anticonvulsants, carbamazepine, valproate/valproic acid, lamotrigine, and topiramate have been the most extensively studied, but none of these agents have demonstrated sufficient efficacy to support a recommendation in people with residual positive symptoms. There is little evidence to support the efficacy of lithium for these symptoms.

#### *Benzodiazepines for Anxiety, Depression, or Hostility*

**Summary Statement.** Individuals with schizophrenia often experience symptoms of anxiety, depression, and hostility, which are not amenable to antipsychotic treatment. Adjunctive treatment with benzodiazepines is frequently used to treat these ancillary symptoms. However, there are almost no RCTs to formally examine the efficacy of these agents. In light of the lack of such studies, the current level of evidence is insufficient to support

a recommendation for the use of benzodiazepines for treating the symptoms of anxiety, depression, or hostility in people with schizophrenia.

#### *Antidepressant Treatment for Depression*

**Summary Statement.** Many people with schizophrenia experience symptoms of depression, which can interfere with role functioning and negatively impact quality of life. Although antidepressants are widely prescribed for people with schizophrenia, there are a number of important gaps in the empirical evaluation of the efficacy of adjunctive antidepressants for the treatment of co-occurring depression in this population, including the limited number of trials evaluating new generation antidepressants (eg, selective serotonin reuptake inhibitors) and the lack of any controlled trials of new generation antidepressants with SGA medications. In light of these gaps, the level of evidence is currently insufficient to support a recommendation for the use of adjunctive antidepressants for the treatment of co-occurring depression in people with schizophrenia.

#### **Pharmacological Treatment of Non-Positive Symptom Outcome Measures**

##### *Pharmacological Treatment of Negative Symptoms*

**Summary Statement.** A significant proportion of people with schizophrenia presents with primary or persistent negative symptoms. These symptoms are robustly associated with poor outcomes in schizophrenia and represent an important unmet treatment need. Antipsychotic medications have not been shown to be effective for treating primary or persistent negative symptoms. Trials of selective monoamine oxidase B inhibitors, mirtazapine, and selective serotonin reuptake inhibitors appear promising but require replication. In light of these limitations, the level of evidence is currently insufficient to support a treatment recommendation for any pharmacological treatment of negative symptoms in schizophrenia.

##### *Pharmacological Treatments to Improve Cognition*

**Summary Statement.** People with schizophrenia are characterized by a broad range of cognitive impairments. These impairments are a core component of the illness, are robustly associated with poor outcomes in schizophrenia, and represent a major unmet treatment need. A large number of studies have examined the efficacy of FGA and SGA medications for cognitive impairments, with little evidence that these agents have significant cognitive-enhancing effects. In addition, there is currently insufficient evidence to support the use of any adjunctive agent for the treatment of cognitive impairments in people with schizophrenia.

#### *Antipsychotics, Quality of Life, and Functional Outcomes*

**Summary Statement.** Achieving functional recovery and leading a satisfying life is important for individuals with schizophrenia. However, antipsychotic medication treatment is associated with only small to modest improvements in psychosocial functioning, vocational functioning, and quality of life. There is insufficient evidence to support a recommendation for the preferential use of SGAs over FGAs or the use of particular antipsychotic medications to achieve gains in these outcome domains in individuals with first-episode, multi-episode, or treatment-resistant schizophrenia.

#### **Treatment of Antipsychotic-Related Side Effects**

##### *Antipsychotic Choice and Treatments for TD*

**Summary Statement.** TD is an abnormal movement disorder, which is frequently caused by antipsychotic treatment and may be distressing or disabling to the person with such movements. SGA medications, including clozapine, and several adjunctive agents have been evaluated for the treatment of TD. However, there is insufficient evidence to support a recommendation for the use of any specific agent to treat TD.

##### *Antipsychotics and NMS*

**Summary Statement.** NMS occurs rarely but has been associated with treatment with both FGA and SGA medications. Since the last update, there is additional evidence available on the risk of NMS with antipsychotic medications, including clozapine, and therefore, the previous recommendation to select clozapine as the first-line treatment for individuals with previous NMS is no longer being included. There is insufficient evidence to recommend the use of a specific antipsychotic medication for people who have previously developed NMS.

##### *Pharmacological Prevention and Treatment of Antipsychotic-Associated Weight Gain in Schizophrenia*

**Summary Statement.** In comparison to the general population, people with schizophrenia have higher rates of morbidity and mortality, which are thought to be due, in part, to increased rates of obesity. Antipsychotic-induced weight gain is thought to be an important modifiable contributor to the high rates of obesity in this population. Treatment approaches for excess weight gain associated with antipsychotic medications are important to help improve the physical health and quality of life of people with schizophrenia. Three possible pharmacological interventions have been evaluated for antipsychotic-associated weight gain: (1) switching the current antipsychotic medication to an antipsychotic medication with a lower weight gain liability, (2) addition of a medication when an antipsychotic agent is initiated to prevent weight

gain, and (3) addition of a medication during current antipsychotic therapy to promote weight loss. There is currently insufficient evidence to recommend a specific pharmacological intervention for the prevention or treatment of antipsychotic-induced weight gain. However, clinicians should monitor weight gain due to antipsychotic medications and consider the use of an evidence-based psychosocial weight loss intervention, which is recommended for this indication (see Dixon *et al.*,<sup>135</sup> this issue).

#### *Antipsychotic-Induced Prolactin Elevations, Hormonal Side Effects, and Sexual Dysfunction*

**Summary Statement.** Antipsychotic medications may elevate prolactin levels, which can cause secondary side effects. While side effects related to prolactin elevation and sexual dysfunction warrant attention and treatment, there is currently insufficient evidence to support a recommendation for either switching from a prolactin-raising antipsychotic to a prolactin-sparing antipsychotic or using an adjunctive pharmacological treatment to mitigate these side effects.

#### **Treatment of Co-occurring Substance Misuse Disorders**

##### *Pharmacological Interventions for Alcohol and Substance Abuse/Dependence in Schizophrenia*

**Summary Statement.** Co-occurring alcohol and illegal substance misuse is a serious problem in people with schizophrenia. However, few studies have evaluated the pharmacological treatment of alcohol or illegal substance abuse or dependence for people with co-occurring schizophrenia and substance misuse disorders. In general, the studies that have examined this issue have had small samples sizes and are significantly underpowered. At this time, there is insufficient evidence to support a recommendation for a pharmacological intervention to treat alcohol or illegal substance misuse disorders in schizophrenia over and above what is known about the pharmacological agents developed to treat substance abuse/dependence in the general population. Clinicians should evaluate their patients for co-occurring substance use disorders and consider using an evidence-based psychosocial intervention for this indication (see Dixon *et al.*,<sup>135</sup> this issue).

#### **Other Summary Statements**

##### *ECT for the Treatment of Schizophrenia*

**Summary Statement.** ECT has a long history of use in people with schizophrenia. ECT has been shown to be effective for acute positive psychotic symptoms but shows no efficacy advantage compared with antipsychotic medications and is not as easy to use as antipsychotic medications for the ongoing treatment of these

symptoms. There is currently insufficient evidence to support a recommendation for the use of ECT for the core symptoms of schizophrenia for treatment-resistant individuals.

#### **Discussion**

The Schizophrenia PORT Psychopharmacology ERG reviewed over 400 studies on pharmacological and other somatic treatments of schizophrenia, which resulted in 16 treatment recommendations: we updated 11 previous treatment recommendations; we identified 5 additional treatment areas for which the evidence was sufficiently strong to support a treatment recommendation; and we eliminated 3 previous recommendations. We reviewed for the first time pharmacological treatments for a number of health conditions that disproportionately affect individuals with schizophrenia, including cigarette smoking, drug addiction, and weight gain resulting from antipsychotic treatment. These reviews led to a new PORT recommendation for a combined psychopharmacological and psychosocial approach to smoking cessation, a significant unmet treatment need and major public health concern in this population. The other new recommendations include the choice of antipsychotic agent for the treatment of people with first-episode schizophrenia, monitoring clozapine levels, antipsychotic treatment of acute agitation, and rTMS for the short-term treatment of refractory auditory hallucinations. There were 13 reviewed areas for which the scientific evidence was currently insufficient to support a treatment recommendation.

Three previous 2004 Schizophrenia PORT treatment recommendations were dropped: (1) clozapine for NMS, tardive dystonia, and TD; (2) monitoring antipsychotic blood levels; and (3) the use of antidepressants to treat depression in people with schizophrenia. In the place of the treatment recommendation for clozapine and NMS, tardive dystonia, and TD, 2 summary statements have been written, which review the epidemiology of TD and NMS and the current status of the treatment or management of these antipsychotic side effects. The decision to drop the antidepressant treatment recommendation reflected the surprising lack of evidence for this practice. Since the last PORT update, few rigorous studies on the effectiveness of newer antidepressants (eg, selective serotonin reuptake inhibitors [SSRIs]) for depressive symptoms in schizophrenia, particularly among people treated with SGAs, have been published. The previous PORT recommendation for antidepressant treatment was largely based on studies of older tricyclic antidepressants in people treated with FGAs, both medication classes that have fallen out of widespread use in clinical practice. Moreover, on reevaluation, these previous studies were judged to provide less compelling



evidence for this practice than originally thought.<sup>1,2</sup> Therefore, in light of the lack of new evidence with SGAs and selective serotonin reuptake inhibitors (SSRIs) and the lack of compelling evidence for tricyclic antidepressants, the current level of evidence for antidepressant treatment in schizophrenia was determined to be insufficient to support a treatment recommendation, and the previous recommendation was rescinded.

There are a number of review outcomes that are worthy of specific mention. First, since its inception almost 15 years ago, the Schizophrenia PORT has been consistent in not recommending the preferential use of SGAs vs FGAs in the acute or maintenance treatment of people with treatment-responsive, multi-episode schizophrenia. Although initially an unpopular stance that was inconsistent with prevailing prescribing patterns and public opinion, the relative efficacy/effectiveness of FGAs and SGAs was not a controversial issue in the current Schizophrenia PORT update. In large part, this was due to the recent completion of 2 large pragmatic clinical trials: the CATIE and CUtLASS studies.<sup>6,7,48</sup> These publicly funded investigations, which featured head-to-head comparisons of the relative effectiveness of multiple SGAs and representative FGAs, found very few effectiveness differences across these agents. The results of CATIE and CUtLASS, thus, provided strong support for the long-standing Schizophrenia PORT position that antipsychotic medication selection should not be limited to a particular agent or class of drug but rather tailored to the individual characteristics and preferences of each person with schizophrenia.

Second, the CATIE and CUtLASS studies, along with recent investigations in individuals experiencing their first episode of schizophrenia, have added to the growing evidence base regarding the differential side effect profiles across antipsychotic agents. Of particular concern has been the mounting evidence that certain SGAs are associated with significant weight gain and metabolic abnormalities that may lead to long-term adverse health consequences in an already at-risk population. The relative clinical equivalence of FGAs and SGAs has, thus, shifted the focus of antipsychotic selection to the side effects of these agents, and because of the propensity of olanzapine, in particular, to induce metabolic side effects, this PORT update includes a new recommendation for withholding the use of olanzapine as a first-line choice for antipsychotic treatment in first-episode schizophrenia. This new recommendation, however, should not be construed as an absolute proscription against the use of olanzapine in the treatment of schizophrenia. Rather, the PORT recommends that other antipsychotic medications be considered before a trial of olanzapine in newly diagnosed individuals for whom maximizing the acceptability of the initial treatment experience and minimizing both short- and long-term treatment risks is especially crucial.

Third, the CATIE and CUtLASS studies also made major contributions to the already strong body of research, demonstrating that clozapine is the most effective antipsychotic medication available for individuals who continue to experience persistent and clinically significant positive symptoms after adequate trials of other antipsychotic agents. The PORT continues its strong endorsement of the use of clozapine for this indication as well as for the treatment of hostility and violence and suicidal behaviors, domains for which effective treatments are not otherwise available. Although the gap between science and service has been typically more evident for psychosocial treatments than for psychopharmacological treatments,<sup>136</sup> clozapine represents an important exception. Although the precise reasons for the persistent underutilization of clozapine in clinical practice are not entirely understood, concerns about required monitoring for agranulocytosis and the development of other troublesome adverse effects are likely contributory.<sup>137</sup> Efforts to more fully understand the reluctance on the part of both prescribers and eligible patients to consider a trial of this widely available, evidence-based treatment are clearly needed.

Fourth, in marked contrast to the strong evidence supporting the effectiveness of clozapine and other antipsychotic medications for the core symptoms of schizophrenia, there is a relative paucity of information on the effectiveness of adjunctive pharmacological agents for the treatment of persistent positive symptoms or other symptom domains, including depressive symptoms, anxiety, cognitive impairments, and persistent negative symptoms. The lack of evidence-based treatments for these indications is notable given the extent to which adjunctive antidepressants, mood stabilizers, anti-anxiety agents, antipsychotics, and other medications are used in typical clinical practice.<sup>138</sup> The discrepancy between the relatively widespread use of adjunctive psychotropic medications and the lack of evidence to support these practices reflects, in part, the quandary that clinicians face when confronted with the person who has failed to adequately respond to antipsychotic monotherapy or has additional symptoms for which antipsychotic agents are known to be ineffective. Under these circumstances, the use of non-evidence-based practices requires that the clinician be especially conscientious in documenting whether the patient is responding to the intervention and be prepared to discontinue the treatment if a desired response is not achieved.<sup>2</sup> The development of effective treatments for the ancillary symptoms of schizophrenia is of critical importance because these domains are often major barriers to recovery.

Finally, our most recent review of the literature revealed a number of areas of psychopharmacological treatment for schizophrenia for which the determination of whether the scientific evidence was sufficiently strong to support a recommendation was not straightforward. A

major area of discussion among the PORT Expert Panel involved the nature of the evidence for the effectiveness of switching antipsychotic medications for the treatment of antipsychotic-related weight gain. The process of switching antipsychotic agents due to side effects, especially in individuals who are experiencing a significant reduction in symptoms or improvement in functional outcomes, should consider the potential benefits from side effect reduction vs the risks of symptom exacerbation. In clinical practice, if the risk/benefit ratio is appropriate, physicians in consultation with their patients should allow for trials of antipsychotic switching with the goal of the treatment of weight loss or any other medication side effect. The practice of switching an antipsychotic medication has been a very effective strategy for the treatment of a number of medication side effects including EPS, prolactin elevation, and sedation. However, to develop a PORT treatment recommendation in this area, we required a minimal level of evidence that the majority of individuals would experience significant weight loss without clinical deterioration. While the studies we reviewed suggest that switching antipsychotic medications does lead to weight loss, especially among individuals treated with olanzapine, there is only one un-replicated RCT that has directly examined this issue, and some participants in that study who switched from olanzapine to aripiprazole experienced worsening of their clinical status. The ongoing Comparison of Antipsychotics for Metabolic Problems) study<sup>49</sup> should help clarify the usefulness of switching antipsychotic medications for the treatment of weight gain in schizophrenia and may lead to a future treatment recommendation in this important area. Other evidence-based approaches to weight loss for people with schizophrenia are available because the evidence supporting psychosocial interventions is currently sufficient to support a PORT treatment recommendation (see Dixon *et al.*,<sup>135</sup> this issue).

The other area for which there was notable discussion among the Expert Panel concerned the decision to recommend specific dosage ranges for the acute and maintenance treatment of schizophrenia and the treatment of first-episode schizophrenia. In particular, there was concern over the quality of the data used to select the lower and upper dose ranges and the potential adverse policy impact that might result from the stipulation of a dose range. The recommended dose ranges represent those doses for which there is documented efficacy from RCTs and for which the observed side effects do not compromise the beneficial effects of the particular agent. The lower end of the dose range has been fairly well established for most drugs through industry-sponsored, double-blind, fixed-dose studies. The problem lies with the upper range for a number of the SGAs, for which adequate upper dose range data are not available for aripiprazole, olanzapine, quetiapine, and ziprasidone. In addition, as discussed in the previous Schizophrenia

PORT update,<sup>2</sup> there is the problem of central tendency, in which the results of clinical trials provide information on the mean effect in the population studied. There are multiple reasons why an individual may not respond to a drug prescribed within the recommended dose range, including increased sensitivity to side effects or rapid metabolism of the drug. Therefore, the PORT recommended dose ranges should serve only as guidelines for the clinician. They are not proscriptions against the use of doses outside the recommended range but a reminder that there should be some rationale provided for the use of a non-recommended dosage.

In summary, over the past 5 years, there have been marked gains in our knowledge of evidence-based pharmacological treatments for schizophrenia. In order to ensure that all people with schizophrenia receive the highest quality pharmacological treatment, providers of mental health services should strive to ensure that each of these evidence-based practices is readily available for those patients for whom the treatments are indicated. However, despite these recent advances, there remain a number of important gaps in our knowledge of how to address treatment needs that lie outside the core symptom domains of schizophrenia. These gaps are important barriers to the ultimate goal of improving the individualized treatment of the person with schizophrenia and optimizing their opportunity for recovery from the illness.

### Supplementary Material

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

### Funding

National Institute of Mental Health (R13 MH080593 to J.K.); the Department of Veterans Affairs (Mental Health Enhancement Grant to J.K.).

### Acknowledgments

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health, the National Institutes of Health, or the Department of Veterans Affairs. The authors would like to acknowledge the following members of the Schizophrenia PORT Psychopharmacology Advisory Board: Susan M. Essock, PhD; Donald C. Goff, MD; Richard S. E. Keefe, PhD; Stephen R. Marder, MD; John W. Newcomer, MD; Diana O. Perkins, MD, MPH; T. Scott Stroup, MD, MPH. The authors would also like to acknowledge Jeanette Robinson for retrieving copies of articles and organizing and managing the database of studies reviewed for this update of the

Schizophrenia PORT Psychopharmacological Treatment Recommendations. R.W.B.: Data and Safety Monitoring Board member: Cephalon and Pfizer; Consultant: Abbott, Glaxo-Smith-Kline, Natixis Bleichroeder, Sanofi-Aventis, Schering-Plough; Advisory Board: Astra-Zeneca, Merck, Pfizer, Roche, Solvay Pharmaceuticals, Inc., Wyeth, Grant Support: Janssen Pharmaceutica; D.L.K.: Advisory Board: Bristol Myers Squibb, Janssen Pharmaceutica, and Solvay. Julie Kreyenbuhl, Jason M. Noel, Douglas L. Boggs, Bernard A. Fischer, Seth Himelhoch, Beverly Fang, Eunice Peterson, Patrick R. Aquino, and William Keller have no competing interests or financial support to disclose.

## References

- Lehman AF, Steinwachs DM. Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. *Schizophr Bull.* 1998;24:1–10.
- Lehman A, Kreyenbuhl J, Buchanan R, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. *Schizophr Bull.* 2004;30:193–217.
- Miller AL, Hall CS, Buchanan RW, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2003 update. *J Clin Psychiatry.* 2004;65:500–508.
- Moore TA, Buchanan RW, Buckley PF, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry.* 2007;68:1751–1762.
- Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry.* 2004;161(2 Suppl):1–56.
- Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353:1209–1223.
- Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry.* 2006;63:1079–1087.
- Kahn RS, Fleischhacker WW, Boter H, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet.* 2008;371:1085–1097.
- McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry.* 2006;163:600–610.
- Kreyenbuhl J, Buchanan RW, Dickerson F, Dixon L. The Schizophrenia Patient Outcomes Research Team (PORT): Updated Treatment Recommendations. *Schizophr Bull.* In press; doi:10.1093/schbul/sbp130.
- Cutler AJ, Marcus RN, Hardy SA, O'Donnell A, Carson WH, McQuade RD. The efficacy and safety of lower doses of aripiprazole for the treatment of patients with acute exacerbation of schizophrenia. *CNS Spectr.* 2006;11:691–702.
- Davidson M, Emsley R, Kramer M, et al. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebo-controlled study. *Schizophr Res.* 2007;93:117–130.
- Kane J, Canas F, Kramer M, et al. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res.* 2007;90:147–161.
- Marder SR, Kramer M, Ford L, et al. Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. *Biol Psychiatry.* 2007;62:1363–1370.
- McEvoy JP, Daniel DG, Carson WH, Jr, McQuade RD, Marcus RN. A randomized, double-blind, placebo-controlled, study of the efficacy and safety of aripiprazole 10, 15 or 20 mg/day for the treatment of patients with acute exacerbations of schizophrenia. *J Psychiatr Res.* 2007;41:895–905.
- Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs.* 2005;19:1–93.
- Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. *Can J Psychiatry.* 2006;51:480–491.
- Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTx in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol.* 2004;24:62–69.
- Kelly DL, Conley RR, Carpenter WT. First-episode schizophrenia: a focus on pharmacological treatment and safety considerations. *Drugs.* 2005;65:1113–1138.
- Stolberger C, Huber JO, Finsterer J. Antipsychotic drugs and QT prolongation. *Int J Clin Psychopharmacol.* 2005;20:243–251.
- Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs.* 2007;21:911–936.
- Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry.* 2002;63:763–771.
- Potkin SG, Saha AR, Kujawa MH, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry.* 2003;60:681–690.
- El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. *Cochrane Database Syst Rev.* 2006;2:CD004578.
- Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL. QTc-Interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet.* 2000;355:1048–1052.
- Strachan EM, Kelly CA, Bateman DN. Electrocardiogram and cardiovascular changes in thioridazine and chlorpromazine poisoning. *Eur J Clin Pharmacol.* 2004;60:541–545.
- Kang UG, Kwon JS, Ahn YM, et al. Electrocardiographic abnormalities in patients treated with clozapine. *J Clin Psychiatry.* 2000;61:441–446.
- Cohen H, Loewenthal U, Matar M, Kotler M. Association of autonomic dysfunction and clozapine heart rate variability and risk for sudden death in patients with schizophrenia on long-term psychotropic medication. *Br J Psychiatry.* 2001;179:167–171.
- Warner B, Hoffman P. Investigation of the potential of clozapine to cause torsades de pointes. *Adverse Drug React Toxicol Rev.* 2002;21:189–203.

30. Emsley RA. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. risperidone working group. *Schizophr Bull.* 1999;25:721–729.
31. Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *Am J Psychiatry.* 2003;160:1396–1404.
32. Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry.* 2005;162:947–953.
33. Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. *Am J Psychiatry.* 2008;165:1420–1431.
34. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naïve first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology.* 2003;28:995–1003.
35. Green AI, Lieberman JA, Hamer RM, et al. Olanzapine and haloperidol in first episode psychosis: two-year data. *Schizophr Res.* 2006;86:234–243.
36. Gaebel W, Riesbeck M, Wölwer W, et al. Maintenance treatment with risperidone or low-dose haloperidol in first-episode schizophrenia: 1-year results of a randomized controlled trial within the German research network on schizophrenia. *J Clin Psychiatry.* 2007;68:1763–1774.
37. Robinson DG, Woerner MG, Napolitano B, et al. Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. *Am J Psychiatry.* 2006;163:2096–2102.
38. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry.* 2007;164:1050–1060.
39. Oosthuizen PP, Emsley RA, Turner J, Keyter N. Determining the optimal dose of haloperidol in first-episode psychosis. *J Psychopharmacol.* 2001;15:251–255.
40. Arato M, O'Connor R, Meltzer HY. ZEUS Study Group. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol.* 2002;17:207–215.
41. Beasley CM, Jr, Sutton VK, Hamilton SH, et al. A double-blind, randomized, placebo-controlled trial of olanzapine in the prevention of psychotic relapse. *J Clin Psychopharmacol.* 2003;23:582–594.
42. Pigott TA, Carson WH, Saha AR, et al. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. *J Clin Psychiatry.* 2003;64:1048–1056.
43. Buckley PF. Efficacy of quetiapine for the treatment of schizophrenia: a combined analysis of three placebo-controlled trials. *Curr Med Res Opin.* 2004;20:1357–1363.
44. Kramer M, Simpson G, Maciulis V, et al. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol.* 2007;27:6–14.
45. Marder SR, Glynn SM, Wirshing WC, et al. Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. *Am J Psychiatry.* 2003;160:1405–1412.
46. Rosenheck R, Perlick D, Bingham S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. *JAMA.* 2003;290:2693–2702.
47. Kongsakon R, Trinidad-Oñate P, Chaudhry HR, et al. Asian outpatients with schizophrenia: a double-blind randomized comparison of quality of life and clinical outcomes for patients treated with olanzapine or haloperidol. *J Med Assoc Thai.* 2006;89:1157–1170.
48. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry.* 2006;163:611–622.
49. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. *Am J Psychiatry.* 2007;164:415–427.
50. Csernansky JG, Mahmoud R, Brenner R. Risperidone-USA-79 Study Group. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med.* 2002;346:16–22.
51. Dixon LB, Lehman AF, Levine J. Conventional antipsychotic medications for schizophrenia. *Schizophr Bull.* 1995;21:567–577.
52. Kane JM, Davis JM, Schooler N, et al. A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. *Am J Psychiatry.* 2002;159:554–560.
53. Kane JM, Eerdekens M, Lindenmayer JP, Keith SJ, Lesem M, Karcher K. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry.* 2003;160:1125–1132.
54. Chue P, Eerdekens M, Augustyns I, et al. Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. *Eur Neuropsychopharmacol.* 2005;15:111–117.
55. Simpson GM, Mahmoud R, Lasser RA, et al. A 1-year double-blind study of 2 doses of long-acting risperidone in stable patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry.* 2006;67:1194–1203.
56. Gaebel W, Jänner M, Frommann N, et al. First vs multiple episode schizophrenia: two-year outcome of intermittent and maintenance medication strategies. *Schizophr Res.* 2002;53:145–159.
57. Gitlin M, Nuechterlein K, Subotnik KL, et al. Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. *Am J Psychiatry.* 2001;158:1835–1842.
58. Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry.* 2007;68:654–661.
59. Lewis SW, Barnes TR, Davies L, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull.* 2006;32:715–723.
60. Conley RR, Kelly DL, Richardson CM, Tamminga CA, Carpenter WT, Jr. The efficacy of high-dose olanzapine versus clozapine in treatment-resistant schizophrenia: a double-blind crossover study. *J Clin Psychopharmacol.* 2003;23:668–671.

61. Bitter I, Dossenbach MR, Brook S, et al. Olanzapine versus clozapine in treatment-resistant or treatment intolerant schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;28:173–180.
62. Bender S, Dittmann-Balcar A, Schall U, et al. Influence of atypical neuroleptics on executive functioning in patients with schizophrenia; a randomized, double-blind comparison of olanzapine versus clozapine. *Int J Neuropsychopharmacol*. 2006;9:135–145.
63. Shaw P, Sporn A, Gogtay N, et al. Childhood onset schizophrenia: a double-blind, randomized clozapine olanzapine comparison. *Arch Gen Psychiatry*. 2006;63:721–730.
64. Kumra S, Kranzler H, Gerbino-Rosen G, et al. Clozapine and “high-dose” olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. *Biol Psychiatry*. 2008;63:524–529.
65. Meltzer HY, Bobo W, Roy A, et al. A randomized double blind comparison of clozapine and high dose olanzapine in treatment resistant patients with schizophrenia. *J Clin Psychiatry*. 2008;69:274–285.
66. Buchanan RW, Ball MP, Weiner E, et al. Olanzapine treatment of residual positive and negative symptoms. *Am J Psychiatry*. 2005;162:124–129.
67. Perry PJ, Miller DD, Arndt SV, Cadoret RJ. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients. *Am J Psychiatry*. 1991;148:231–235.
68. Kronig MH, Munne RH, Szymanski S, et al. Plasma clozapine levels and clinical response for treatment-refractory schizophrenic patients. *Am J Psychiatry*. 1995;152:179–182.
69. Hasegawa M, Gutierrez-Esteinou R, Way L, Meltzer HY. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. *J Clin Psychopharmacol*. 1993;13:383–390.
70. Potkin SG, Bera R, Gulaskaram B, et al. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. *J Clin Psychiatry*. 1994;55(Suppl B):133–136.
71. Vanderzwaag C, McGee M, McEvoy JP, Freudenreich O, Wilson WH, Cooper TB. Response of patients with treatment-refractory schizophrenia to clozapine within three serum level ranges. *Am J Psychiatry*. 1996;153:1579–1584.
72. Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 2006;63:622.
73. Volavka J, Czobor P, Nolan K, et al. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychopharmacol*. 2004;24:225–228.
74. Citrome L, Volavka J, Czobor P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. *Psychiatr Serv*. 2001;52:1510–1514.
75. Swanson J, Swartz M, Van Dom R, et al. Comparison of antipsychotic medication effects on reducing violence in people with schizophrenia. *Br J Psychiatry*. 2008;193:37–43.
76. Kahn R, Schulz S, Palazov V, et al. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68:832–842.
77. Volavka J, Czobor P, Citrome L, et al. Efficacy of aripiprazole against hostility in schizophrenia and schizoaffective disorder: data from 5 double-blind studies. *J Clin Psychiatry*. 2005;66:1362–1366.
78. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry*. 1995;152:183–190.
79. Walker AM, Lanza LL, Arellano F, Rothman KJ. Mortality in current and former users of clozapine. *Epidemiology*. 1997;8:671–677.
80. Reid WH, Mason M, Hogan T. Suicide prevention effects associated with clozapine therapy in schizophrenia and schizoaffective disorder. *Psychiatr Serv*. 1998;49:1029–1033.
81. Spivak B, Roitman S, Vered Y, et al. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenia patients maintained on clozapine. *Clin Neuropharmacol*. 1998;21:245–250.
82. Ciapparelli A, Dell’Osso L, Pini S, et al. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: a 24-month naturalistic study. *J Clin Psychiatry*. 2000;61:329–334.
83. Sernyak MJ, Desai R, Stolar M, Rosenheck R. Impact of clozapine on completed suicide. *Am J Psychiatry*. 2001;158:931–937.
84. Modestin J, Dal Pian D, Agarwalla P. Clozapine diminishes suicidal behavior: a retrospective evaluation of clinical records. *J Clin Psychiatry*. 2005;66:534–538.
85. Meltzer HY, Alphas L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: international Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*. 2003;60:82–91.
86. Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. *Schizophr Res*. 2005;73:139–145.
87. Ascher-Svanum H, Kennedy JS, Lee D, Haberman M. The rate, pattern, and cost of use of antiparkinsonian agents among patients treated for schizophrenia in a managed care setting. *Am J Manag Care*. 2003;9:20–24.
88. Park S, Ross-Degnan D, Adams AS, Sabin J, Kanavos P, Soumerai SB. Effect of switching antipsychotics on antiparkinsonian medication use in schizophrenia. *Br J Psychiatry*. 2005;187:137–142.
89. Miller DD, Caroff SN, Davis SM, et al. Extrapyramidal side-effects of antipsychotics in a randomised trial. *Br J Psychiatry*. 2008;193:279–288.
90. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373:31–41.
91. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Health-IV-TR* Washington, DC American Psychiatric Association. 2000.
92. Pilowsky LS, Ring H, Shine PJ, Battersby M, Lader M. Rapid tranquillisation. A survey of emergency prescribing in a general psychiatric hospital. *Br J Psychiatry*. 1992;160:831–835.
93. Battaglia J. Pharmacological management of acute agitation. *Drugs*. 2005;65:1207–1222.
94. Salzman C, Green AI, Rodriguez-Villa F, Jaskiw GI. Benzodiazepines combined with neuroleptics for management of severe disruptive behavior. *Psychosomatics*. 1986;27(1 Suppl):17–22.

95. Foster S, Kessel J, Berman ME, Simpson GM. Efficacy of lorazepam and haloperidol for rapid tranquilization in a psychiatric emergency room setting. *Int Clin Psychopharmacol.* 1997;12:175–179.
96. Dorevitch A, Katz N, Zemishlany Z, Aizenberg D, Weizman A. Intramuscular flunitrazepam versus intramuscular haloperidol in the emergency treatment of aggressive psychotic behavior. *Am J Psychiatry.* 1999; 156:142–144.
97. Bodkin JA. Emerging uses for high-potency benzodiazepines in psychotic disorders. *J Clin Psychiatry.* 1990;(51 Suppl): 41–46 ; discussion. 50–53.
98. Salzman C, Solomon D, Miyawaki E, et al. Parenteral lorazepam versus parenteral haloperidol for the control of psychotic disruptive behavior. *J Clin Psychiatry.* 1991;52: 177–180.
99. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med.* 1997;15:335–340.
100. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology.* 2001; 155:128–134.
101. Lessem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP. Intramuscular ziprasidone. 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry.* 2001;62:12–18.
102. Wright P, Birkett M, David SR, et al. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am J Psychiatry.* 2001;158:1149–1151.
103. Breier A, Meehan K, Birkett M, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatry.* 2002;59: 441–448.
104. Andrezina R, Josiassen RC, Marcus RN, et al. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology.* 2006;188:281–292.
105. Citrome L. Comparison of intramuscular ziprasidone, olanzapine, or aripiprazole for agitation: a quantitative review of efficacy and safety. *J Clin Psychiatry.* 2007;68: 1876–1885.
106. Tran-Johnson TK, Sack DA, Marcus RN, Auby P, McQuade RD, Oren DA. Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry.* 2007;68:111–119.
107. Satterthwaite TD, Wolf DH, Rosenheck RA, Gur RE, Caroff SN. A meta-analysis of the risk of acute extrapyramidal symptoms with intramuscular antipsychotics for the treatment of agitation. *J Clin Psychiatry.* 2008;69:1869–1879.
108. Daniel DG, Currier GW, Zimbardo DL, et al. Efficacy and safety of oral aripiprazole compared with haloperidol in patients transitioning from acute treatment with intramuscular formulations. *J Psychiatr Pract.* 2007;13:170–177.
109. Kinon BJ, Ahl J, Rotelli MD, McMullen E. Efficacy of accelerated dose titration of olanzapine with adjunctive lorazepam to treat acute agitation in schizophrenia. *Am J Emerg Med.* 2004;22:181–186.
110. Baker RW, Kinon BJ, Maguire GA, Liu H, Hill AL. Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. *J Clin Psychopharmacol.* 2003;23:342–348.
111. Lejeune J, Larmo I, Chrzanowski W, et al. Oral risperidone plus oral lorazepam versus standard care with intramuscular conventional neuroleptics in the initial phase of treating individuals with acute psychosis. *Int Clin Psychopharmacol.* 2004;19:259–269.
112. Evins AE, Mays VK, Rigotti NA, Tisdale T, Cather C, Goff DC. A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. *Nicotine Tob Res.* 2001;3:397–403.
113. George TP, Vessicchio JC, Termine A, et al. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biol Psychiatry.* 2002;52:53–61.
114. Evins AE, Cather C, Deckersbach T, et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *J Clin Psychopharmacol.* 2005;25:218–225.
115. Fatemi SH, Stary JM, Hatsukami DK, Murphy SE. A double-blind placebo-controlled cross over trial of bupropion in smoking reduction in schizophrenia. *Schizophr Res.* 2005;76:353–356.
116. Evins AE, Cather C, Culhane MA, et al. A 12-week double-blind, placebo-controlled study of bupropion sr added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. *J Clin Psychopharmacol.* 2007;27:380–386.
117. George TP, Vessicchio JC, Sacco KA, et al. A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia. *Biol Psychiatry.* 2008;63:1092–1096.
118. Evins AE, Cather C, Rigotti NA, et al. Two-year follow-up of a smoking cessation trial in patients with schizophrenia: increased rates of smoking cessation and reduction. *J Clin Psychiatry.* 2004;65:307–311.
119. George TP, Ziedonis DM, Feingold A, et al. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry.* 2000;157:1835–1842.
120. Chen R, Ku CH, Lu RB, Chou KR. The impact of smoking cessation programs on smoking-related health beliefs and rate of quit-smoking among schizophrenic patients. *J Med Sci.* 2002;22:215–220.
121. Baker A, Richmond R, Haile M, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *Am J Psychiatry.* 2006; 163:1934–1942.
122. Aleman A, Sommer IE, Kahn RS. Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. *J Clin Psychiatry.* 2007;68:416–421.
123. McIntosh AM, Semple D, Tasker K, et al. Transcranial magnetic stimulation for auditory hallucinations in schizophrenia. *Psychiatry Res.* 2004;127:9–17.
124. Saba G, Verdon CM, Kalalou K, et al. Transcranial magnetic stimulation in the treatment of schizophrenic symptoms: a double blind sham controlled study. *J Psychiatr Res.* 2006;40:147–152.
125. Rosa MO, Gattaz WF, Rosa MA, et al. Effects of repetitive transcranial magnetic stimulation on auditory hallucinations refractory to clozapine. *J Clin Psychiatry.* 2007;68:1528–1532.

126. Tranulis C, Sepehry AA, Galinowski A, Stip E. Should we treat auditory hallucinations with repetitive transcranial magnetic stimulation? A metaanalysis. *Can J Psychiatry*. 2008;53:577–586.
127. Chibbaro G, Daniele M, Alagona G, et al. Repetitive transcranial magnetic stimulation in schizophrenic patients reporting auditory hallucinations. *Neurosci Lett*. 2005;383:54–57.
128. Hoffman RE, Gueorguieva R, Hawkins KA, et al. Temporoparietal transcranial magnetic stimulation for auditory hallucinations: safety, efficacy and moderators in a fifty patient sample. *Biol Psychiatry*. 2005;58:97–104.
129. Poulet E, Brunelin J, Bediou B, et al. Slow transcranial magnetic stimulation can rapidly reduce resistant auditory hallucinations in schizophrenia. *Biol Psychiatry*. 2005;57:188–191.
130. Fitzgerald PB, Benitez J, Daskalakis JZ, DeCastella A, Kulkarni J. The treatment of recurring auditory hallucinations in schizophrenia with rTMS. *World J Biol Psychiatry*. 2006;7:119–122.
131. Poulet E, Brunelin J, Kallel L, et al. Is rTMS efficient as a maintenance treatment for auditory verbal hallucinations? A case report. *Schizophr Res*. 2006;84:183–184.
132. Chung YC, Im ES, Cho GH, Ko MH. Second run of transcranial magnetic stimulation has no effects on persistent auditory hallucinations. *World J Biol Psychiatry*. 2007;8:48–50.
133. Poulet E, Brunelin J, Kallel L, D'Amato T, Saoud M. Maintenance treatment with transcranial magnetic stimulation in a patient with late-onset schizophrenia. *Am J Psychiatry*. 2008;165:537–538.
134. Thirthalli J, Bharadwaj B, Kulkarni S, Gangadhar BN, Kharawala S, Andrade C. Successful use of maintenance rTMS for 8 months in a patient with antipsychotic-refractory auditory hallucinations. *Schizophr Res*. 2008;100:351–352.
135. Dixon LB, Dickerson F, Bellack AS, et al. The 2009 PORT Psychosocial Treatment Recommendations and Summary Statements. *Schizophr Bull*. In press; doi:10.1093/schbul/sbp115.
136. Lehman AF, Steinwachs DM. The Survey Co-Investigators of the PORT Project. Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) Client Survey. *Schizophr Bull*. 1998;2:11–20.
137. Fayek M, Flowers C, Signorelli D, Simpson G. Psychopharmacology: underuse of evidence-based treatments in psychiatry. *Psychiatr Serv*. 2003;54:1453–1456.
138. Chakos MH, Glick ID, Miller AL, et al. Baseline use of concomitant psychotropic medications to treat schizophrenia in the CATIE trial. *Psychiatr Serv*. 2006;57:1094–1101.