ABSTRACT

Patients with first-episode (FE) schizophrenia have an 81.9% chance of relapse within five years of initial episode, and only 13.7% of FE patients experience ≥2 years of sustained recovery. Medication non-adherence is the greatest predictor of relapse. Approximately 40% of FE patients are non-adherent, and ~60% have intermittent periods of non-adherence. Antipsychotic switching/augmentation strategies may be required in order to stabilize patients and prepare them for a maintenance regimen. To achieve the desired 60% to 80% striatal dopamine blockade and avoid EPS/akathisia, careful consideration must be given to many practical intra-individual and inter-individual variations relating to drug absorption and metabolism. It is especially important to account for the receptor profiles of the pre- and post-switch antipsychotics. Quantitative assessments are very helpful in determining baseline severity and worsening/improvement. Second-generation antipsychotics have demonstrated better rates of adherence in schizophrenia compared to first-generation antipsychotics, although a long-acting injectable medication may be necessary in cases of chronic non-adherence.
Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

The Mount Sinai School of Medicine designates this educational activity for a maximum of 2 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Faculty Disclosure Policy Statement

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Statement of Need and Purpose

Patients with first-episode schizophrenia generally show high positive symptom improvement with antipsychotic treatment. First-episode patients often respond to a lower medication dose than is required for response in patients with multi-episodes of schizophrenia. Importantly, however, first-episode patients are also more likely than multi-episode patients to experience adverse events. Clinicians treating early-phase patients must be particularly vigilant about assessing for potential side effects.

The goal of antipsychotic dosing is to achieve sufficient dopamine blockade in areas where dopamine excess can lead to psychosis, mania, or aggression. There is, however, considerable intra-individual variability in achieving the desired 60% to 80% striatal dopamine blockade. Careful and knowledgeable evaluation of these variations can help physicians find the optimal antipsychotic dose that leads to sufficient efficacy, without reaching the threshold of extrapyramidal symptoms or akathisia.

Medication non-adherence is one of the major reasons for the significant rates of relapse and re-hospitalization in schizophrenia. Adherence must be assessed and blood levels should be done (if feasible) to ensure that patients have an adequate amount of medication in their system. It is strongly recommended that treatment decisions in schizophrenia be measurement-based so that the clinicians are using quantitative assessment to help guide their decision-making process.

Learning Objectives

At the completion of this activity, participants should be better able to:

- Interpret clinical evidence regarding the dosage, efficacy, and safety profiles of pharmacotherapeutic agents to treat first-episode schizophrenia
- Formulate dosing strategies to achieve optimal antipsychotic efficacy with minimal adverse events
- Discuss the timeframe associated with the onset of action for antipsychotics

Target Audience

This activity is designed to meet the educational needs of psychiatrists.

Faculty Affiliations and Disclosures

Delbert Robinson, MD, is professor of psychiatry and behavioral sciences, Albert Einstein College of Medicine. Dr. Robinson has, within the past one year, received grant support from the National Institute of Mental Health (MH 60004); Bristol-Myers Squibb and Janssen provide medication supplies for Dr. Robinson’s research.

Christoph U. Correll, MD, is medical director of the Recognition and Prevention Program, The Zucker Hillside Hospital; and is associate professor of psychiatry at the Albert Einstein College of Medicine. Dr. Correll, has, within the past one year, served as a consultant to and/or is on the advisory board of Actelion, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Medirecure, Otsuka, Pfizer, Schering-Plough, Supernus, Takeda, and Vanda; and received grant support from the American Academy of Child and Adolescent Psychiatry, the Feinstein Institute for Medical Research, the National Alliance for Research on Schizophrenia and Depression, and the NIMH. This presentation includes discussion of off-label or investigational use of antipsychotic agents.

John M. Kane, MD is chairman of the department of psychiatry at The Zucker Hillside Hospital; and is professor of psychiatry, neurology and neuroscience at The Albert Einstein College. Dr. Kane has, within the past one year, served as a consultant to/received speaking honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Novartis; has served on the advisory board of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Novartis; and received honoraria from Eli Lilly and Janssen.

CME Course Director James C.-Y. Chou, MD, is associate professor of psychiatry at Mount Sinai School of Medicine. Dr. Chou has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Novartis, and Pfizer.

Eran Chemerinski, MD, is assistant professor of psychiatry at the Mount Sinai School of Medicine. Dr. Chemerinski reports no affiliations with, or financial interests in, any organization that may pose a conflict of interest.

Activity Review Information

The activity content has been peer reviewed and approved by Eran Chemerinski, MD.

Review Date: March 22, 2010.

Acknowledgment of Commercial Support

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To Receive Credit for this Activity

Read this Expert Review Supplement, reflect on the information presented, and complete the CME posttest and evaluation on pages 18 and 19. To obtain credit, you should score 70% or better. Early submission of this posttest is encouraged. Please submit this posttest by April 1, 2012 to be eligible for credit.

Release date: April 30, 2010

Termination date: April 30, 2012

The estimated time to complete this activity is 2 hours.
Introduction

Clinicians treating patients with first-episode (FE) schizophrenia can draw upon the vast literature on the treatment of patients with multiple-episode schizophrenia. Studies with multi-episode patients, however, may not fully generalize to the treatment of FE patients. Studies with multi-episode patients typically recruit from hospitals or other acute care units, settings where patients usually have been either non-responsive or non-adherent to previous treatment, or mixtures of both. Studies of multi-episode patients therefore tend to include patients who are not fully responsive to treatment. Without the filter of prior treatment history, FE compared with multi-episode patients may show a broader range of treatment patterns, ranging from extremely good to very poor. Further, studies of FE patients may be very instructive about side effects, as the confounding effect of prior medication use is particularly important with side effects. Finally, data suggest that much of the deterioration (eg, more severe negative symptoms) associated with schizophrenia may occur during the 5 years following illness onset. Providing patients with better treatment at illness onset offers the hope of improving their long-term outcome.

FE studies do have limitations. Relatively few new cases of schizophrenia occur each year. The typically chronic course of schizophrenia results in a large number of patients with multi-episode schizophrenia for every FE patient at any one time. Recruitment for studies of FE schizophrenia compared with those of multi-episode schizophrenia is often more difficult given the smaller number of available patients. We systematically know less about the treatment of FE patients than we do about the treatment of multi-episode patients.

Treatment of the Initial Episode of Schizophrenia

Five major contemporary studies of FE schizophrenia with strict, albeit varied, response criteria all found higher response rates (primarily based upon positive symptom improvement) than the rates typically found in studies of multi-episode schizophrenia. This is especially remarkable, because response criteria are usually more stringent in FE compared with multi-episode studies. No antipsychotic has shown superior efficacy for the treatment of an initial psychotic episode, which may be due to the overall high rate of response by FE patients. For example, chlorpromazine and clozapine showed equal efficacy after 1 year in a study comparing them as the initial treatment for FE schizophrenia. This outcome differs from the results with treatment-resistant multi-episode patients, where clozapine shows superior efficacy. Another notable feature about FE treatment is that the average doses of medication are usually lower than those used with multi-episode patients. Quetiapine, and possibly ziprasidone, dosing may be an exception.

Cognitive Outcomes

Studies with FE patients comparing scores on cognitive tests longitudinally have found modest improvements with treatment with a variety of antipsychotics. However, these improvements in test scores may not be due solely to improvement in cognitive ability. Effect sizes allow assessment of the magnitude of improvement with a treatment. An effect size of 0.2 is consistent with a small effect, 0.5 with a medium effect, and 0.8 with a large effect. Goldberg and colleagues assessed cognition at baseline and at weeks 6 and 16 in a group of FE patients being treated with olanzapine or risperidone and a matched sample of healthy control subjects. Cognition improved in all groups to a small to moderate degree (effect size for cognitive change was 0.33 in the healthy control group and 0.36 in the FE patients). We would not anticipate that the actual cognitive ability of the health control group would improve over time, as they were receiving no treatment. The very similar improvement between patient and control subjects suggests that cognitive test score improvement was likely due to practice effects, ie, patients and controls did better on subsequent tests because they had seen the tests before. In contrast to the small effect size for cognitive change, the effect size for positive symptom improvement in the same study was extremely large—between 1.25 and 1.5. Available treatments have the ability to improve positive symptoms greatly, but, unfortunately, may have very little effect on cognitive symptoms.
Adverse Events in First-Episode Schizophrenia

Even with low dose medication strategies, patients with FE schizophrenia often experience substantial side effects. Typical of side effect patterns with FE patients are results from the CAFE trial comparing olanzapine, quetiapine, and risperidone. Side effects across multiple domains were frequent for all the medications (Slide 1). Clinicians treating early-phase patients must be particularly vigilant about assessing for potential side effects. Metabolic side effects have important implications for long-term health outcomes. Unfortunately, early-phase patients tend to be more susceptible to antipsychotic metabolic side effects than older patients.

Maintenance Treatment of Early-Phase Schizophrenia

Although the initial psychotic episode typically is very responsive to treatment, relapse rates are high during the first years of the illness, with as many as 81.9% of early-phase patients suffering relapse within the first five years of treatment (Slide 2). Given the frequency of relapse, a critical question is how to minimize relapse risk. Placebo-controlled studies have demonstrated a significant advantage for maintenance antipsychotic treatment for relapse prevention with FE patients.

Medication adherence is by far the most powerful predictor of relapse. Patients who stop maintenance medication have a relapse rate ~5 times greater than those who continue on their antipsychotic medications. Although no particular agents are superior to others for treatment of the initial episode of schizophrenia, second-generation agents (SGAs) may be more effective as maintenance treatment for first-episode patients, at least in comparison with haloperidol (Slide 3).

A randomized, placebo-controlled comparison of risperidone (mean modal dose 3.3 mg) and haloperidol (mean modal dose 2.9 mg) found equal efficacy for acute treatment of the initial episode but a better chance of remaining relapse-free on risperidone. The

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**SLIDE 1**

*CAFE: Percentage of Subjects Experiencing the Most Common Adverse Events*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Olanzapine n=133</th>
<th>Quetiapine n=134</th>
<th>Risperidone n=133</th>
<th>All Subjects N=400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime drowsiness</td>
<td>53.4%</td>
<td>57.5%</td>
<td>49.6%</td>
<td>53.5%</td>
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<tr>
<td>Weight gain</td>
<td>51.1%</td>
<td>40.3%</td>
<td>41.4%</td>
<td>44.3%</td>
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<tr>
<td>Increased sleep hours</td>
<td>33.8%</td>
<td>41.8%</td>
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<td>34.3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>38.4%</td>
<td>29.1%</td>
<td>33.8%</td>
<td>33.8%</td>
</tr>
<tr>
<td>Menstrual irregularities</td>
<td>31.3%</td>
<td>23.8%</td>
<td>47.1%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Sex drive</td>
<td>27.8%</td>
<td>26.1%</td>
<td>27.1%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Akinesia</td>
<td>24.1%</td>
<td>24.6%</td>
<td>27.1%</td>
<td>25.3%</td>
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<tr>
<td>Dry mouth</td>
<td>21.8%</td>
<td>34.3%</td>
<td>15.8%</td>
<td>24.0%</td>
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<tr>
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<td>18.7%</td>
<td>22.6%</td>
<td>20.5%</td>
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<tr>
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<td>16.4%</td>
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<tr>
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<tr>
<td>Orthostatic faintness</td>
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<td>19.4%</td>
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<td>11.3%</td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>5.3%</td>
<td>6.0%</td>
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<td>8.3%</td>
</tr>
</tbody>
</table>

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**SLIDE 2**

*The Risk for Psychotic Relapse is High*

<table>
<thead>
<tr>
<th>Year*</th>
<th>Relapse rate (%)</th>
<th>Lower</th>
<th>Upper</th>
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<tr>
<td>1</td>
<td>16.2</td>
<td>8.9</td>
<td>23.4</td>
</tr>
<tr>
<td>2</td>
<td>53.7</td>
<td>43.4</td>
<td>64.0</td>
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<td>3</td>
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<td>74.7</td>
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</tr>
<tr>
<td>5</td>
<td>81.9</td>
<td>70.6</td>
<td>93.2</td>
</tr>
</tbody>
</table>

n=104 first-episode schizophrenia patients

*Year(s) since previous episode

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**SLIDE 3**

*FGAs vs. SGAs for Maintenance Treatment*

<table>
<thead>
<tr>
<th>Study</th>
<th>FGAs</th>
<th>SGAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schooler*</td>
<td>Relapse rate of haloperidol treated subjects (n=203): 54.7%</td>
<td>Relapse rate of risperidone treated subjects (n=197): 42.1%</td>
</tr>
<tr>
<td>Green*</td>
<td>Mean days until discontinuation of haloperidol: 230</td>
<td>Mean days until discontinuation of olanzapine: 322</td>
</tr>
</tbody>
</table>

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median time to relapse was 466 days for patients given risperidone and 205 days for those given haloperidol.

A recent maintenance study comparing haloperidol with amisulpride (not approved for use in the United States), olanzapine, quetiapine, and ziprasidone found that patients maintained on haloperidol discontinued their medication significantly sooner than patients on the SGAs.6 There was no statistically significant difference between the three SGAs. These results suggest that SGAs as a group may be more beneficial than haloperidol for maintenance treatment. Whether SGAs are more beneficial for maintenance treatment than first-generation agents, other than haloperidol, has not been studied.

FE patients have, unfortunately, a strong tendency to become non-adherent with treatment. Rates of non-adherence range from 40% to 60% (Slide 4).21–26 Some of the factors common to non-adherence in multi-episode patients—lack of income, substance use, Parkinsonian side effects—are also associated with non-adherence by FE patients. In addition, FE patients with poor executive function, and other cognitive deficits, have been shown to be less likely to continue their medication.23

**SLIDE 4**

*Retention and Adherence: Pharmacological Treatment*

- Approximately 40% of FE patients are non-adherent22
- Approximately 60% have intermittent periods of non-adherence27,28
- Predictors of medication nonadherence21–26
  - Lack of insight
  - Negative attitudes towards medication
  - Substance misuse
  - Severe positive symptoms
  - Parkinsonism
  - Executive dysfunction

**Recovery**

Proposed recovery criteria for schizophrenia29 require that patients do well in four separate domains (symptoms remission, appropriate role functioning, performing day-to-day living tasks, and social interactions outside the family) continuously for a 2-year period. An investigation30 of 118 FE patients found that by 5-year follow-up 47.2% of subjects had symptom remission for 2 years or longer and 25.5% had adequate social functioning for ≥2 years. Only 13.7% of patients had, however, a ≥2 year period of full recovery. The low rate of full recovery highlights the need for further efforts to improve outcomes for FE patients.

**Psychosocial Interventions for Individuals at the First Episode of Psychosis**

Psychosocial interventions are an important part of improving outcomes for patients with FE psychosis. Some of the modalities studied individually include psychoeducation with patients and families, cognitive behavioral therapy for symptom control, vocational and educational programs, and family work. Substance misuse is very common with FE patients and requires its own intervention.

The efficacy of treatment programs offering several psychosocial modalities provided by specialized teams, along with medication treatment, is an area of active research. Two large studies, one in the United Kingdom and one in Denmark, have evaluated integrated treatment programs. The LEO trial21 demonstrated a reduced risk of relapse over an 18-month follow-up for patients in an integrated treatment program. The OPUS trial22 found that patients in an integrated program, compared with care as usual, showed positive symptom improvement and better treatment adherence at two years. At 5-year follow-up, however, the differences between patients given integrated treatment versus usual care were marginal. The National Institute of Mental Health has recently initiated the RAISE (Recovery After an Initial Schizophrenia Episode) study, which will evaluate the efficacy of integrated treatments in the United States. RAISE is in the start-up phase, with the study projected to begin in 2010.

**Case Report**

Ms. A was a 17-year-old high school student who had been doing well academically and socially. She began to believe that people outside her home were conspiring to harm her and her family and began hearing noises from the conspirators. Ms. A’s family brought her to the hospital after repeated unsuccessful attempts to persuade her that no one was conspiring to harm them. Her medical and psychiatric history before the current episode was unremarkable. She was started on a low dose of risperidone, eventually reaching a dose of 2 mg/day. After four weeks of treatment Ms. A had no hallucinations and no specific delusions, but remained globally suspicious. These symptoms, too, resolved after 10 weeks. Despite being on a very low dose, she experienced sedation and extrapyramidal symptoms.

Ms. A did not want her peers to know about her psychiatric hospitalization. With the support of her therapist, she resumed her education at a different high school. After 9 months of successful treatment, Ms. A decided to stop treatment, because she did not want her new boyfriend to know that she had a problem. Four months after treatment cessation, her hallucinations and delusions returned. The content was similar, but the hallucinations and delusions were more intense than during her first episode. She resumed treatment and responded well, but it took longer the second time for her to experience a full resolution of her illness.

Ms. A illustrates some of the points we have discussed. Her response to treatment in terms of positive symptom improvement was very good. Despite the low dose of medication, she had side effects. She also shows that even patients who do very well are at great risk for relapse when they stop maintenance treatment. Even though she responded well to medication treatment, she benefited by psychosocial support to maximize her potential for recovery.

**References**


Introduction

Pharmacologic knowledge can inform clinical decision-making, particularly the dosing and switching decisions made with antipsychotics. Of relevance are the pharmacokinetic (what does the body do to the drug) and the pharmacodynamic (what does the drug do to the body) properties of antipsychotics.

Real-Life Antipsychotic Dosing

The goal of antipsychotic dosing is to achieve sufficient dopamine blockade in areas where dopamine excess can lead to psychosis, mania, or aggression. Using positron emission topography, one investigation showed that response rates were considerably higher in patients who achieved >65% striatal dopamine blockade. Conversely, striatal dopamine blockade >80% predicted the emergence of extrapyramidal symptoms (EPS) or akathisia.

There is, however, considerable intra-individual variability in achieving the desired 60% to 80% striatal dopamine blockade. Such variability is likely due to inter-individual differences in the absorption, distribution, metabolism and elimination of medications. At the same time, antipsychotics themselves differ in their general pharmacokinetic profiles. For example, ziprasidone absorption is ~50% less when ingested on an empty stomach than when taken with a meal; the degree of absorption depends on the caloric content, while the fat content is not relevant.

The bioavailability of individual antipsychotics is also affected by the liver enzymes principally related to the metabolism of each particular medication. The principal enzymes involved in metabolism of antipsychotics are cytochrome P450 3A6, 2A4, 2D6, and 1A2 (Slide 1). Aripiprazole and risperidone are chiefly metabolized by 2D6, and quetiapine by 3A4. The 2D6 system is very much affected by polymorphisms, and has less capacity than 3A4. Therefore, medications that are chiefly metabolized by 2D6 may have greater variations. Clozapine and olanzapine are metabolized by 1A2. Smoking can accelerate 1A2, and smokers may require higher dosages, depending on changes in smoking patterns. Also, taking several medications that are metabolized by the same CYP 450 enzymes can slow down the metabolism of these medications. Paliperidone and ziprasidone are least metabolized by CYP 450 enzymes, leading to the lowest metabolic drug-drug interactions.

The half-life of antipsychotics varies greatly. Shorter half-life medications, such as quetiapine and ziprasidone, have a 7–12-hour half-life. Risperidone has a 3-hour half-life, but it is metabolized to 9-hydroxy risperidone (paliperidone), which has a 24–28-hour half-life, while olanzapine has a 30-hour half-life. The longest half-life, about 3 days, is seen with aripiprazole.

A meta-analysis, designed to detect the near-maximal effective antipsychotic dose, found that the near-maximal dosages (ie, the threshold dose necessary to produce all or almost all the clinical response) of all first line antipsychotics was somewhat lower in the analyzed, randomized controlled trials than what clinicians would use for chronically-ill patients. The near-maximal dosages of second-generation antipsychotics (SGAs) were: olanzapine 16 mg, risperidone 4 mg, aripiprazole 10 mg, quetiapine 150–600 mg, and ziprasidone 120–160 mg.

In terms of real life dosing, finding the optimal dose that leads to sufficient efficacy, without reaching the threshold of EPS or akathisia, depends first upon the consideration of a number of pharmacologic variables. But, in patients not reaching efficacy who do not develop EPS, the physician should check for and ensure appropriate levels of adherence, and consider increasing the dose until efficacy is reached or side effects become dose limiting.

Dr. Correll is the medical director for the Recognition and Prevention program at The Zucker Hillside Hospital and an associate professor of psychiatry at The Albert Einstein College of Medicine

Disclosures: Dr. Correll has, within the past one year, served as a consultant to and/or is on the advisory board of Actelion, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Mediceure, Otsuka, Pfizer, Schering-Plough, Supernus, Takeda, and Vanda; and received grant support from the American Academy of Child and Adolescent Psychiatry, the Feinstein Institute for Medical Research, the National Alliance for Research on Schizophrenia and Depression, and the NIMH. This presentation includes discussion of off-label or investigational use of antipsychotic agents.

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Pharmacologically-Informed Antipsychotic Switching

Switching strategies should be informed by the clinical situation, as well as the pharmacology of the pre-switch and the post-switch antipsychotic. Regarding clinical situations, there are five broad categories: 1) Adverse-effect switch: a stable patient has developed side effects that do not require an emergent/fast switch; 2) Efficacy switch: the patient’s psychiatric symptoms are not adequately covered by the prior antipsychotic. A faster action is typically required; 3) Mixed adverse effect and efficacy switch: since both adverse effect(s) and inefficacy need to be addressed, the more clinically pressing aspect will generally guide the switch strategy; 4) Non-adherence switch: consider supervised medication intake, as well as orally disintegrating medications or intramuscular long-acting formulations; 5) Treatment-refractory patients: this usually involves a switch to clozapine.

In addition to the clinical scenario, the pharmacodynamic and pharmacokinetic profiles of the pre- and post-switch medications are important in choosing the appropriate switch strategy. The pharmacodynamic profile has to do with the receptor affinity—how tightly the medication binds to specific receptors. Slide 2 shows the specific binding affinities of selected antipsychotics to relevant neuroreceptors, with lower numbers indicating tighter binding. The more the relative receptor affinity compared to dopamine (ie, drug binding to that receptor more tightly or less tightly than to dopamine) differs between the pre- and the post-switch antipsychotic, the more care must be taken, as pharmacodynamic rebound phenomena can otherwise complicate the switch (Slide 3).

For example, when switching from a tightly binding anticholinergic or antihistaminergic medication (eg, olanzapine, quetiapine, clozapine) to one with less anticholinergic or antihistaminergic affinity (eg, aripiprazole, risperidone, ziprasidone), often transient rebound anxiety, insomnia, agitation and restlessness can occur. In addition, when switching from a tighter D2 binding agent to a looser-binding agent (eg, from risperidone to clozapine or quetiapine) or, particularly, to a partial dopamine agonist (eg aripiprazole) dopamine rebound symptoms, such as often transient worsening of psychosis, mania or aggression/agitation, can occur. A pharmacokinetic dopamine rebound may also occur when switching from a short half-life antipsychotic to a longer half-life antipsychotic (Slide 1).

### SLIDE 2
**Approximate Receptor Binding Profiles and Half-Life of Selected Atypical and Typical Antipsychotics**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>ARI</th>
<th>OLA</th>
<th>PAL</th>
<th>RIS</th>
<th>QUE</th>
<th>ZIP</th>
<th>CLO</th>
<th>HAL</th>
<th>PER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor Binding Affinity Expressed as Equilibrium Constant (Ki)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>D2</td>
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<td>2.8</td>
<td>3.8</td>
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<td>5-HT2A</td>
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<td>300</td>
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</table>

**Pharmacokinetic Profiles: Half-life**

| t1/2 h | 72  | 30  | 24  | 3   | 7   | 7   | 16  | 20  | 8–12 |

Data based exclusively on human brain receptors; *Data represented as Ki (nM), ie, nanomolar concentration of the antipsychotic required to block 50% of the receptors in vitro (ie, lower number equals stronger receptor affinity/binding. †Partial agonism; ‡Data from cloned human brain receptors; ARI=aripiprazole; OLA=olanzapine; PAL=paliperidone; QUE=quetiapine; ZIP=ziprasidone; CLO=clozapine; HAL=haloperidol; MOL=molindone; PER=perphenazine

### SLIDE 3
**Pharmacodynamic Side Effects During Switching: Acute Rebound from Complementary Blockade of Previous Antipsychotic**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Blockade</th>
<th>Dopamine Rebound Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td>Antipsychotic, antimanic, antiaggressive, EPS/akathisia, increased prolactin, tardive dyskinesia</td>
<td>Agitation, akathisia, mania, psychosis, withdrawal dyskinesia</td>
</tr>
<tr>
<td>H1</td>
<td>Anxiolytic, anti-EPS/akathisia, calming, sedation, sleep-inducing, weight gain</td>
<td>Agitation, anxiety, EPS/akathisia, insomnia</td>
</tr>
<tr>
<td>M1 (central)</td>
<td>Anti-EPS/akathisia, cognition, dry mouth, memory</td>
<td>Agitation, anxiety, confusion, EPS/akathisia, insomnia, psychosis, sialorrhea</td>
</tr>
<tr>
<td>M2-4 (peripheral)</td>
<td>Blurry vision, constipation, hypertension, tachycardia, urinary retention</td>
<td>Bradycardia, diaphoresis, diarrhea, hypotension, nausea, syncope, vomiting</td>
</tr>
<tr>
<td>5-HT2A</td>
<td>Anti-EPS/akathisia, antipsychotic</td>
<td>EPS/akathisia, psychosis</td>
</tr>
</tbody>
</table>

EPS=extrapyramidal symptoms.
The abrupt switch has the greatest potential for rebound and withdrawal phenomena. Even the conventional cross-titration can lead to problems when the pre-switch antipsychotic has a shorter half life and/or blocks more tightly cholinergic, histaminergic or dopaminergic receptors than the post-switch antipsychotic. Rebound phenomena can be minimized by avoiding abrupt or fast switching when the pre- and post-switch receptor affinities and/or half-lives differ considerably. Instead, an overlapping or “plateau” switch should be used. This consists of decreasing the pre-switch antipsychotic slowly (eg, 25% to 50% every 5 half-lives) and only after the post-switch antipsychotic has reached steady state (ie, ≤5 half lives on target dose). Adding calming medications during the switch period, such as benzodiazepines, antihistamines or sleep aids, can also minimize rebound phenomena.

A meta-analysis comparing antipsychotic switch strategies did not find outcome differences to be dependent upon whether the pre-switch antipsychotic was discontinued gradually or abruptly, or whether the post-switch antipsychotic was initiated gradually or abruptly. These studies were, however, inpatient trials with 24-hour supervisions, and usually undisclosed amounts of benzodiazepines were allowed. Moreover, none of the studies investigated true “plateau switch” strategies, which recent trials have shown to lead to fewer dropouts due to adverse effects than more abrupt switch procedures.10,11

Augmentation Strategies

When a patient demonstrates insufficient or, particularly, only partial treatment response, augmentation strategies of antipsychotics, either with a second antipsychotic or with a non-antipsychotic, are frequently employed.

There are several important reasons for employing antipsychotic polypharmacy. These include ongoing or aborted cross-titration, hopes of enhancing or hastening antipsychotic efficacy, targeting different symptoms (eg, agitation, negative symptoms) or symptom domains (eg, insomnia, anxiety, depression) that are insufficiently addressed by the first antipsychotic. Antipsychotic polypharmacy can, however, also result from poor communication between services, family pressure or preferences, or prescriber habits. Antipsychotic polypharmacy is only endorsed by treatment guidelines after failure or refusal of clozapine. Concerns include a higher than necessary total dosage, increased acute long-term side effects, drug-drug interactions, increased mortality or non-adherence rates, difficulty determining the cause and effect of the combination treatment, increased cost, and lack of evidence-base.

A recent meta-analysis of >1,200 patients from 19 randomized controlled studies found that antipsychotic co-treatment could be helpful in certain circumstances. However, the authors concluded that the data base was insufficient to make treatment recommendations, as most of the studies included clozapine, making it difficult to generalize these findings to the much more prevalent practice of combining two non-clozapine antipsychotics.

A number of non-antipsychotic augmentation strategies have also been tested in schizophrenia patients with insufficient response to antipsychotic monotherapy. Of these, lithium, carbamazepine, and beta blockers were not superior to placebo when added to antipsychotic. Similarly, benzodiazepine and valproate augmentation also did not show long-term superiority compared to placebo, although both agents might speed up the initial response. Although two large-scale studies showed no superiority of lamotrigine augmentation of antipsychotics compared to placebo, a meta-analysis demonstrated significant superiority regarding global ratings of psychopathology, positive and negative symptom change, as well as study-defined response when outcomes of patients were combined in whom lamotrigine was added to clozapine. This, however, has not been verified in a prospective study.

Electroconvulsive therapy augmentation has also been shown to be superior, both for acute efficacy and in maintenance treatment, when added to antipsychotic monotherapy in patients who have failed antipsychotic monotherapy.

One meta-analysis suggested that augmentation of antipsychotics with antidepressants may be more helpful than placebo for schizophrenia patients with predominantly negative symptoms. Larger, validating studies are needed, however, and specific effects on negative symptoms need to be distinguished from proven effects of antidepressants on depressive symptoms in schizophrenia patients.

Conclusion

Exclusion criteria and randomization bias limit the dosage recommendations based on registration and labeling trials. Switching and dosing can be optimized, taking into consideration the receptor binding potential, as well as the half-life of both the pre- and post-switch antipsychotic. In general, abrupt switching of antipsychotics is neither advisable nor necessary. Temporary rescue medications can help during the initial switch period minimizing potential rebound or destabilization phenomena, although often unspecified rescue medications limit recommendations from randomized switching studies.

Case Report

Ms. L is a 37-year-old female with schizophrenia since age 23. At her last inpatient admission she was treated with olanzapine 20 mg. Lithium 900 mg was added for mood symptoms. During the following 9-month outpatient phase she had mild residual positive and relevant negative symptoms. Ms. L complained of a 7-kg weight gain, and daytime sedation. Her fasting triglycerides level was 265 mg/dL; glucose: 95 mg/dL. The decision was made to switch to aripiprazole.

Aripiprazole 10 mg was started, with taper of olanzapine over 1 week. Ms. L presented on day 10 with agitation, restlessness, insomnia, worsening of psychosis (voices telling her that an old colleague has gotten a group of people together that want to “destroy her life”). Olanzapine 20 mg was restarted due to “failure of aripiprazole to maintain efficacy of olanzapine.” Ms. L experienced further weight gain (4 Kg), daytime sedation and an elevated triglycerides level: 280 mg/dL; glucose: 116 mg/dL. The decision was made to switch back to olanzapine.
partial D₂ agonism and a longer half life. Third, rebound phenomena (agitation, insomnia, anxiety, mania) were mistaken for lack of efficacy of aripiprazole, and there was a failure to treat rebound phenomena with transient adjunctive medications.

In a second treatment scenario, the decision was made to reattempt a switch to aripiprazole. Aripiprazole was added at 15 mg/day for 1 week, then increased to 20 mg/day. Only after 2 weeks of aripiprazole 20 mg/day, olanzapine was reduced by 5 mg every 7 days (“plateau switch”). Ms. L remained stable off olanzapine with no more sedation, was more active, and experienced 3 kg weight loss; triglycerides: 155 mg/dL, glucose 100 mg/dL.

References

MAINTENANCE STRATEGIES IN SCHIZOPHRENIA

John M. Kane, MD

Introduction

A key consideration in the discussion of maintenance treatment in schizophrenia is how to first help bring patients to the point where acute psychopathology is sufficiently controlled, so that we can focus on consolidating the gains achieved and prevent a recurrence of illness.

The different phases of treatment and response in schizophrenia include the acute phase, wherein we look for response and resolution; remission, where we control symptoms to levels of mild or less and work toward preventing relapse or any exacerbation of psychopathology; and recovery, meaning the ability to function in the community in the workplace, school, family roles, etc.

In preparing patients with schizophrenia for maintenance treatment, clinicians must ensure that they have done everything possible to alleviate the acute signs and symptoms of illness to the extent possible.

There are several questions to consider at this stage: How much improvement is enough? When do we change treatments, and why? What about adverse effects and the locus of care? In the context of this process of deciding how to bring about the best possible treatment response, we must consider that, if a patient is not responding, the diagnosis may need to be reevaluated. Adherence must be assessed and blood levels should be done (if feasible) to ensure that patients have an adequate amount of medication in their system. If blood levels are unavailable and adherence is an issue, the use of long-acting injectable medication should be considered. The clinician might decide to alter the medication dose—to increase it, or perhaps decrease it if significant side effects are impeding therapeutic response. Adjunct medications or a switching strategy may be employed. Non-pharmacologic therapy, such as cognitive behavioral therapy, which can be effective at reducing symptoms of schizophrenia, should also be considered.

The Value of Measurement

It is strongly recommended that treatment decisions in schizophrenia be measurement-based so that the clinicians are using quantitative assessment to help guide their decision-making process. Quantitative measurements can be helpful in establishing baseline severity, providing targets for treatment goals, and evaluating the progress made in achieving those goals. Examples of quantifiable psychopathology from the Brief Psychiatric Rating Scale include depression, guilt, hostility, elevated mood, disorientation, and self-neglect. Quantitative assessment of tolerability and adverse events should also be conducted.

Unfortunately, a lot of clinicians do not use measurements efficiently. Some clinicians may feel that their overall clinical impression is sufficient, or that quantitative assessments are prohibited by time constraints, or that there may be reimbursement concerns, wherein an insurance company may use the quantitative measurements to question the locus of care or another aspect of the treatment. None of these obstacles should ultimately get in the way of quantitative assessment.

Onset of Medication Response

The actual onset of antipsychotic drug response is another area of concern for clinicians. For example, does early response predict later response, and should early response be used as a guide on whether to continue the current treatment? The observation that response to medication can occur early has been confirmed and extended, but there is always the possibility of no substantial response, regardless of time on medication.

A survey of 47 schizophrenia experts around the United States posed an extensive series of questions, including “what is the minimum number of weeks [to] wait before making a major change in treatment regimen in a patient with a psychotic disorder?” Clinician responses varied anywhere from a minimum of ~3 weeks to a maximum of ~6 weeks, a broad range, suggesting that there is no clear-cut demarcation of when one might consider a trial unsuccessful. This is also important, because the current average duration of hospitalization for someone with schizophrenia is probably <6 weeks and may in fact be <3 weeks.

Evidence suggests that evaluating response after 2 weeks may be a valuable predictor of how patients will ultimately respond. This study’s response criterion was 20% improvement on the total Positive and Negative Syndrome Score (PANSS) at 2 weeks. There was a dramatic difference in response at 24 weeks between patients with ≥20% improvement and patients with <20% improvement at 2 weeks. The disparity in response was still fairly dramatic even after 24 weeks, suggesting that there is no clear-cut demarcation of when one might consider a trial unsuccessful. This is also important, because the current average duration of hospitalization for someone with schizophrenia is probably <6 weeks and may in fact be <3 weeks.

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A post-hoc, pooled analysis of four different clinical trials lasting 24–28 weeks, with >1,600 patients, suggested that patients who experience a 20% improvement after 2 weeks are actually more likely to complete the trial (Slide 1). This suggests that if
patients can notice some improvement in the first 2 weeks they are more likely to continue on that treatment. These findings clearly hold implications for adherence as well. In addition, patients categorized as early responders did better in terms of subjective well-being, quality of life and cost of care.10

Remission Criteria

Once the best-possible level of response is achieved, the clinical focus shifts onto maintaining that response and trying to prevent relapse.

We developed a set of criteria defining remission. These criteria require that patients have no more than mild levels of several major symptoms associated with the diagnosis of schizophrenia.11 They also represent the treatment standard, in terms of acute treatment (i.e., we want patients to achieve remission), and what we are trying to sustain in maintenance treatment. Patients must meet these criteria for a minimum of 6 months to be considered remitted, i.e., no rating greater than mild on any of these 8 items for 6 continuous months (Slide 2).

SLIDE 1

Early Response Predicted Staying on Treatment

![Graph showing early response in treatment](image)

Diagnoses: schizophrenia 78.5%; schizoaffective 20.84%; schizophreniform 0.6%

* P < .001 between group difference. Early response predicted study completion: a 20% improvement in Positive and Negative Syndrome Scale (PANSS) Total Score by 2 weeks was associated with an ~80% greater likelihood of study completion (odds ratio 1.76, CI: 1.4, 2.21, P < .0001).

Remission Criteria in Schizophrenia

Patient achieves PANSS intensity level of mild or less on all 8 symptom items for ≥6 months

- Delusions
- Conceptual disorganization
- Hallucinatory behavior
- Unusual thought content
- Blunted affect
- Social withdrawal
- Lack of spontaneity/flow of conversation
- Time criteria of at least 6 months

SLIDE 2

Remission Criteria in Schizophrenia

FGAs versus SGAs

First-generation antipsychotics (FGAs) have been compared to second-generation antipsychotics (SGAs) with relapse as the outcome measure.12 All the trials included in this review lasted one year and compared an FGA and an SGA. The meta-analysis showed that the relapse rate of the SGAs is significantly lower than the relapse rate of the FGAs, showing a reduction in the relapse rate from 23% on the FGAs to 15% on the SGAs. The number needed to treat was 13, putting these findings into perspective. An alternative interpretation of these results is that there was a relative risk reduction of 35%, which is quite substantial. Some individual trials in this meta-analysis did not show a significant difference, however, underscoring the potential value of combining data from multiple studies to garner a more meaningful perspective. Among first-episode patients, there do not appear to be major differences in relapse rates among patients taking SGAs.13 The potential for differential rates of recovery between medications has not been adequately studied in controlled, long-term trials.

Treatment Adherence

In maintenance treatment, clinicians and patients sometimes consider discontinuing medications completely with the understanding that the patient, clinician, and social/familial support system will help monitor their symptoms. Theoretically, if any early signs of worsening or relapse emerge, the patient will immediately restart medication and hopefully prevent relapse. This notion has been tested by a number of large, very carefully conducted studies demonstrating that patients who had their medications interrupted were significantly more likely to relapse than those who stayed on continuous treatment.14,15 With such a considerable risk of relapse, we would argue that there is rarely any justification for discontinuance of treatment during the maintenance phase. (Although there is no universally accepted definition of relapse, most investigators use a significant increase in psychopathology, aggressiveness or suicidality and/or an increase in the dosage of medication or level of supervision required.)

One of the major reasons for the significant rates of relapse and re-hospitalization is medication non-adherence.17,18 Other reasons include psychosocial stressors and substance abuse, but some patients relapse for reasons we do not understand. Adherence is poor across physical and psychiatric disorders, and particularly in persistent disorders, where treatments are designed to prevent symptom onset or recurrence, and the consequences of stopping treatment are delayed.19,20 A medication gap as short as 10 days can double the risk of re-hospitalization for schizophrenia, and there is a steady—nearly linear—increase of risk as the gap widens (Slide 3).18,21 Non-adherence is a very serious problem in schizophrenia, with ~75% of patients having some degree of non-adherence within two years of hospital discharge.17,19,22

Non-adherence has also been associated with an increase in the risk of suicide. Dutch investigators demonstrated that a medication interruption of ≥30 days led to a very substantial increase in the risk of suicide attempts (adjusted relative risk, 4.2; 95% CI 1.7–10.1), compared to patients who continued to take their medication without interruption.22

A pharmacy records analysis comparing the fill rates of older and newer antipsychotics suggests that there is some potential adherence advantage with the newer medications.24 Newer medications, however, have certainly not solved the problem of medication non-adherence. We as clinicians must continue to struggle with this issue and seek better solutions.

Researchers asked schizophrenia experts to state what percentage of patients in clinical trials have been found to be fully adherent,
based on their individual knowledge of the literature. The experts’ average reply was that 28% of all schizophrenia patients adhere to treatment. When asked what proportion of their own patients were fully adherent, the same sample of experts reported that 43% of their patients adhere to treatment. This interesting illustration suggests that we as clinicians tend to believe that our patients are more adherent than other clinicians’ patients. That is unlikely to be the case, according to the literature, and such an idea may lull individual clinicians into a false sense of security about their patients’ adherence.

New information technology (IT) might be brought to bear in helping to reduce non-adherence. A pilot study tested home teleconferencing and PC-to-mobile text messaging monitoring in 45 patients with psychotic illness. Patients and families reported early warning signs in this study, as well. There was a 60% decrease in the number of hospitalizations in the IT group. Patient participation in monitoring efforts, and the involvement of a family member, were associated with lower numbers of relapse and lower rates of re-hospitalization. We also believe that the use of long-acting injectable medication can be of enormous value in helping patients to ensure that they are getting the full benefits of the medication.

Patients’ Perception of Treatment

The Medication Interest Model is one approach to discussing treatment with patients, providing a framework for working with patients to help them achieve better rates of adherence: 1) Efficacy: we want the patients to appreciate that the drug does make them feel better and is helping them to achieve their own goals; 2) Cost: it is worth it for patients to take the drug; 3) Stigma: the meaning of taking the drug—"What does it say about me that I have to take this drug?" These are three domains that must be addressed with the patient to ensure that he or she has sufficient interest in actually taking the medication.

Case Report

CV is a 24-year-old single male currently living with his family. He is employed part-time by a messenger service.

He had two prior hospitalizations, the first at 21 years of age and the second at 23 years of age. After his first hospitalization he continued treatment for ~5 months. He then decided, against medi-

References

**PRACTICAL DOSING STRATEGIES IN THE TREATMENT OF SCHIZOPHRENIA**

**CME QUESTIONS**

1. Antipsychotic treatment with first-episode patients:
   A. Produces large improvements in positive and negative symptoms
   B. Produces large improvements in positive symptoms and in cognitive deficits
   C. Produces large improvements in positive and negative symptoms and in cognitive deficits
   D. Produces large improvements in positive symptoms but limited improvement in cognitive deficits

2. Which statement about maintenance treatment following an initial episode of psychosis is correct?
   A. Haloperidol is as effective as second-generation antipsychotics for maintenance treatment
   B. Haloperidol is less effective than second-generation antipsychotics for maintenance treatment
   C. Olanzapine has been shown to be more effective than quetiapine for maintenance treatment
   D. Quetiapine has been shown to be more effective than ziprasidone for maintenance treatment

3. Very few patients can experience long periods (2 years or more) of symptom remission following treatment for a first episode of psychosis.
   A. True  B. False

4. Which of the following statements about the variability across individuals regarding the dosing/levels of medication is false?
   A. Plasma levels of ziprasidone can be as much as 50% lower if not taken with food
   B. Plasma levels of olanzapine and clozapine can be up to twice as high if a patient starts smoking
   C. Paliperidone and ziprasidone are least likely to lead to drug-drug interactions due to interfering with drug metabolism by liver enzymes
   D. Aripiprazole takes the longest time to reach orally dosed steady state levels, and quetiapine and ziprasidone take the shortest time to reach orally dosed steady state levels

5. Which strategies can help avoid rebound and withdrawal phenomena when switching between antipsychotics with markedly different affinity to the histamine, muscarinic and/or dopamine receptor or agents with markedly different half-lives?
   A. Use plateau cross-titration
   B. Use transiently adjuvant medications, such as benzodiazepines, sleep aids, etc.
   C. Educate patients about potential signs and symptoms of rebound phenomena
   D. All of the above

6. Combining antipsychotics with valproate increases antipsychotic efficacy beyond the initial treatment phase.
   A. True  B. False

7. Data suggest that using the following response measure at two weeks can be a significant predictor of subsequent improvement:
   A. 10% reduction in PANSS total score
   B. 20% reduction in PANSS total score
   C. 30% reduction in PANSS total score
   D. 40% reduction in PANSS total score

8. Research has shown that providing medication on an intermittent or targeted basis, meaning only when patients show early signs of relapse, is associated with:
   A. Higher rates of relapse
   B. Fewer suicide attempts
   C. Better patient adherence
   D. No difference in relapse rates
1. Please rate how well this CME activity met the stated learning objectives:
   A. Interpret clinical evidence regarding the dosage, efficacy, and safety profiles of pharmacotherapeutic agents to treat first-episode schizophrenia
   B. Formulate dosing strategies to achieve optimal antipsychotic efficacy with minimal adverse events
   C. Discuss the timeframe associated with the onset of action for antipsychotics

2. Please indicate how well this CME activity met your expectations regarding the following:
   A. Translating clinical information/trial data to patients I see in my practice
   B. Providing new information
   C. Increased my knowledge and/or skills in delivering patient care
   D. Communicated information in an effective, accessible manner

3. Compared to other CME activities in which I have participated this year, I would rate this activity as:

4. As a result of participating in this educational activity, I will (please check one)
   □ Change my practice
   □ Seek additional information
   □ Confirm my current practice

4a. If “change my practice,” please describe:

5. Did this CME activity provide a balanced, scientifically rigorous presentation of therapeutic options related to the topic without commercial bias and influence? Yes □ No □

5a. If “no,” please explain:

6. Do you feel these topics should be repeated/updated in future CME activities? Yes □ No □

6a. If “yes,” what suggestions would you make to improve this activity?

7. Please indicate your three preferred formats for CME activities:
   □ Print media
   □ Internet
   □ Multimedia/video
   □ Live meeting
   □ PDA
   □ Podcast

8. Please indicate three professional education gaps you would like to be addressed in future CME activities:
   Topic 1:
   Topic 2:
   Topic 3:

Name ___________________________ Degree ____________ Affiliation __________________________

Street __________________________

City ____________ State ____________ Zip Code ____________

Tel: ____________ Fax: ____________ Specialty ____________

Email __________________________

I certify that I completed this CME activity (signature) ____________ Date ____________

I have read the CME article and completed this activity in ____________ hour(s).