

Long-Term Considerations After Switching Antipsychotics

Peter J. Weiden, M.D.; Ralph Aquila, M.D.;
Marianne Emanuel, R.N.; and Annette Zygmont, M.S.

The so-called "atypical" antipsychotics are rapidly becoming the de facto standard pharmacologic treatment of schizophrenia. This article reviews some common psychopharmacologic and psychological issues that may arise after an outpatient with schizophrenia is switched to one of the newer antipsychotics. Important issues to consider in the first few months after switching include assessment of response to the new medication, dealing with subsequent psychological reactions, and management of an unsatisfactory response. Once the response is established, there are other pharmacologic and psychological issues that arise during the next year or two. Pharmacologic issues that emerge later on include the role of long-term combination antipsychotics, management of new side effects, and deciding whether and when to switch again. Some of the long-term psychological issues include changes in self-image that arise from being less visibly ill, sexuality and intimacy concerns, and recovery issues.

(J Clin Psychiatry 1998;59[suppl 19]:36-49)

This is a companion article of an earlier report on switching antipsychotic medications published in a supplement to the *Journal*.¹ The previous article focused on the immediate switching process as patients transition from conventional antipsychotics to one of the newer atypical antipsychotics. This article starts where the last one left off, focusing on patient management after the switch is well under way or has been successfully completed.

The article is divided into 3 sections (see Table 1). The first section deals with special issues pertaining to the first few months on treatment with the new medication. Tasks in the first few months after switching are to assess the new medication, to manage psychological issues that come up as a consequence of switching, and to evaluate for nonresponse. The second section describes the management of patients who ultimately do not respond to the new medication. The third section deals with some of the long-term psychopharmacologic and psychological issues that may arise for patients who do respond.

Setting and Patient Sample

Over the past 6 years, the Neurobiologic Disorders Service at St. Luke's-Roosevelt Hospital Center in New York

City has been a research site for outpatient Food and Drug Administration phase 3 trials of some of the newer atypical antipsychotic compounds, including olanzapine, quetiapine, risperidone, and ziprasidone.^a The setting is described in greater detail elsewhere.² All patients had a clinical diagnosis of chronic schizophrenia or schizoaffective disorder and had been ill for most of their adult lives. The following discussion is based on the authors' experience with the long-term follow-up of patients who were switched to one of these newer medications.

ASSESSING PHARMACOLOGIC RESPONSE

Because a wider range of medication options is available, it becomes more important than ever for clinicians to be able to accurately assess (and document) the response to the medication trial. Assessment of the response can sometimes be straightforward. But, on occasion, judging the medication response is complex and can require a fair amount of clinical sophistication. This section will focus on some of the complicated or contradictory situations that may arise when assessing response after switching.

Choosing an Appropriate Time Frame for Assessing Symptom Response

The evaluation needs to be done within the context of an appropriate time frame of the medication trial. The time frame of the treatment trial, in turn, depends on the treatment setting.³ An appropriate time frame for an acute episode is 3 to 6 weeks of treatment. In contrast, the time frame is considerably longer for chronic but stable outpatients who are switched for elective (rather than acute) indications.

From the Neurobiologic Disorder Service, St. Luke's-Roosevelt Hospital Center, New York, N.Y.

Supported in part by the Psychiatric Epidemiology Training Program at the Columbia University School of Public Health (Dr. Weiden).

Presented at the symposium "The Routine Use of Atypical Antipsychotic Agents," held July 25, 1997, Dallas, Tex., which was supported by an unrestricted educational grant from Eli Lilly and Company.

Reprint requests to: Peter J. Weiden, M.D., Department of Psychiatry, St. Luke's-Roosevelt Hospital Center, 411 West 114th Street, New York, NY 10025.

Table 1. Overview of Long-Term Issues After Switching Medications

| |
|--|
| I. Assessing and managing the switching response |
| Assessing the pharmacologic response |
| Assessing the psychological response |
| II. Managing an unsatisfactory response |
| Pharmacologic option |
| Psychological management |
| III. Long-term issues after switching |
| Long-term pharmacologic issues |
| Long-term psychological issues |

Among the new drugs, the time course of clozapine response has been the best studied. The minimum recommended duration of a clozapine trial is about 3 months.⁴ In our experience, the 3-month duration rule generalizes to all of the atypical agents when used for elective reasons among outpatient populations. Also, remember that the therapeutic trial time is not the same as calendar time. The start of the therapeutic trial is not the day the patient takes the first pill; rather, it is the first day the patient achieves a therapeutic dose.

Ideally, stable outpatients who switch for elective reasons should get a full 3-month trial of the new medication at therapeutic doses. The 3-month point can become a pivotal target date. Ambivalent or symptomatic patients can be encouraged to persevere in their trial to reach that point. Then, at 3 months, the physician, patient, and treatment team can review the course of symptoms and come to a judgment about the degree of response. If clinical circumstances make a 3-month period unrealistic, a 6-week trial (at therapeutic doses) represents a minimal time period. For disappointing responses, a key factor is to distinguish no improvement from a small improvement. In general, small improvements call for extending the evaluation period further (about 6 to 12 months), whereas one should consider other pharmacologic approaches when there is no improvement (see nonresponse section below).

Assessing Positive Symptom Response

One of the basic goals of the psychiatric assessment is to elicit positive symptoms and to estimate their impact on the patient's well-being, behavior, and functioning. This section will review some situations that complicate the assessment of positive symptom response to a new medication.^b

When an apparent worsening of positive symptoms is really an improvement. Assessing positive symptoms is often complicated by the patients' being unable or unwilling to disclose them. Patients may conceal their psychotic symptoms for a variety of reasons, including lack of insight, paranoid fears, stigma, or concerns about the consequences of revealing them.⁵ Sometimes, symptoms can be inferred despite the lack of disclosure, but sometimes the clinician will remain unaware of the full extent of positive symptoms.

The assessment gets complicated when a patient becomes more willing to disclose psychotic symptoms as a result of a favorable response to the medication. Symptoms will get reported that had previously gone unrecognized by their clinicians. The clinician may get the false impression that these are new symptoms and conclude that the psychosis is worsening when, in fact, it is improving. Such a misinterpretation is unfortunate when it leads to abandoning the medication because it is more effective.

The most important part of managing this phenomenon is to recognize it. Recognition is usually based on clinical inference. The patient sounds worse but looks better. Behavioral symptoms are better, not worse. The patient may appear less guarded and more cooperative to treatment. When asked directly, the patient might admit that the newly disclosed symptoms are long-standing but had previously been undisclosed.

Once this pattern of symptom disclosure is recognized, the most important management step is to reassure the patient and educate the caretakers (including family, case managers, and residential care providers) about the need to continue the therapeutic trial of the new medication. The issue should resolve on its own as the patient continues to improve.

When an early improvement in positive symptom response is followed by an exacerbation 4 to 6 weeks after the previous antipsychotic was stopped. Positive symptom responses should be viewed cautiously until 6 weeks after the previous antipsychotic has been discontinued. Remember, the neuropharmacologic action of antipsychotics persists in the CNS up to 6 weeks beyond any measurable plasma levels.⁶ The previous medication may continue to actively suppress psychotic symptoms during this time. Therefore, it is hard to predict the long-term effectiveness of monotherapy with the new antipsychotic until 6 weeks have passed since the old medication was discontinued. Some patients who show dramatic early responses may be at risk of a symptom recurrence around 4 to 6 weeks after the old antipsychotic was stopped (longer when the medication is given by depot route).

Patients who are elated at their early symptom improvements need to be warned that they are not really "out of the woods" until then. Another clinical implication is to make sure that the new antipsychotic is titrated to usual therapeutic doses, even if it seems that the patient has an apparent early response to lower doses of the new medication.

Assessing Negative Symptom Response

It is best to have modest expectations for negative symptoms. Improvements tend to be partial; that is, the negative symptoms may get somewhat better but do not go away entirely. Therefore, it is important to keep hopes and expectations modest. Patients and families should know that even a partial alleviation of persistent negative symptoms should be considered a treatment success.

Negative symptom responses can be subtle and difficult to detect using standard negative symptom rating scales. Many of the negative symptom improvements are quite subtle and are not fully captured by standard psychiatric symptom assessments such as the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), or Scale for the Assessment of Negative Symptoms (SANS). Often there is a clinical consensus that “something has changed” and that the patient seems more “like his old self.” The family may report something like “there is a twinkle in her eye that I haven’t seen in years.” But, when the same patient is given a structured negative symptom rating scale, the negative symptom scores may not have changed. Either the clinicians and families are overenthusiastic, or the negative symptom scales are not sensitive enough. In any event, these “soft” or “intuitive” impressions often prove themselves to be on target and are followed months later by more obvious improvements in negative symptoms.

Some negative symptoms may respond better than others. Negative symptoms are multidimensional, and a patient may respond to a new medication better on one dimension than another. For example, a person’s baseline negative symptoms might include both apathy and poor social functioning. The response to the new medication might be more robust for the apathy than for asocial symptoms, or vice versa. We have also noticed that this kind of a mixed negative symptom response seems to be fairly common. It remains to be seen whether there are any differences among the newer medications on targeting specific subtypes of negative symptoms.

Assessing Affective Symptom Response

The newer drugs seem to be helpful in reducing the co-existing affective symptoms of schizophrenia. For example, in the context of an acute 6-week trial, olanzapine has been shown to be better than haloperidol at reducing concomitant depressive symptoms.⁷ Similarly, clozapine treatment lowers the risk of suicide among refractory patients.⁸ Therefore, there is good reason to think that the newer antipsychotics will decrease the overall burden of persistent depressive symptoms in schizophrenia. However, certain individuals may be at greater risk for depressive symptoms during specific phases of their treatment. The following section deals with some of the complicating issues that may need to be assessed during the post-switching period.

Distiguishing long-term benefits in depressive symptoms from a temporary postpsychotic depression. Postpsychotic depression refers to an acute depressive episode that arises shortly after an acute psychotic episode improves. The period of greatest risk is roughly 3 to 6 months after the positive symptoms improve. During a postpsychotic depression, the depressive symptoms worsen as the psychotic symptoms improve.^c Postpsychotic depres-

sion can occur with any antipsychotic medication, be it atypical or conventional. *The primary risk factors for postpsychotic depression are having a past history of depressive episodes, combined with a recent history of positive symptom improvements.*^{9,10} Therefore, the newer drugs are linked to postpsychotic depression inasmuch as patients experience better positive symptom control from these medications. A person who has a marked improvement in positive symptoms after switching may be at a higher risk of postpsychotic depression.^d Because the postpsychotic depression happens after a period of symptom improvement, it can come just when the person’s social or treatment network becomes less vigilant and is less involved in close symptom monitoring and support.

Signs of postpsychotic depression include feelings of hopelessness, worthlessness, guilt, and suicidal ideation. Often the depressive symptoms are intertwined with a renewed psychological awareness that comes with symptom improvements. For example, the patient might suddenly feel the cumulative losses resulting from having schizophrenia. There may be an intense self-loathing that arises from equating the disability from the illness with a character flaw or moral weakness. Given the hardships of schizophrenia, these feelings are very understandable. During a postpsychotic depression, these thoughts can spiral out of control, and the patient loses sight of any personal strengths and hope for the future.

Psychosocial management includes increasing the level of psychosocial support and monitoring, with hospitalization a consideration when severe suicidal ideation is present or when outside supports are lacking. Psychopharmacologic management includes ruling out other syndromes that present with depressive symptoms and then adding an adjuvant antidepressant medication. The management of a postpsychotic depression is generally not affected by the type of antipsychotic being prescribed. Although the tricyclic antidepressants (TCAs) have been the class of antidepressants best studied,¹¹ many clinicians use selective serotonin reuptake inhibitors (SSRIs) because they seem to be as effective as the TCAs and are much safer in case of overdose.¹² All of the SSRIs seem helpful and should be titrated to usual antidepressant doses.^e

Assessing Side Effect Responses

Reversal of persistent parkinsonism and akathisia. The reversal of persistent parkinsonism (tremor, rigidity, and akinesia) or persistent akathisia after switching to an atypical antipsychotic is more reliable than symptom responses. Many patients will eventually be able to discontinue their anticholinergic or antiakathisia agent.

Minimizing anticholinergic burden. One approach would be to slowly taper and discontinue any concomitant anticholinergic or antiakathisia medication during the second postswitching month, and then evaluate whether there are any residual signs of persistent extrapyramidal symp-

toms (EPS) by the third month of treatment with the new medication. Benefits include reducing the overall anticholinergic burden as well as reducing the complexity of the medication regimen. Most of the time, the anticholinergic does not need to be restarted while a patient is taking the newer atypical antipsychotic. After approximately 3 months of treatment with the new medication, any residual EPS that remain on examination are probably caused by the new medication.^f

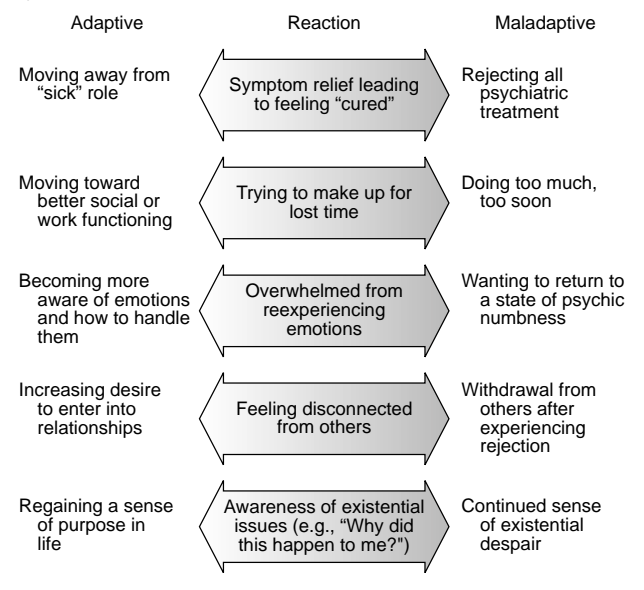
Reversal of amenorrhea and galactorrhea. Many women experience amenorrhea or galactorrhea as a result of the hyperprolactinemia caused by the conventional antipsychotics or risperidone. Amenorrhea and galactorrhea will eventually reverse and normalize after the switching to one of the atypical antipsychotic drugs that normalize prolactin (clozapine, olanzapine, or quetiapine). Keep in mind that prolactin will be reliably lowered only when the older drug is completely discontinued. Even then, there is a lag time of about 3 months before menses resume (longer for patients who were previously on depot therapy). Menses may be irregular at first and then resume normal functioning later on.

When women are switched to a new medication because of other indications, it is easy to forget to tell them that the amenorrhea will reverse. A return of menstrual bleeding may be frightening for those who are not forewarned about it. Also, some women may be using their amenorrhea as de facto birth control, and switching antipsychotics may then lead to accidental pregnancies. Therefore, anticipated effects on the menstrual cycle need to be explained to all premenopausal women for whom medication is switched regardless of whether this is the reason for switching. When amenorrhea or galactorrhea continues beyond 6 months after the cross-taper is completed, a prolactin level and a pregnancy test should be obtained, and the patient should be evaluated for other causes of amenorrhea or galactorrhea.

Reversal of preexisting tardive dyskinesia. Assessing for any reversal of preexisting tardive dyskinesia is complicated by the fact that there may be a superimposed withdrawal dyskinesia during the crossover period.¹ Therefore, within the time frame of the first 6 months after switching, it is very hard to predict whether the dyskinesia will eventually resolve. The question of whether the new medication might ultimately reduce the tardive dyskinesia can only be answered with follow-up dyskinesia examinations done for at least a year. Even then, strictly speaking, it is impossible to disentangle the natural history of the patient's dyskinesia from any potential beneficial effect on the dyskinesia that came from changing medication.

Prevention of tardive dyskinesia. It is well accepted that clozapine has a much lower risk of causing tardive dyskinesia than do the conventional antipsychotics.¹³ It seems likely that the other atypical antipsychotics share at least some of clozapine's advantages with regard to de-

Figure 1. Common Psychological Reactions After Achieving a Symptom Response



creased risk of tardive dyskinesia. A double-blind prospective study comparing olanzapine and haloperidol in maintenance treatment showed a significantly lower rate of new-onset dyskinesia in the olanzapine group.⁷ Retrospective studies of risperidone suggest that risperidone also has a lower dyskinesia rate than conventional antipsychotics. Taken together, the atypical antipsychotics, as a group, are probably less likely to cause tardive dyskinesia than the conventional antipsychotics. But, lower risk of tardive dyskinesia is not the same as zero risk. Someone taking an atypical antipsychotic who develops what would otherwise have been a spontaneous dyskinesia will have it diagnosed as a tardive dyskinesia.¹ It is virtually certain that all of the atypical antipsychotics will be reported to cause tardive dyskinesia. Dyskinesias arise spontaneously without exposure to any antipsychotic.¹⁴ Thus, using atypical antipsychotics does not change the need to give informed consent about tardive dyskinesia and to monitor periodically for tardive dyskinesia using an Abnormal Involuntary Movement Scale (AIMS) examination or similar tardive dyskinesia scale.

ASSESSING PSYCHOLOGICAL REACTIONS

Psychological Reactions After Responding to the New Medication

Patients will have strong psychological reactions to their symptom improvement. The exact nature of the emotional response will be determined partly by inherent personality characteristics, partly by the person's social environment, and partly by the nature of the pharmacologic response.^{15,16} Figure 1 illustrates some of the more

common psychological reactions we have observed in our outpatient service and outlines some of the ensuing maladaptive and adaptive responses to these psychological changes.

“Feeling cured” and “making up for lost time.” There may be a tremendous feeling of relief after long-standing symptoms improve. In physical terms, the relief may be described as a weight taken off the person’s back, or, in mental terms, patients have described a sense of a fog lifting with their thinking returning back to normal for the first time since getting ill. The person feels well and feels reemerged from years of deprivation. A natural reaction to this response is a wish to make up for lost time. What happens next is a sudden attempt to behave normally. This may mean taking on too many new things at once, such as leaving home, finding a job, and trying to date after years of isolation or attempting to recontact long-lost family members. To an outside observer, the sudden shifts in behavior seem odd, even psychotic. Certainly, these responses almost always lead to setbacks. Years of emotional losses and atrophied personal growth simply are not recovered in months. Often, however, the person will have to discover these lessons the hard way, through setbacks.

“Overwhelmed by emotions” and “feeling disconnected.” Another aspect of responding to a new medication may mean coming out of a kind of emotional numbness. But, people who are emotionally numb do not feel emotional pain. Lifting the numbness means feeling more pain, at least for a while. It can be difficult to understand this kind of pain when, on a behavioral level, the patient seems to be better.

Patients may become aware of how disconnected they have felt from other people. On the old medication, being socially isolated before was not bothersome, but becomes bothersome once the person experiences loneliness. Another example of painful emotions that can come up after switching medication is a reliving of traumatic memories from being psychotic. The person may reflect on the psychotic experience in a way that was not possible beforehand. In doing so, there may be a new awareness of just how terrible or frightening the psychotic symptoms were, or there may be painful feelings of humiliation from remembering what was said or done during the psychosis. Just like other posttraumatic experiences of terrible events, the person has to be able to come to terms with what happened in order to continue on in the healing process.

“Existential issues.” The term *existential* is defined as “relating to, or dealing with, existence.” Schizophrenia is a life experience that puts existential questions right in the foreground. Although schizophrenia is a “no-fault” illness, many patients suffering from this illness struggle with questions like “Why did this happen to me?” and “Why am I here?” Existential questions can arise at any time but seem to be particularly common several months after the person responds to the new medication.

A common theme in the management of these responses is to help the patient identify them, to normalize them (“It’s normal to try to catch up with everything right away, but . . .”), to minimize the consequences of any misjudgments, and to facilitate adaptive rather than maladaptive coping responses. Also, patients having maladaptive emotional responses should be carefully evaluated for postpsychotic depression and, if it is present, treated appropriately. These kinds of challenges point to the need to continue any psychosocial or psychological therapy going for at least 6 months—preferably a year—after achieving a better symptom response, even if the patient seems better.

MANAGING AN UNSATISFACTORY RESPONSE

Managing patients with unsatisfactory responses to switching is as important as managing good responses. It can be harder to put one’s heart into this phase of treatment because of the shared sense of disappointment in the outcome from switching. Fortunately, the recent advances in the treatment of schizophrenia offer good reason to continue to be enthusiastic and good reason not to lose the momentum gained during the initial medication switch.

Assessing the Cause of Unsatisfactory Response

Because of all the time and effort that has gone into trying a new medication, it is important to rule out alternate, nonpharmacologic explanations of lack of improvement before abandoning the new medication. The first step is to look for other common complications that might have preempted potential pharmacologic benefits. In particular, surreptitious noncompliance and substance abuse should be considered and ruled out as much as possible. It is also important to review the technical aspects of the pharmacologic treatment plan. The most common mistakes made in this area are inadequate dosing of the new medication, and not giving the treatment trial adequate time. Table 2 summarizes some of the key points involved in assessing for nonresponse to an elective outpatient switching trial.

Pharmacologic Options After Nonresponse

At some point, after ruling out possible explanations of poor response, the clinician will decide that the patient had an inadequate pharmacologic response. It is hard to justify keeping the patient on an expensive medication that does not work. The revised psychopharmacologic goal should then usually be to switch to another antipsychotic. Options include going back to the patient’s previous antipsychotic, switching to a depot medication, switching to another first-line atypical antipsychotic, or switching to clozapine.⁸ The advantages and disadvantages of some of the major options are covered in Figure 2.¹¹

When to go to clozapine? There is a general consensus that clozapine remains the single most effective antipsy-

Table 2. Treatment Considerations Before Abandoning the New Antipsychotic

| Problem | Recommendations |
|--|--|
| No improvement in baseline symptoms by 6 weeks | <p>Check for adequacy of therapeutic dosage</p> <p>Review compliance status and whether patient has adhered to crossover regimen</p> <p>Check for surreptitious substance or alcohol use</p> <p>Increase dose of the new agent to the high end of the recommended therapeutic range</p> <p>If possible, try to finish a full 12-week trial at high therapeutic doses</p> |
| Initial improvement followed by worsening of positive symptoms between weeks 3 and 6 | <p>Check if the “worsening” is not actually clinical improvement^a</p> <p>If true worsening, try to restabilize the patient and attempt to complete a full 12-week trial at high therapeutic dose</p> <p>Acute management options include adding a benzodiazepine or continuing (restarting) the old antipsychotic</p> |
| Partial but unsatisfactory improvement with new medication between 6 and 12 weeks | <p>Increase the dose to higher end of therapeutic range</p> <p>Extend medication trial to at least 6 months</p> |

^aSee the earlier section “Assessing Positive Symptom Response.”

chotic for refractory patients, but there is no clear consensus about how many other first-line atypical antipsychotics should be tried before switching to clozapine. So the question is not whether to eventually recommend clozapine, but when to recommend it. The trade-off here is that, of all atypical antipsychotics, clozapine is statistically the single agent that is most likely to be effective for persistent symptoms. But, of course, clozapine’s numerous other side effects make it a very difficult medication for many patients to tolerate (Figure 3). Furthermore, once the person has been on and responded to clozapine, going back and trying another first-line atypical antipsychotic becomes more risky and generally should be avoided. Therefore, for those reasons, patients who “skip” first-line atypical antipsychotics on their way to clozapine are unlikely to ever try them once a clozapine response has been established.

Therefore, when planning a sequence of atypical antipsychotic trials, clozapine should be tried last. It is still an open question about the most appropriate number of other first-line atypical antipsychotics to try before recommending clozapine. This issue is best discussed in advance with the patient and family to help clarify their opinion(s) and their willingness/reluctance to try clozapine. In general, the more desperate the patient is to control his or her positive symptoms, the sooner clozapine should be used. Also, one might switch to clozapine if there were any reason to believe that failing a trial with another atypical agent would jeopardize an ultimate clozapine trial. In contrast,

there should be other trials of first-line atypicals when the patient is very reluctant to try clozapine.

Psychological Management of Medication Nonresponse

The patient whose new medication has not elicited a satisfactory response will be disappointed and demoralized. The patient—and family—now realizes that the efforts that went into switching will not translate into any tangible benefits. It is important to try to avert a crisis of demoralization and hopelessness. It is helpful to frame the non-response as a failure on the part of the medication to do its “job” rather than being a failure on the part of the patient. It can also be helpful to praise the patient for his or her efforts in taking a chance toward recovery. The patient may have shown character strengths such as courage or perseverance during this time. These strengths can be acknowledged and praised with the hope of providing the patient some solace for an otherwise frustrating experience.

It is likely that morale will be quite low in the patient’s family. The family or other caretakers may be overwhelmed or tired from dealing with any symptom flare-ups or increased monitoring that may have happened during the medication crossover period. While empathizing with the disappointment, it can be helpful for the physician to remind everyone in the patient’s social network of the long-term nature of the illness and that many patients try several medications before finding the one that works best for them.

LONG-TERM PSYCHOPHARMACOLOGIC ISSUES

In this section, we will cover some of the ways that maintenance psychopharmacology of schizophrenia seems to be changing as a result of the new medications. Some of the more interesting and unresolved topics include the role of combination antipsychotics, maintenance dosing strategies with newer drugs, the impact of the decreased burden of EPS over long-term treatment management of new side effects, and when to switch to another atypical for patients who have improved but still have problems.

Monotherapy Versus Combining Antipsychotics

This section discusses when to use 2 or more antipsychotics simultaneously during long-term maintenance therapy (combination therapy).¹ This is a very tricky issue, one for which the absence of good data is matched only by the strength of opinions on this topic. Actually, the question of combination antipsychotics really is not a new one. Never totally dead, combination therapy seems to be experiencing a renaissance as a result of the influx of the new antipsychotics. Anecdotal reports support the notion that some patients benefit from combination antipsychotics over and above either medication alone. Unfortunately, there are

Figure 2. Treatment Options After Pharmacologic Nonresponse Has Been Established*

| Advantage | Option | Disadvantage |
|--|---|---|
| <p>Patient's response to prior medication is known and predictable</p> <p>Helpful when patient (or caretaker) cannot tolerate uncertainty of another medication trial</p> <p>Less expensive (when going back to a conventional antipsychotic)</p> | Switching back to the previous antipsychotic | <p>Loss of momentum when switch made for elective reasons</p> <p>Should be avoided when symptom response to prior medication was unacceptable</p> <p>Should be avoided when there were intolerable or dangerous side effects on prior medication</p> |
| <p>Can be helpful when compliance is a potential problem</p> <p>Can be helpful when substance abuse has complicated the clinical situation</p> <p>Can be helpful when there are possible metabolic or malabsorption explanations for poor responses</p> | Switching to a long-acting depot regimen | <p>Some patients may be reluctant to accept depot medication</p> <p>May take some time to achieve therapeutic levels from depot therapy so oral supplementation is usually needed</p> <p>Depot medications have the EPS profile of high-potency conventional antipsychotics</p> |
| <p>Continues the attempt to find a better therapeutic regimen</p> <p>There may be differential efficacy between the atypical antipsychotics so patients can respond to another first-line atypical agent despite nonresponse to another</p> <p>A first-line atypical medication, if successful, will be less burdensome in the long-run than switching directly to clozapine</p> | Switching to another first-line atypical antipsychotic (other than clozapine) | <p>Patient (or caretaker) has to go through another period of uncertainty before response to another atypical is known</p> <p>Clinician may be "burned out" from prior attempt at switching and is reluctant to try again</p> <p>May delay eventual trial of clozapine</p> |
| <p>Clozapine remains the antipsychotic most likely to be effective for refractory symptoms</p> <p>Clozapine is well established to be useful for other difficult treatment situations including violence, psychogenic polydipsia, and severe tardive dyskinesia</p> | Switching to clozapine | <p>Although excellent for EPS, clozapine has many burdensome side effects (see Figure 3)</p> <p>Many patients are reluctant to try clozapine</p> <p>Need for continuous complete blood cell count monitoring</p> <p>Once clozapine treatment is begun, it is more difficult to switch from clozapine to an alternate atypical antipsychotic</p> |

*Abbreviation: EPS = extrapyramidal symptoms.

very few data on this topic, especially concerning the efficacy of combination therapy when the patient fails a trial of monotherapy. Having an occasional success with combination therapy does not justify its routine use. It is very easy to overuse, and misuse, antipsychotic combinations.

Basic principles of psychopharmacology are a useful starting point. One basic principle is to use 1 drug alone if that drug can do the job by itself. Therefore, it is difficult to justify long-term combination antipsychotic therapy unless there has been some good-faith attempt to try monotherapy. Careful attention to this simple rule would go a long way to reducing the confusion in this area.

Possible justifications for using long-term combination antipsychotics. There are situations where long-term combination antipsychotic treatment might be appropriate. These situations include the following:

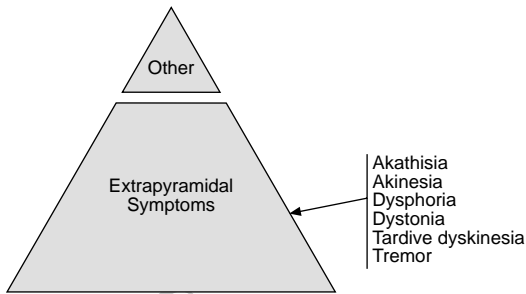
- *For clozapine intolerance.* Some clozapine-responsive patients cannot tolerate optimal clozapine doses because of dose-related side effects such as seizures, sedation, or gastrointestinal symptoms.

Here, a second antipsychotic is added to augment the subtherapeutic clozapine dose. Because they are well tolerated and have structural similarities to clozapine, olanzapine or quetiapine may be helpful for the clozapine-intolerant patient.^j

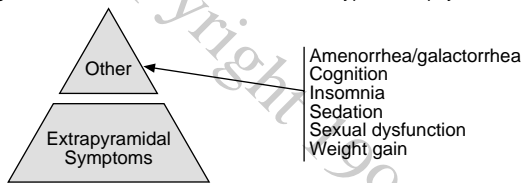
- *For partial response to clozapine.* There are several factors that support trying combination therapy for cases of clozapine nonresponse. Many patients taking clozapine do better than before but still are far from well, but switching options are very limited. Clozapine is often placed last in treatment planning, so the patient may have already tried and failed the other atypical antipsychotics. Even if there are other untried medications, there are significant risks from doing a complete crossover from clozapine. Combination therapy becomes a safer alternative plan.^k
- *When discontinuing depot therapy is too risky.* Some patients need depot therapy for compliance reasons but are only partially responsive to adequate depot doses. Going off depot is judged to be

Figure 3. Side Effect Concerns With Antipsychotics

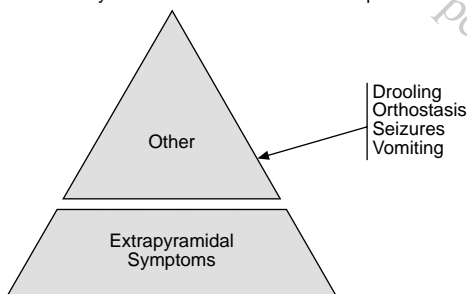
A. Hierarchy of Side Effect Concerns: Conventional Antipsychotics



B. Long-Term Side Effect Concerns: First-Line Atypical Antipsychotics



C. Hierarchy of Side Effect Concerns: Clozapine



too risky because of the risk of noncompliance to oral medications. For those patients, adding an atypical agent to the depot regimen is a practical way to try to augment the depot response.

- *For patients who refuse to go off their old antipsychotic or refuse to try clozapine.* Sometimes, combination therapy is a second-line alternative when the patient is unwilling or unable to go off of the old antipsychotic medication. Combining antipsychotics is also reasonable when the patient has failed monotherapy with all of the first-line atypical medications and refuses clozapine.

All of these possible indications for long-term combination treatment have in common the fact that the patient either has failed monotherapy or has other problems that prevent a full monotherapy trial.

Inappropriate reasons to use long-term combination antipsychotics. Unfortunately, probably the single most

common reason for combination therapy is poor communication among clinicians. Patients are often discharged from the hospital on combination therapy with the goal that the cross-taper will be completed later by the outpatient clinicians. Given the short lengths of stay these days, discharging patients taking combination antipsychotics is appropriate. However, it is wishful thinking on the inpatient clinician's part that the outpatient service will know to finish the crossover. There has to be a proactive effort at communicating the crossover plan to the outpatient service. Instead, all too often the new medication is dropped,¹⁷ or the combination medication regimen simply is continued as written, leaving the patient in a type of "psychopharmacology purgatory." *Long-term combination therapy is unacceptable when it substitutes for failing to adequately communicate a treatment plan that includes finishing the crossover.*

Another common and inappropriate reason to use long-term combination antipsychotics has to do with shortcuts taken during the crossover period. One example is when the patient shows signs of improvement before the cross-taper is completely finished and the clinician decides to "quit while you are ahead" and not change the regimen any further. Or perhaps there was a symptom flare-up during the cross-taper that responded to restarting the person's old medication. Then, there is a feeling of "let's not rock the boat," and the patient stays on both antipsychotics indefinitely. In these situations, the clinician is taking an easy shortcut without thinking about the long-term problems that come from never really having an adequate trial of monotherapy.

Advantages of long-term monotherapy. Why is the goal of monotherapy important? The long-term advantages of finishing the transition and staying on treatment with a single antipsychotic medication include the following:

- It allows physicians to be better able to judge the long-term effectiveness of the new medication. As there are more medications available now than before, it is more important than ever to determine a person's response to each medication.
- It helps keep the medication regimen simpler. Both doctors and patients can fall into the trap of continually adding medications to the person's regimen. Within a few years, the person can be taking multiple medications, and it can be next to impossible to sort out what is going on.
- The higher risk of tardive dyskinesia with conventional antipsychotics is only reduced if the person is no longer taking any conventional antipsychotic.
- Clinicians need to be mindful of the mess that gets created in terms of medication-induced behavioral toxicities that are intertwined with psychiatric symptoms when medications are continuously added to a regimen.¹⁸

Therefore, the goal of the cross-taper should include finishing the transition, getting off the old antipsychotic, and taking only the new antipsychotic.¹ Generally, a person should be completely off treatment with the old antipsychotic within 3 months of starting the cross-taper.^m Therefore, with few exceptions,ⁿ the goal of switching is to get the patient completely off the old medication and completely on the new medication.

There should be a good-faith effort to have the patient take the new antipsychotic alone. That means eventually ending the overlap period during which the old medication is coprescribed with the new one. If relapse is a major concern, the new medication can be titrated upward and added to the old medication for some time without any lowering of the old medication. Then, the old medication can be tapered down *very* slowly.

To summarize, while there is a role for long-term combination antipsychotic therapy, it should be the exception rather than the rule. Clinicians thinking about adding a second antipsychotic medication to the current medication should make sure that they have optimized the current plan and that there are no other, simpler alternates. Because long-term combination therapy is not considered to be standard practice, clinicians should document their rationale for using combination therapy. Also, when a combination trial is used, the second antipsychotic should be stopped if there is no improvement over and above the previous antipsychotic alone. Remember, the *goal* is monotherapy.

Maintenance Dosing Issues

Problems with EPS and tardive dyskinesia led to considerable research in the 1970s and 1980s on optimizing maintenance dosing of conventional antipsychotics. The fundamental aim of these studies was to develop strategies that maximized relapse prevention without forcing the patient to pay a heavy price in terms of EPS and tardive dyskinesia.¹⁹ Ultimately, the results of these studies showed that for many patients taking the conventional antipsychotics, there is a trade-off between choosing the most effective relapse prevention dose and choosing a dose that offers some relief from the burden of persistent EPS.²⁰ *Because the EPS profile of the newer medications is so much better, there is less pressure to reduce the maintenance doses with atypical antipsychotics compared with conventional antipsychotics.*

One of the most consistent findings in maintenance treatment with the newer medications is that they are more effective in relapse prevention.² The explanation for relapse benefits is not well understood.^{21,22} One possibility is that it is easier to maintain patients taking atypical antipsychotics on optimal relapse prevention doses. One can avoid the dilemma of having to choose between dosing for relapse prevention and dosing for patient comfort. We have found that patients are much more comfortable on high therapeu-

Table 3. Potential Effects of Newer Antipsychotics on Compliance

| |
|--|
| Atypical antipsychotics may improve long-term compliance by causing fewer EPS, which are the most distressing side effects; more effectively treating negative symptoms that cause noncompliance from inability to follow regimen (e.g., disorganization); |
| better controlling positive symptoms, decreasing the likelihood of noncompliance that comes from the effects of a symptom exacerbation; |
| decreasing the "medicated look" and thereby decreasing the person's sense of stigma from taking antipsychotic medication; |
| increasing the enthusiasm for which other people in the person's life support medication compliance |
| Atypical antipsychotics may trigger noncompliance by switching patients from depot to oral route, which may trigger noncompliance for patients unable to comply with oral therapy; successfully treating negative symptoms, thus giving patients more energy to be noncompliant; |
| inability to tolerate painful emotions related to the symptom improvement ^a ; |
| providing better relief of ongoing positive symptoms, which can foster a patient's belief that ongoing antipsychotic medications are no longer needed |

^aThese patients may insist on returning to their previous conventional antipsychotic because the intrapsychic numbness is preferable to the intrapsychic pain.

tic maintenance doses of the newer medications than they are on even lower maintenance doses of conventional antipsychotics. There is some evidence to support this clinical impression. For example, in a large multicenter, random-assignment, double-blind trial comparing maintenance haloperidol and olanzapine, clinicians reduced haloperidol more often than olanzapine.⁷ It appears that the favorable EPS profile of the newer agents moves the risk/benefit ratio back toward higher maintenance doses.

The impact of the newer drugs on long-term compliance has not been well studied. It has been our clinical observation that there may be mixed effects on long-term compliance (see Table 3 for details). Certainly, research on maintenance dosing and on compliance needs to be revisited as atypical agents become standard therapy.

Side Effects Issues

Increasing concern about non-EPS side effects. Another change will be increased attention to other side effects of antipsychotics. As the EPS burden diminishes, the relative importance of other side effects will increase. Persistent EPS will no longer be acceptable. As EPS go into the background, other side effects will be in the foreground. Patients will be more concerned by other side effect problems, such as sedation, weight gain, and sexual disturbances. It will be important to be able to evaluate and treat common side effect concerns of weight gain, sedation, and sexual dysfunction.

Figure 3 shows a model of how patient concerns about antipsychotic side effects will evolve over the next few years as the newer antipsychotics become more routinely used and largely replace the conventional antipsychotics.

Weight gain. Some degree of weight gain is associated with almost all antipsychotic medications, old and new.²³ But the atypical antipsychotic agents are more likely to cause weight gain over and above the older conventional antipsychotics.⁹ Among the currently available atypical antipsychotics, risperidone and quetiapine seem to cause less weight gain than olanzapine or clozapine.²⁴ As the newer atypical antipsychotics replace the older ones, problems from weight gain seem to be replacing EPS as the most common and vexing side effect from antipsychotics. The mechanism for the weight gain is not totally understood, but may be related to the altering of appetite or satiety by serotonin receptors.

Patients should be warned about the possibility of weight gain when switching from an older to a newer medication. For patients who are concerned about weight gain or for whom weight gain may cause medical problems, baseline weight and dietary habits should be noted even before switching. In general, weight gain after switching to a newer agent plateaus within the first 6 months of treatment. Data from fixed-dose olanzapine trials suggest that the amount of weight gain does not correlate with dose, at least between the doses of 5 and 15 mg/day. Thus, dose reductions probably will not be very helpful.

The long-term course of weight gain is not well understood. Although weight gain persists for many patients, for some patients the increased activity and sense of well-being from a new medication can ultimately help the patient lose weight. There may be a lag time of about a year before the secondary health benefits from increased energy and activity become apparent.²⁵

There are a variety of approaches to the management of weight gain. Behavioral approaches include dietary counseling and exercise programs modified to the abilities of patients with schizophrenia. Pharmacologic options include evaluating whether the patient is taking other adjuvant medications causing weight gain that could be discontinued, reviewing the risks and benefits of switching medications again, and adding on another medication to induce weight loss.

- Some patients are taking multiple medications, many of which also cause weight gain. For example, weight gain can be a side effect of mood stabilizers, antidepressants, and anticholinergic medications. After a patient responds to the new antipsychotic medication, it may then be possible to cautiously lower and discontinue any adjuvant medication that also causes weight gain.
- Very little is known about the usefulness of adding other medications to promote weight loss.²⁶ One report found that amantadine, when used as an antiparkinsonian agent, was associated with weight loss.²⁷ Sibutramine is a serotonin reuptake inhibitor that was recently approved for weight

loss for obese patients.²⁸ However, nothing is known about the safety and efficacy of giving sibutramine to psychiatric patients who are taking antipsychotics. Until more is known, adding adjuvants specifically for weight loss should probably be avoided.

- Finally, for persistent problems with weight gain, switching to another antipsychotic medication with fewer weight gain problems (e.g., the conventional antipsychotic molindone²⁹ or, if available, the atypical antipsychotic ziprasidone) can be helpful.³⁰

Sedation. Overall, compared with most conventional antipsychotics, most of the atypical antipsychotics have sedation as a common side effect. Among the atypical agents, sedation is most common with clozapine, and clozapine sedation is most likely to persist over time, with long-term sedation rates on clozapine treatment being approximately 50%.³¹ Sedation is also common when starting olanzapine or quetiapine but, unlike for clozapine, the sedative effects of these medications is more likely to abate over time. Based on our clinical experience, long-term sedation from either olanzapine or quetiapine occurs in about 10% of patients. Risperidone may also occasionally cause persistent sedation, but for other patients may cause insomnia. Ziprasidone is least likely to cause sedation; rather, insomnia seems to be a fairly common side effect, at least in our patient population. Other common causes of daytime sleepiness should be considered, including daytime rebound from caffeine-induced insomnia, psychotic symptoms, or sleep apnea.

Management of sedation depends on several factors, such as when it occurs and whether sedation is a desired or undesired side effect. As mentioned, sedation is often self-limited, occurring when the medication is started or raised. Watchful waiting is quite appropriate. When sedation persists or is intolerable, some straightforward approaches include scheduling most or all of the medication at bedtime or trying various daytime dosage schedules to maximize daytime alertness. If these steps are unsuccessful, sedation is very sensitive to downward dosage adjustments and often responds to a dosage lowering. Using caffeine late in the day to counteract sedation is not recommended because it leads to a vicious cycle of insomnia and daytime sedation. Caffeine should either be discontinued or, more realistically, taken only in the morning. Adding a stimulant medication (either prescribed or over-the-counter) is not recommended. Finally, switching to a less sedating antipsychotic such as a conventional one should be considered for intractable sedation.

When to Switch Again?

Although it sounds obvious, it is important to keep in mind that most patients will continue to suffer from a se-

vere illness despite being on better medications. Otherwise, it is easy to minimize the remaining frustrations and hardships that can happen after the patient adjusts to the improvement from the new medication. Most “responders” are better but suffer from symptoms. Persistent negative symptoms are unlikely to have resolved completely. Persistent positive symptoms may, on occasion, disappear, but for the most part the patient will still have some psychotic symptoms, perhaps with lessened intensity or frequency.

Consider the situation from the patient’s point of view. Part of being human is to be dissatisfied. Initial enthusiasm with the new medication can evolve into frustration over time as the patient adjusts to a new level of functioning and ultimately learns about its limitations. As the frustration mounts, the patient will be asking about other treatments.

There are 4 atypical antipsychotics currently available in the United States (clozapine, risperidone, olanzapine, and quetiapine) and a fifth atypical (ziprasidone) might be available soon. A common clinical question will be “I’m now better on drug X but still have symptoms (or side effects). I have not tried drug Y or Z. Should I switch again?” Few patients have tried all of them, and there are no data on the likelihood of improvement when switching across atypical antipsychotics. When considering this question, the decision needs to be individualized. Often there are no clear-cut answers. Not surprisingly, the approach to making a second switch is similar to that of the previous switch.^P Our research group has added a few modifications when assessing whether to make a second switch with someone who was a clear responder to the previous switch but remains frustrated with ongoing symptoms or side effects:

- It is important for patients to get used to a new baseline level of functioning and not make a second switch too quickly. When there is a clear-cut but partial response, it makes sense to let the person equilibrate to his or her new level of functioning. Then once the response is incorporated into the person’s life, another switch can be considered. It is our impression that it takes at least a year after responding for the person to get oriented to a new baseline, and we usually recommend waiting a year before attempting another medication switch.
- If the patient has already responded to one of the atypical antipsychotics, there may be a ceiling effect with less upside potential for further improvements. At the very least, the patient should be informed that doing better from the previous switch in no way guarantees a successful second switch. In fact, because they are better than they were before their previous switch, the potential risks may be relatively greater.

- The atypical antipsychotics still have some potential to cause EPS. Among the atypical agents, risperidone is the most likely to cause EPS and clozapine the least likely.³² The specific ordering of EPS liability is risperidone > olanzapine > quetiapine > clozapine. Therefore, when switching patients who have clinically significant EPS despite being treated with an atypical antipsychotic, it makes sense to try to choose an antipsychotic with less EPS liability than the current medication that is causing the EPS.
- For problems with persistent weight gain, it seems that ziprasidone will be the atypical antipsychotic of choice for patients who develop medically serious complications of obesity.

One factor that makes a second switch easier is that the patient has already had experience with switching. Therefore, the patient will be more familiar with the switching process, and the switching process can be reviewed on the basis of the past experience. However, patients should be told that future switching may still be different (easier or more difficult) than the one beforehand.

LONG-TERM PSYCHOLOGICAL ISSUES

Many of the long-term psychological issues are identical to those discussed in the earlier section on assessing psychological responses. We will briefly cover a few other selected long-term issues here involving changes in self-perception, self-awareness, and the recovery process.

Better Self-Image From Fewer EPS

EPS are visible. Other people notice them. People may not know the technical names, but will know enough to connect the motor signs of EPS they see (e.g., “Thorazine shuffle”) with strong psychiatric medication. Until recently, the visibility of EPS often made it obvious that the person was being treated for a mental disorder.

Patients are aware that they look different when they have EPS. They know that others can tell they are in treatment for a severe mental illness. Of course, there are other visible differences such as poor hygiene that can identify someone as mentally ill. But, even when these factors are present, there can be striking changes in appearances as the EPS from an atypical antipsychotic resolve. Our group has noted some remarkable improvements in self-image and confidence in patients who were previously embarrassed by their “medicated look.”

Sexuality and Intimacy Issues

Keep in mind that there may be an increase in the patient’s sexuality after responding to the new medication. Women who choose to switch their medications because of amenorrhea often do so out of issues related to their

self-image of femininity and fertility. Return of menses may be interpreted by the woman that she is emotionally ready for a relationship or pregnancy. These wishes should be explored in a way that reaffirms the legitimacy of these wishes on the one hand, while on the other also trying to help guide the patient away from impulsive or reckless sexual behavior.

Increased Psychological Mindedness

As cognitive functioning improves and symptoms abate, patients may become increasingly psychologically minded. They may be more attuned to their own internal emotional state and may be more motivated to reveal their inner emotional lives to their friends, family, or mental health clinicians. These psychological changes seem to be delayed and happen long after other symptoms improve, and they seem to develop gradually. Once noticed, such a shift in psychological mindedness can take other people by surprise. Mental health clinicians need to consider re-orienting their therapeutic technique(s) as the patient is better able to report emotional issues, consider psychological alternatives, and participate more fully in a therapeutic process. For example, while one patient was taking conventional antipsychotics, her psychotherapy consisted of discussing concrete steps she needed to take to get a job and make friends. One year after switching medications, she improved to the point where she was working full-time, but also got involved in an "unhealthy" romantic relationship. The therapy had to shift away from concrete, directive advice and focus more on other difficult relationships she had with men before she became ill. Although analytically oriented psychotherapy is generally not appropriate in schizophrenia,³³ it is important to stay flexible enough to adapt any ongoing therapy to the psychological changes that can happen as patients continue to respond to their new medication.

When Positive Symptoms Recur

This section considers the problem of when a patient experiences a recurrence of positive symptoms well after having a dramatic symptom improvement. To simplify the discussion, let us assume that the symptom exacerbation is not a full relapse, and that the patient is cooperative, compliant, and otherwise doing better on the newer medication.

A recurrence of symptoms after a long period of remission can be a devastating emotional experience for a patient who is hoping that his or her new medication has "cured" the illness. The psychotic symptoms are often relatively mild and transient (at least when compared with the patient's symptoms prior to switching). The emotional reaction is often based not so much on the severity of the current symptom per se but more on what a symptom recurrence portends for the future. A comparable reaction in a medical situation might be the fearful reaction that oc-

curs when someone with a history of breast cancer finds a new lymph node. Even if the lymph node is probably benign—for example, it appeared after a flu—the anxiety can be overwhelming until the uncertainty is resolved. Reassurance becomes an important message: it is very important for patients to know that symptom recurrence does not mean that the new medication has stopped working, or that the patient is back to "Square 1." Instead, the clinician needs to acknowledge that such a symptom exacerbation is disappointing but is usually a part of the fluctuating nature of the illness.

DISCUSSION

Limitations

The reader needs to keep in mind that there are significant limitations inherent in this kind of clinical reporting, including potential biases in the accuracy and interpretation of our clinical observations, as well as limitations in generalizability due to the use of a local patient sample receiving their psychosocial treatments within the confines of the ecology of our treatment service setting.

Another cautionary note is to be aware that none of these observations are new and are not restricted solely to response to the atypical antipsychotics. What is different is the frequency and magnitude of these changes because of a cohort effect. Just as society has to prepare for the cohort of aging baby boomers, the mental health treatment system needs to prepare for a cohort of schizophrenia patients who have responded in ways that were unimaginable a decade ago.

CONCLUSION

The new antipsychotic medications are now widely used and are rapidly becoming the de facto standard pharmacologic treatment for schizophrenia. This article reviewed some common psychopharmacologic and psychological issues that arise after an outpatient with schizophrenia is switched to one of the newer antipsychotics. Psychopharmacologic issues that come up after switching include assessing the medication response, managing unsatisfactory responses, finishing the cross-taper to get the patient to monotherapy, and knowing when to consider switching again.

For many patients, switching to a new medication can lead to remarkable improvements—improvements that often create their own psychological challenges. As patients attempt to cope with the profound inner and external changes that come with better symptom control, they can experience a number of psychological reactions. Clinicians need to be able to identify and help patients cope with these reactions to help make it through these transitional life adjustments in a safe and maturing way. Some other aspects of the psychological effects will appear later on. These

include improvements in self-image from being less visibly mentally ill and coping with fear and demoralization engendered by stress-induced symptom exacerbations.

As these changes evolve, our mental health systems will have to change to better meet these patients' needs. Mental health clinicians need to be prepared to deal with patients who are improving and are becoming more demanding as a result of their improvements. We will need to be able to help patients who dramatically respond to a new medication regain their autonomy and independence.

Drug names: amantadine (Symmetrel), clozapine (Clozaril), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), pimozone (Orap), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia).

NOTES

- a. At the time of this article (September 1998), ziprasidone has not yet been approved.
- b. The previous article on switching antipsychotic medications¹ reviewed other, more common causes of transient symptom exacerbation that usually happen early (e.g., first few weeks) during the crossover process. This section covers more complicated clinical presentations that usually happen later on, after the crossover is completed.
- c. In contrast, sometimes depressive symptoms increase when there is an acute psychotic episode. When this happens, the depressive symptoms are part of an acute episode and should not be treated with antidepressants.
- d. One might ask whether the risk of postpsychotic depression nullifies any potential gain from switching to atypical antipsychotics. Fortunately, research on this question shows that, in the long run, the atypical antipsychotics are better than the conventional antipsychotics for treating depressive symptoms. For example, a rigorous study on the epidemiology of suicide among clozapine-treated patients showed that the risk of suicide was much lower during periods of clozapine treatment.¹⁰
- e. Recall that potential drug-drug interactions may occur when adding an antidepressant to an antipsychotic.
- f. Exceptions include patients previously treated with long-acting depot preparations (for whom signs of antipsychotic-induced parkinsonism can take up to 6 months to resolve), patients with parkinsonism from other causes, and elderly patients.
- g. Using more than 1 antipsychotic (combination antipsychotic) for long-term maintenance treatment of nonresponsive patients is not recommended unless the patient is known to be refractory to several trials of monotherapy and has either failed or refused a clozapine trial.
- h. Table 4 is not meant to be exhaustive. It does not cover adding adjunct therapies because adjuncts are increasingly considered to be second-line for treatment nonresponse in schizophrenia (see reference 12). It also does not cover the use of electroconvulsive therapy (ECT) because ECT is rarely used in outpatient settings. Combination antipsychotic therapies are becoming increasingly popular but are not included in this table. See text in the next section for a more detailed discussion of combination antipsychotic therapy.
- i. Specifically, we are not considering in this discussion the temporary overlap period when switching from one antipsychotic to another. Also, occasional use of a second antipsychotic for p.r.n. use or insomnia does not really represent a combination antipsychotic approach. Finally, this discussion does not pertain to simultaneous use of different classes of psychotropic agents, such as combining an antipsychotic with a mood stabilizer.
- j. This recommendation is speculative.

- k. Expert clinicians use a variety of different agents, including low doses of high-potency conventional antipsychotics, pimozone, low doses of depot therapy, and the other atypical antipsychotics.
- l. This transitioning to one antipsychotic does not mean that the person should quit the other psychiatric medications he or she is taking. In most instances, these medications will continue to be prescribed for some time after the antipsychotic medications have been changed.
- m. Going off clozapine treatment is an exception for which the cross-taper can take as long as 6 months.
- n. Like most generalizations, there are some exceptions. Long-term combinations of antipsychotic medications may be appropriate for (1) patients who respond to clozapine but cannot tolerate high doses of clozapine; (2) patients who require depot antipsychotic therapy for compliance reasons but might benefit from the addition of an atypical antipsychotic; or (3) patients who have clearly failed several antipsychotic trials, including depot therapy and clozapine.
- o. The atypical antipsychotic ziprasidone seems to be the exception. Unlike the other atypical antipsychotics, ziprasidone is not associated with clinically significant weight gain.
- p. These recommendations assume that there have been unsuccessful attempts at optimizing the current atypical regimen.

REFERENCES

1. Weiden P, Aquila R, Standard J, et al. Switching antipsychotic medications. *J Clin Psychiatry* 1997;58(suppl 10):63–72
2. Weiden P, Aquila R, Standard J. Atypical antipsychotic drugs and long-term outcome in schizophrenia. *J Clin Psychiatry* 1996;57(suppl 11):53–60
3. Keck P, Cohen B, Baldessarini R, et al. Time course of antipsychotic effects of neuroleptic drugs. *Am J Psychiatry* 1989;146:1289–1292
4. Carpenter W, Conley R, Buchanan R. Patient response and resource management: another view of clozapine treatment of schizophrenia. *Am J Psychiatry* 1995;152:827–832
5. Schiller L, Bennett A. *The Quiet Room: A Journey Out of the Torment of Madness*. New York, NY: Warner Books; 1994
6. Pickar D, Labarca R, Doran A, et al. Longitudinal measurements of plasma homovanillic acid levels in schizophrenic patients. *Arch Gen Psychiatry* 1986;43:669–676
7. Tollefson GD, Beasley CM Jr, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997;154:457–465
8. Walker A, Lanza L, Arellano F, et al. Mortality in current and former users of clozapine. *Epidemiology* 1997;8:671–677
9. Drake R, Cotton PG. Depression, hopelessness and suicide in chronic schizophrenia. *Br J Psychiatry* 1986;148:554–559
10. Drake R, Gates C, Whitaker A. Suicide among schizophrenics: a review. *Compr Psychiatry* 1985;26:90–100
11. Siris S, Morgan V, Fagerstrom R, et al. Adjunctive imipramine in the treatment of postpsychotic depression. *Arch Gen Psychiatry* 1987;44:533–539
12. McEvoy J, Weiden P, Smith T, et al. The Expert Consensus Guideline Series: Treatment of Schizophrenia. *J Clin Psychiatry* 1996;57(suppl 12B): 2–59
13. Lieberman J, Saltz BL, Johns CA, et al. The effects of clozapine on tardive dyskinesia. *Br J Psychiatry* 1991;158:503–510
14. Jeste D, Wyatt R. *Understanding and Treating Tardive Dyskinesia*. New York: Guilford; 1982
15. Weiden P, Scheifler P, Diamond R. My patient is better: now what? part I: managing psychological reactions. *J Practical Psychiatry Behav Health* 1998;4:175–181
16. Duckworth K, Nair V, Patel J, et al. Lost time, found hope and sorrow: the search for the self, connection, and purpose during “awakenings” on the new antipsychotics. *Harv Rev Psychiatry* 1997;5:227–233
17. Luchins D, Malan R, Hanrahan P, et al. Continuity of medication in a mental health system. In: *New Research Program and Abstracts of the 142nd Annual Meeting of the American Psychiatric Association*; May 20, 1997; San Diego, Calif. Abstract NR218:127
18. Preskorn S. Do you believe in magic? *J Practical Psychiatry Behav Health* 1997;3(2):99–100

19. Schooler NR. Maintenance medication for schizophrenia: strategies for dose reduction. *Schizophr Bull* 1991;17:311–324
20. Schooler NR, Keith S, Severe J, et al. Relapse and rehospitalization during maintenance treatment of schizophrenia: the effects of dose reduction and family treatment. *Arch Gen Psychiatry* 1997;54:453–463
21. Essock S, Hargreaves W, Covell N, et al. Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacol Bull* 1996;32:683–697
22. Rosenheck R, Cramer J, Xu W, et al. A randomized trial of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. *N Engl J Med* 1997;337:809–815
23. Stanton J. Weight gain associated with neuroleptic medication: a review. *Schizophr Bull* 1995;21:461–472
24. Allison D, Mentore J, Heo M, et al. Weight gain associated with conventional and newer antipsychotics: a meta-analysis. Paper presented at the annual meeting of the Collegium Internationale Neuropsychopharmacologicum; 1998; Glasgow, Scotland
25. Emanuel M, Dalheim L, Aquila R, et al. Weight gain and atypical antipsychotics. Paper presented at the annual meeting of the New Clinical Drug Evaluation Unit; 1998; Boca Raton, Fla
26. Silverstone T. The place of appetite-suppressant drugs in the treatment of obesity. In: Stunkard A, Wadden T, eds. *Obesity: Theory and Therapy*. New York: Raven Press; 1993:275–285
27. Correa N, Opler L, Kay S, et al. Amantadine in the treatment of neuroendocrine side-effects of neuroleptics. *J Clin Psychopharmacol* 1987;7:91–95
28. Bray G, Ryan D, Gordon D, et al. A double-blind randomized placebo-controlled trial of sibutramine. *Obesity Res* 1996;4:263–270
29. Clark ML, et al. Molindone in chronic schizophrenia. *Clin Pharmacol Ther* 1970;2:668–688
30. Tandon R, Harrigan E, Zorn S. Ziprasidone: a novel antipsychotic with unique pharmacology and therapeutic potential. *J Serotonin Res* 1997;4: 159–177
31. Lauriello J, Laframboise D, Paine S. Prevalence of persistent clozapine induced sedation (CIS) and the effect on treatment [abstract]. *Schizophr Res* 1997;24(March)
32. Casey D. Side effect profiles of new antipsychotic agents. *J Clin Psychiatry* 1996;57(suppl 11):40–45
33. Stanton AH, Gunderson JG, Knapp PH. Effects of psychotherapy in schizophrenia. I: design and implementation of a controlled study. *Schizophr Bull* 1984;10:520–563

DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their clinical estimation, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.