Rational use of Atypical Antipsychotic Medications

The purpose of this series, *Putting Evidence Into Practice*, is to give physicians and their staff the information necessary to ensure quality and effective drug therapy. This monograph presents a snapshot of relevant findings in the area of atypical antipsychotic medication use.

Identifying the appropriate medication regimen for the treatment of psychotic disorders is only half the challenge. Effective therapy also depends on the willingness of the patient to adhere to the treatment regimen long after the symptoms associated with the illness have abated. This is the reason why ongoing communication between doctor and patient is vital. We believe that informed patient participation is the cornerstone of effective treatment and we encourage you and your patients to work together to plan and implement an effective and sustained treatment program.

When should atypical antipsychotic medication be used?

Antipsychotics are used to treat symptoms associated with schizophrenia, bi-polar and related psychotic disorders. Conventional antipsychotic medications, referred to as *neuroleptics* were first introduced in the early 1950's. Neuroleptics include: chlorpromazine (Thorazine), fluphenazine (Prolixin), haloperidol (Haldol), loxapine (Loxitane), molindone (Lidone, Moban), perphenazine (Trilafon), thioridazine (Mellaril), thiothixene (Navane), and, trifluoperazine (Stelazine). Although neuroleptic medications are generally successful treating the symptoms of schizophrenia, patients sometimes report and physicians sometimes observe unpleasant side effects.

Newer antipsychotic medications, referred to as *atypical antipsychotics* were first introduced in the 1990's. Atypical Antipsychotics include: aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon). While no medication is side effect free, the *atypicals* appear to have fewer extrapyramidal side effects and less tardive dyskinesia than do their predecessors, the neuroleptics. However, some of the atypicals have been associated with weight gain, changes in lipids and the development of diabetes mellitus (FDA September 2003). Despite these possible side effects, the atypical antipsychotics are first-line drugs in the treatment of schizophrenia and schizoaffective disorders. The FDA recently approved olanzapine, quetiapine and risperidone for treatment of bipolar disorder.

When should antipsychotic medication be changed?

A medication may not effectively control associated symptoms for every patient. In fact, some patients may need to try several antipsychotic medications before finding the one that works best for them. However, before terminating a medication due to a perceived lack of response, it is important to ensure that the medication in question is given an adequate trial period in which to work and that the patient is adhering to the prescription. If medication is not taken under recommended conditions it will be impossible to judge its efficacy. Therefore, before terminating a medication that may not appear to be

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working, the doctor and patient should ensure that the medication is taken at the maximum tolerated recommended dosage and the trial period is long enough to recognize its therapeutic effects. Similarly, care should be taken to ensure that side effects associated with the medication are tolerable or cannot be controlled with additional medications to counteract their impact, because patients will find it difficult to adhere to the treatment regimen with intolerable side effects.

1. **Duration**: Because medications require minimum time periods in which to work it is important to ensure that all new medications are given adequate trial periods, provided the side effects are tolerable. This is particularly important since the goal is to ensure that medications are not discarded before they have an opportunity to demonstrate efficacy. For patients in an **acute exacerbation** of psychosis, improvement sufficient to relieve negative and positive symptoms of their illness associated with risk of harm to self or others, as well as provide discernable improvement to the patients comfort, should be observed after **treatment at a therapeutic dose level for one week**. Patients who have not shown discernable improvement from a therapeutic dose level during this time period are not likely to show significant response and should be switched to a different medicine. For patients who show some but not significant improvement**,** the trial period should be continued for **10 days to two weeks after treatment at a therapeutic dose level**. If no significant response is observed after this time the patients' illness can be considered non-responsive to the particular treatment prescribed. On the other hand, if satisfactory partial response is observed within this period, the trial period should be extended to four weeks.

2. **Dosage:**

   The following chart provides current FDA recommended dosage ranges for adults for atypical antipsychotic medications. Please note that the **low strength dose levels are the therapeutic minimums**. Practitioners report that in their experience the **therapeutic dose level** for patients with **acute exacerbation** of schizophrenia and related psychotic disorders is **at a higher strength per day**.

Drug Name Generic (Brand)	FDA Low Strength per Day	FDA High Strength per Day
aripiprazole (Abilify)	10 mg	30 mg
clozapine (Clozaril)	100 mg	900 mg
olanzapine (Zyprexa)	5 mg	20 mg
quetiapine (Seroquel)	150 mg	800 mg
risperidone (Risperdal)	1 mg	6-8 mg (age dependent)
ziprasidone (Geodon)	40 mg	160 mg

3. **Side effects:** Side effects are important to consider because side effects impact the patient's quality of life and adherence to the medication regimen. *Atypical Antipsychotic* medications appear to have fewer extrapyramidal side effects and less tardive dyskinesia than do their predecessors, the neuroleptics. However, these side effects might occur, and an evaluation for these symptoms should be conducted every six months. If a patient has difficulty tolerating a specific drug, he or she will be far less willing to take it. Most importantly the side effects of some medications, among which are atypical antipsychotics, include serious physical illnesses. One example of such a side effect is diabetes, related to use of atypicals. Please review the sections below on metabolic and cardiovascular risks of antipsychotic medications.

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In summary, prior to terminating a trial drug period consider asking three questions:

- Has the patient taken the medication for a long enough period of time to recognize its therapeutic effects?
- Has the patient taken the medication at the recommended, therapeutic dosage level?
- Are the medication side effects tolerable or do the medication side effects require multiple, additional medications to counteract their negative impact?

What metabolic issues should be considered when treating patients with antipsychotic medications?

Patients with schizophrenia are at greater risk for heart disease and diabetes. Additionally, some antipsychotic medications pose increased risk for weight gain, high cholesterol, high triglycerides and type II diabetes. Therefore, it is suggested that before initiating treatment, fasting glucose and lipids be established. The Body Mass Index (BMI) should also be calculated, and monitored every visit for six months and quarterly thereafter. Fasting glucose and lipids should be obtained quarterly for one year and then every six months, thereafter. Patients should also be educated on the symptoms of ketoacidosis. In September 2003, the FDA issued an advisory indicating metabolic risks associated with the atypical antipsychotic class of medications.

What cardiac issues should be considered when treating patients with antipsychotic medications?

Some drugs used to treat schizophrenia prolong the QT interval, a condition associated with the increased risk of life threatening arrhythmias. In their review, Al-Khatib, SM, Allen, NM, LaPointe, A, Kramer, JM, Califf, RM. (2003), state that thioridazine (Mellaril) was deemed by experts to have a very probable potential for causing QT prolongation and chlorpromazine (Thorazine), haloperidol (Haldol), olanzapine (Zyprexa), risperidone (Risperdal), and ziprasidone (Geodon) have a probable potential for causing QT prolongation. These medicines should not be prescribed to patients taking other medicines that are known to prolong the QT interval. Baseline and post-treatment ECGs are recommended for these patients and with the addition of medications that may increase the plasma concentration of the antipsychotic (e.g., the addition of fluvoxamine to olanzapine). Finally, chlorpromazine (Thorazine), pimozide (Orap), haloperidol (Haldol), mesoridazine (Serentil), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril), and ziprasidone (Geodon) should be avoided in patients with congenital long QT syndrome (See: The University of Arizona Health Sciences Center http://www.torsades.org/medical-pros/drug-lists/drug-lists.htm#). TMAP also provides good guidance on these matters. The information concerning potential risks associated with this class of medications should be discussed with patients in deciding their long-term course of treatment. Please see the FDA prescribing information for these medications for more information.

When should more than one atypical antipsychotic medication be used?

There is little evidence to suggest that combining atypical antipsychotic medications results in any therapeutic gain. Rather, because increased side effects are likely as additional medications are introduced and because the benefits associated with adding psychoactive medications are questionable, monotherapy is recommended for all but the patients with illness that is not responsive to a therapeutically adequate dose of a single

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antipsychotic medication. In these cases, physicians should first establish that the lack of response is not due to poor adherence, before combining typical and atypical antipsychotics, as provided for in TMAP.

If the patient does not respond to the initial antipsychotic medication at an adequate dosage and duration, the second antipsychotic medication should be introduced as the first is being tapered. When switching from one atypical to another there is the risk of assuming that the *combination* of medications and not the *new* medication resulted in improvement. However, it is not possible to make such a conclusion without first tapering the initial medication. Once the initial medication is fully tapered, there should be sufficient evidence to evaluate monotherapy as the preferred course of treatment. Please note that monotherapy can be both clinically and cost effective.

The Need to Know: Questions for the patient/doctor exchange

As noted above, effective therapy depends on the willingness of the patient to adhere to a prescribed treatment regimen long after the symptoms associated with the illness have abated. Fostering communication between the patient and doctor is essential in order to address patient concerns and thus maximize treatment adherence. Presented below is a list of questions that patients might ask their doctors in order to better understand their illness and options.

1. What factors influenced the doctor's decision to prescribe this particular antipsychotic medication?
    a. What is schizophrenia, schizoaffective or bipolar disorder? What is my diagnosis? Why do I have it?
    b. What symptoms is the doctor treating with this medication?
    c. Why does the doctor think that this is the best medication for me?
    d. How can I find out more about my illness and my prescribed medication?
2. What if this medication isn't compatible with my lifestyle?
    a. I may have a hard time remembering to take this medication; are there things I can do to help me remember to take it? Are there other medications I can take instead?
    b. Why is it important to take the medication as prescribed? If I miss a dose, what effect will the missed dose have on me? What should I do if I forget to take my medication? Should I take more if I become symptomatic?
    c. I'm uneasy about taking this medication. What will happen if I refuse to take it?
    d. How long will it take for this medication to start working?
    e. If I start feeling better, can I stop the medication?
3. How will I feel after I begin taking the medication?
    a. What changes should I expect once I start taking the medication?
    b. If the medication makes me feel bad, what should I do?
    c. If the medication doesn't work, are there other medications I can try?
    d. If I have any questions after I start taking this medication, whom can I call?
    e. What are side effects I should be aware of?
    f. Can I just stop the medicine?
    g. How will this interfere with other medications and herbal products that I am taking?

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References

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