

## An Overview of Treatment of Schizophrenia with an Emphasis on Pharmacotherapy: Administration, Efficacy, and Side Effects.

This may be particularly useful for clinicians who have had limited experience with treating schizophrenia or who wish to compare their accustomed methods with those recommended by the IPAP Board. Levels of evidence (A,B,C) are indicated after each statement when appropriate.

### A. Medications

#### General Principles

1. Patients with schizophrenia should (with very few exceptions) be treated with an antipsychotic medication.(A)
2. Identification and administration of the lowest dose of antipsychotic medication that produces optimal outcomes, promotes relapse prevention, and causes the fewest extrapyramidal side effects, metabolic side effects, and sedation.(A)
3. Psychosocial interventions work synergistically with medication to optimize treatment adherence and successful community living.(A)
4. Regular and ongoing evaluations of subjective and objective response and side effects are equally necessary.(A) Standardized rating scales such as the GAPS may be useful tools for baseline and later assessments.
5. Medications must be individualized, because individual response is highly variable. Consider the history of treatment including efficacy and side effects, the stage of illness (the first episode usually requires a lower dose), age (elderly persons require a lower dose), gender (premenopausal women often require a lower dose).(A)
6. Throughout the duration of treatment, patients must be informed of, and evaluated for, the risks and benefits both of their current drug therapy, new options, and of not having drug therapy.
7. Uncomplicated drug regimens (for example, dosing once daily) promote adherence to treatment.(A)
8. Long-acting injectable formulations are preferred for non-compliant patients.(A)

#### The Acute Phase

##### *General Principles*

1. Assess the patient for danger to self or others to decide on optimal drug choice and to determine the treatment setting.
2. Patients may relapse even when taking previously effective doses of antipsychotic medications as prescribed; do not assume medication nonadherence is the cause of relapse.(A)
3. Parenteral formulations of the second-generation drugs are now available for rapid emergency control of the acutely psychotic, agitated patient. Note that intramuscular, short acting ziprasidone and olanzapine are now approved in some countries. The available data on their efficacy and safety compared to IM haloperidol and lorazepam for acute management are encouraging but further evidence for their cost-effectiveness in the short and long term

are needed before endorsing them as preferred treatment over the standard treatment of IM haloperidol combined with IM lorazepam.(B)

4. Ideally the patient should be started on the medication that will be continued into the stabilization phase to minimize the number of medication switches required.(C) However, if IM haloperidol is used in the acute phase, it is preferable to switch to an atypical antipsychotic when oral medication is acceptable(A) or perhaps to a long acting injectable atypical agent.(C)
5. If the reason for a switch is to reduce EPS, it may be useful to prevent worsening of the EPS to maintain treatment with any antiparkinsonian medication until the severity of the EPS has lessened due to the switch.
6. Concomitant benzodiazepine administration can decrease the dose of antipsychotic necessary to control acute behavioural disturbance.(B)
7. Rapid high-dose antipsychotic treatment is almost never warranted. Haloperidol has been reported to produce torsades de pointes.

### **The Stabilization Phase**

#### *General Principles*

1. The medication of choice for the stabilization phase should be an antipsychotic that provides optimal efficacy and tolerability. The goals of pharmacotherapy in this phase are to reduce the intensity and duration of active psychotic symptoms as fully as possible, to improve cognition and negative symptoms, to minimize side effects, and to promote adherence.
2. Avoid polypharmacy with multiple antipsychotics.(C)
3. Medications selected for short-term control of agitated behavior during the acute psychotic phase may not meet the above criteria for optimal efficacy and tolerability.(A)
4. Drugs used for short-term control of agitation (for example, high-potency antipsychotic and sedative hypnotic) can be used as necessary during titration of a better tolerated antipsychotic that is chosen for longer-term use.(B)
5. Adjust the dose to the individual within the given range for each medication.(A)
6. Significant and sustained reduction in acute psychotic symptoms often takes 4-8 weeks. Be patient before raising dosage beyond the optimal dose range. Improvements in other symptoms and functioning may take much longer; improvement may continue over 1 year or more of uninterrupted treatment.(A)
7. Rapidly escalating to high doses of antipsychotic medication during this phase places the patient at risk for adverse events and does not speed recovery.(A)
8. Premature discontinuation or reduction of antipsychotic medication during this phase places the patient at high risk for relapse.(A)

## **The Stable Phase**

### *General Principles*

1. Over the longer term, treatment must aim for improvements beyond relapse prevention, including minimizing negative and comorbid symptoms and promoting maximal functional ability.(A)
2. There is individual variability in the antipsychotic dose required to achieve functional recovery with minimal side effects.(A)
3. In this phase it is crucial to engage and assist the patient to participate in the drug treatment and to address individual barriers and resistance to ongoing therapy.(A)
4. Assessments must take place regularly to achieve optimal doses and choice of antipsychotic medications and to monitor for drug-induced side effects.
5. Intermittent drug therapy, with monitoring for and targeting of emergent prodromal symptoms, is not recommended.(A)
6. There are no predictive factors indicating which patients can be safely and permanently discontinued from antipsychotic medication. This is true for 1<sup>st</sup> episode as well as chronic patients.
7. Treatment with more than 1 antipsychotic medication is only recommended during transitions from one drug to another. There is no well-replicated evidence to support multiple drug use in cases of insufficient efficacy or reduced tolerability.(C)

## **B. Side Effects**

### **General Principles**

1. Antipsychotic drugs are, for the most part, safe drugs; however, they may cause multiple side effects that can have an adverse impact on the patient's ability and willingness to adhere to treatment.(A)
2. Side effects are a "cost" of antipsychotic treatment that must be monitored throughout treatment.(A)
3. Side effects are not constant over the course of treatment; some (for example, acute dystonia) are more likely in the short term and some (for example, tardive dyskinesia) in the longer term.(A)
4. The patient's perception of the severity and importance of a side effect is a crucial component of side effect evaluation.(A)

### **Extrapyramidal Side Effects (EPSE)**

#### *General Principles*

1. Neurological movement disorders, both acute and chronic, are among the most common and problematic adverse effects of treatment with antipsychotic drugs.(A)
2. Treatment with amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone (at lower doses) or ziprasidone reduces acute EPSE compared to doses of haloperidol  $\geq 10$  mg/day.(A)

3. Clozapine is not associated with the development of tardive dyskinesia. The other second-generation drugs also may produce fewer long-term movement disorders; not enough long-term data exist to state this definitively.(B)
4. Individual patients may present with both acute and chronic extrapyramidal symptoms and signs;(A) for descriptions and differential diagnosis see the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*: “Medication-Induced Movement Disorders”.

### **Metabolic and Cardiovascular Side Effects**

1. Metabolic side effects may occur in some patients treated with antipsychotic drugs. These include glucose dysregulation, leading to type II diabetes or difficulty in managing previously controlled type I or II diabetes mellitus, weight gain, abdominal adiposity, increased triglycerides, and increased total cholesterol and LDL cholesterol.(A)

Clozapine and olanzapine appear to be particularly likely to cause weight gain. Intermediate effects have been reported with quetiapine, and to a lesser extent, risperidone. Ziprasidone and aripiprazole appear to be the least likely to produce weight gain.(A) 3. creased rates of diabetes mellitus appear to be most common with clozapine and olanzapine. The other atypicals antipsychotic drugs appear to be safer in this regard.(A)

Triglycerides and cholesterol measures are more likely to be increased with olanzapine and clozapine than with risperidone, aripiprazole, and ziprasidone. Moderate increases are seen with quetiapine.(B)

2. Monitoring of patients for glucose dysregulation and lipid increases should occur on a regular basis for patients treated with clozapine and olanzapine.(A) The frequency depends on the findings. This will be discussed in detail elsewhere. The American Diabetes Association recommends the following at the time of initiating treatment with all atypical antipsychotics: Obtain a personal and family history relevant to diabetes, weight and height to measure body mass index (BMI), waist, blood pressure, fasting blood glucose and fasting lipid levels. BMI should be remeasured at month 1 and 2. At 3 months, determine BMI, blood pressure, fasting blood glucose and lipids. Repeat BMI quarterly. After a year, measure waist, blood pressure, glucose and lipids.

### **Other Cardiovascular Issues**

1. A greater rate of sudden death due to myocardial infarctions or arrhythmias is characteristic of schizophrenia and is increased by antipsychotic drugs.(B)
2. An EKG and lipid profile should be part of the workup of patients started on antipsychotic drugs who have any risk factors for cardiovascular disease.(A)
3. Thioridazine, mesoridazine, and ziprasidone are known to increase the QTc interval. These three drugs should not be used with other drugs that also increase the QTc interval.(B)
4. No baseline measurement of the QTc interval is required before initiating treatment with ziprasidone, but the package insert says do not use ziprasidone if the QTc is over 500 ms.