Organizational Structure

Medical Center Chief II
Chief, Medical and Professional Staff
(Hospital Service)
Chief, Medical and Professional Staff
(Community Service)

Treatment Protocol Committee
(Schizophrenia)

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Algorithm for the Treatment of Schizophrenia

1. Characteristic Symptoms

2. History and Physical Examination

3. Is patient manageable?
   - Y: Choose medication from group 1 or 2, except clozapine
   - N: Go to #7

4. Highly Disturbed

5. Adequate response?
   - Y: Continue medication
   - N: Go to #8

6. Intolerable side effects?
   - Y: Choose another medication from group 1 or 2, except clozapine
   - N: Go to #5

7. Rapid Neuroleptization

8. No improvement

9. Hospitalization

10. Adequate response; No intolerable side effects

11. Increase dosage

12. Adequate response?
   - Y: Continue medications
   - N: Choose another medication from group 1 & 2. May start on clozapine

13. Refer to Psychiatrist

14. Improved?
   - Y: Go to #4
   - N: Hospitalization

15. Not improved

16. Hospitalization

17. Continue medications

18. Refer to Psychiatrist

19. CPM 9th EDITION

20. Adequate response?
   - Y: Continue medications
   - N: Go to #16

21. Hospitalization

22. Adequate response?
   - Y: Continue medications
   - N: Refer to Psychiatrist

23. N

24. N
Guidelines in the Treatment of Schizophrenia

I. Definition

A clinical syndrome characterized by profound disruption in cognition and emotion, affecting the most fundamental attributes: language, thought, perception, affect, and sense of self. The manifestation combine in various ways, creating cumulative effect of the illness can be severe and long lasting.

II. Epidemiology

Lifetime Prevalence: 0.9 - 11.0 cases per 1,000 population
Sex: Equally prevalent in men and women
Age: Men - between 15 and 25 years of age
Women - between 25 and 35 years of age

About 90% of the patients in treatment for schizophrenia are between 15 and 55 years old

Birth and Fetal Complications: Schizophrenic persons as a group experience a greater number of birth complications, especially male infants. Studies have also reported a relationship between perinatal complications and early onset of disease, negative symptoms, and poorer prognosis.

The reason for the increased risk is unknown but the following plausible explanations guide present day research.

1. The genes that create vulnerability for schizophrenia may also alter early embryonic development in a manner that increases the likelihood of gestational and birth complications.
2. Hypoxia: components of the limbic system, the cerebral cortex and the basal ganglia brain regions most frequently implicated, as deviant in schizophrenia are among the areas in the developing brain most susceptible to the adverse effects of hypoxia.

Social Class: Studies report a higher prevalence rate among members of lower social class than upper social class. This would imply that socioeconomic factors found at lower socioeconomic levels are a cause of schizophrenia. Another implication is that a low socioeconomic status is a consequence of the disorder.

III. Etiology

A. Major Biochemical Theories

• The evidence for the role of dopamine, especially dopamine excess remains a viable explanation for the development of the symptoms
• Recent reports have implicated serotonin hyperactivity as well in relation to the suicidal and impulsive behavior seen in schizophrenic patients.
• Other neurotransmitters such as norepinephrine and GABA have been implicated but are still inconclusive.

B. Major Neuroanatomical Theories

• Delineation of the mesolimbic and mesocortical dopaminergic pathways in the brain led to the hypotheses postulating the involvement of the limbic system, the frontal cortex, or both on the pathophysiology of schizophrenia.
• Also implicated are the basal ganglia - thalamocortical neural circuits.

C. Genetic Hypotheses

• Schizophrenia manifestations occur at an increased rate among the biological relatives of patients with schizophrenia and that the likelihood of the correlation with the closeness of the relationship.
• Prevalence of schizophrenia in specific populations:

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontwin sibling of a schizophrenic patient</td>
<td>8.0</td>
</tr>
<tr>
<td>Child with one schizophrenic parent</td>
<td>12.0</td>
</tr>
<tr>
<td>Dizygotic twin of a schizophrenic patient</td>
<td>12.0</td>
</tr>
<tr>
<td>Child of 2 schizophrenic patient</td>
<td>40.0</td>
</tr>
<tr>
<td>Monozygotic twin of a schizophrenic patient</td>
<td>47.0</td>
</tr>
</tbody>
</table>

D. Psychodynamic Theory

• Presence of an ego defect affects the interpretation of reality and the control of inner drives, such as sex and aggression. The disturbances occur as a consequence of distortions in the reciprocal relationship between the infant and the other.
• Object constancy described as a sense of security which results from a close attachment to the mother during infancy is not achieved.
IV. Symptomatology

Symptoms of schizophrenia may be divided into two basic categories namely, the positive symptoms and the negative symptoms.

A. Positive Symptoms

1. Hallucinations - distortions or exaggerations of perception in any of the senses, although auditory hallucinations are the most common followed by visual hallucinations.
2. Delusions - firmly held erroneous beliefs due to distortions or exaggerations of reasoning and/or misinterpretations of perceptions or experience.
3. Disorganized behavior - includes difficulty in goal-directed behavior (leading to difficulties in activities of daily living), unpredictable agitation or silliness, social disinhibition, or behaviors that are bizarre to onlookers.
4. Disorganized Speech/Thinking - also described as “thought disorder” or “loosening of associations,” is a key aspect of schizophrenia. Disorganized thinking is primarily based on the person’s speech.
5. Catatonic behaviors - are characterized by marked decrease in reaction to the immediate surrounding environment, sometimes taking the form of motionless and apparent unawareness, rigid or bizarre postures, or aimless excess motor activity.

B. Negative Symptoms

1. Affective flattening: • unchanging facial expression • decreased spontaneous movement • poor eye contact • lack of vocal inflections
2. Alogia: • poverty of speech • blocking • increased response latency
3. Avolition - Apathy: • poor grooming and hygiene • impersistence at work or school • physical anergia
4. Anhedonia - Asociality: • lack of involvement in recreational interests • poor interpersonal relationships with peers and family members
5. Attention: • Social inattentiveness

Diagnostic Criteria for Schizophrenia Based on DSM IV:

A. Two or more of the following, each presenting for a significant portion of time during a one-month period (or less if successfully treated)
   1. delusions
   2. hallucinations
   3. disorganized speech
   4. grossly disorganized or catatonic behavior
   5. negative symptoms

B. Social/occupational dysfunction: one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.

C. Continuous signs of the disturbance persist for at least six months. This six month period must include at least 1 month of symptoms that meet criterion A and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the negative symptoms or two or more symptoms listed in criterion A present in an attenuated form.

D. Schizophrenia disorder and mood disorder with psychotic features have been ruled out because either: (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during the active phase symptoms, their total duration has been brief relative to the duration of the active and residual symptoms.

E. The disturbance is not due to the direct physiological effects of a substance or a general medical condition.

F. If there is a history of autistic disorder or a pervasive development disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, are also present for at least one month.

The most common course is one of acute exacerbations and remissions, with increasing residual dysfunction between episodes. The course is however not uniform for every patient nor is progressive deterioration inevitable. Some patients recover completely, some improve or recover even after a long period of illness. However, patients usually relapse and a further deterioration in the patient's baseline functioning follows each relapse of the psychosis.

V. Treatment

A. Consultation

B. Hospitalization

• based on the physician's assessment of patient's propensity to harm self and others
• indicated primarily for patient's safety because
of suicidal or homicidal behavior, for grossly disorganized or inappropriate behavior, including the inability to take care of basic needs such as food, clothing, and shelter and for stabilization of medications.

C. Pharmacotherapy

In acute cases wherein the patient poses a threat to self and others, intramuscular medication like olanzapine and haloperidol can be administered. Olanzapine is given intramuscularly at 10 milligrams per 2 mL as a single dose or 5 milligrams (1 mL) one or two hours apart. Olanzapine given intramuscularly should not exceed 20 milligrams per day. In elderly patients, olanzapine should be given at 2.5 milligrams (0.5 ml) and can be repeated after an hour. Olanzapine is now the preferred drug of choice in behavioral emergencies because it is rarely associated with extrapyramidal symptoms.

Haloperidol can be given intramuscularly at 5 milligrams per mL, 5 milligrams every hour until marked sedation of the patient is achieved but not to exceed 20 milligrams per day. In elderly patients, haloperidol should be given at 2.5 milligrams (0.5 mL) every hour until sedation is achieved but not to exceed 10 milligrams. However, when using intramuscular haloperidol, one should watch out for the onset of adverse effects like acute dystonia. Acute dystonia can be relieved by giving biperiden HCl tablets, biperiden lactate or diphenhydramine HCl, the last two given intramuscularly.

The practice of administering hourly intramuscular doses of antipsychotic medication is called rapid neuroleptization. When employing rapid neuroleptization, whether olanzapine or haloperidol, patients must be restrained to avoid accidents which may occur as a result of their agitation or the onset of the sedative effect of the medication. Likewise, the blood pressure must be taken prior to the giving of each intramuscular dose. Whenever a patient is found to be hypotensive, any intramuscular medication should not be given.

- rapid neuroleptization: the practice of administering IM doses of dopamine receptor antagonist medications until marked sedation of the patients is achieved. Haloperidol 5 mg/mL 1 mL/IM is most commonly used given in three hourly doses. During this period, patients must be mechanically restrained to avoid accidents which may occur as a result of their agitation or the onset of the sedative effect of the drug. Blood pressure must be taken prior to the giving of each intramuscular dose and is deferred if values become hypotensive.

- antipsychotics: includes 2 major classes: dopamine receptor antagonist or the typical antipsychotics and the serotonin-dopamine antagonist or the atypical antipsychotics.

A. Typical antipsychotics: effective in the treatment of schizophrenia, particularly of the positive symptoms. The drugs have two major shortcomings however: (1) only a small percentage of patients (about 25%) are helped enough to recover a reasonable amount of normal mental functioning, (2) they are associated with both annoying and serious adverse effects.

B. Atypical antipsychotics: effective in reducing the negative features of psychosis as well as all positive symptoms while causing minimal extrapyramidal side effects.

- long acting depot medications: because of poor compliance with oral medications in patients, long acting depot preparations may be needed. They are usually given every 1 to 4 weeks and may be associated with increased side effects, including tardive dyskinesia. The preparation is injected into an area of large muscle tissue (buttocks or deltoid) from which they are absorbed slowly in the blood. Prior to the administration, the blood pressure is taken and in cases when the value is low (>90/60), the giving of the IM injection is deferred until such time that patient is no longer hypotensive.

- Maintenance treatment:
  - the first 3 to 6 months after the psychotic episodes is a period of stabilization for the patient
  - after 3 to 6 months, decrease the dose about 20% every six month until the minimum effective dose is found
  - patients with 1st psychotic episode maintain from 1 to 2 years
  - after 3rd psychotic episode - lifetime maintenance with attempts to reduce the daily dose every 6-12 months.

- major contraindications to antipsychotic use:
  1. a history of serious allergic response
  2. the possibility that a patient has ingested a substance that will interact with the antipsychotic to induce CNS depression (alcohol opioids, barbiturates, benzodiazepines) or anticholinergic delirium (atropine)
  3. presence of severe cardiac abnormality
  4. A high risk for seizures from organic or idiopathic causes
  5. presence of narrow angle glaucoma if an antipsychotic activity is used
• Dose:

Group 1: Conventional/typical antipsychotics:

<table>
<thead>
<tr>
<th></th>
<th>Acute dose (mg/day)</th>
<th>Maintenance dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>20-60</td>
<td>5-20</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>300-1000</td>
<td>50-400</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>300-1000</td>
<td>25-300</td>
</tr>
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</table>

Group 2: Atypical Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Acute dose (mg/day)</th>
<th>Maintenance dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>4-16</td>
<td>1-4</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10-15</td>
<td>2.5-10</td>
</tr>
<tr>
<td>Clozapine</td>
<td>100-900</td>
<td>25-200</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>300-800</td>
<td>200-400</td>
</tr>
<tr>
<td>Amilsulpiride</td>
<td>400-800</td>
<td>200-400</td>
</tr>
<tr>
<td>Aripaprazole</td>
<td>10-30</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

Available Depot Medications:

• Haloperidol decanoate 50 mg/mL: 100 mg IM at 4 weeks interval
• Flupentixol decanoate 20 mg/mL: 20-40 mg IM every 2-4 weeks
• Fluphenzine decanoate 25 mg/mL: 25 mg every 2-4 weeks
• Risperdal Consta 25-50 mg/mL every 3-4 weeks

Available Medications for Rapid Neuroleptization:

• Haloperidol 5 mg/mL, 1 mL per IM to be given hourly for 3 doses (monitor for hypotension)
• Olanzapine 10 mg/2 ml, given as a single dose IM or 1 mL given IM, one or two hours apart. Maximum of 20 milligrams per day.
• Adverse Effect Profile

Typical Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Sedative effect</th>
<th>Hypotensive effect</th>
<th>Anti-cholinergic effect</th>
<th>Extrapyramidal symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>high</td>
<td>high</td>
<td>medium</td>
<td>low</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>high</td>
<td>high</td>
<td>medium</td>
<td>low</td>
</tr>
</tbody>
</table>

Atypical Antipsychotics:

<table>
<thead>
<tr>
<th></th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Amilsupiride</th>
<th>Aripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>+++</td>
<td>rare</td>
<td>rare</td>
<td>rare</td>
<td>rare</td>
<td>-</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>+++</td>
<td>+/-</td>
<td>++</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>infrequent</td>
</tr>
<tr>
<td></td>
<td>elevation</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>infrequent</td>
</tr>
<tr>
<td>EPS</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>infrequent</td>
</tr>
<tr>
<td>Dose related</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Orthostatic HPN</td>
<td>+++</td>
<td>=</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Sedation</td>
<td>+++</td>
<td>0</td>
<td>=</td>
<td>0</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Seizures</td>
<td>+++</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+/-</td>
<td>?</td>
</tr>
<tr>
<td>Weight gain</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>rare</td>
<td>+/-</td>
</tr>
</tbody>
</table>
# Recommended Therapeutics
(Drugs Mentioned in the Treatment Guideline)

The following index lists therapeutic classifications as recommended by the treatment guideline. For the prescriber's reference, available drugs are listed under each therapeutic class.

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td><strong>Aripiprazole</strong> Abilify</td>
</tr>
<tr>
<td></td>
<td><strong>Amisulpride</strong> Solian</td>
</tr>
<tr>
<td></td>
<td><strong>Chlorpromazine</strong> Drugmaker's Biotech Chlorpromazine HCl Laractyl Psynor Thorazine</td>
</tr>
<tr>
<td></td>
<td><strong>Clozapine</strong> Leponex</td>
</tr>
<tr>
<td></td>
<td><strong>Flupentixol decanoate</strong> Fluanxol Depot</td>
</tr>
<tr>
<td></td>
<td><strong>Flupentixol diHCl</strong> Fluanxol</td>
</tr>
<tr>
<td></td>
<td><strong>Haloperidol</strong> Haldol Serenace</td>
</tr>
<tr>
<td></td>
<td><strong>Levomepromazine</strong> Nozinan</td>
</tr>
<tr>
<td></td>
<td><strong>Olanzapine</strong> Zyprexa</td>
</tr>
<tr>
<td></td>
<td><strong>Perphenazine</strong> Trilafon</td>
</tr>
<tr>
<td></td>
<td><strong>Quetiapine</strong> Seroquel</td>
</tr>
<tr>
<td></td>
<td><strong>Risperidone</strong> Risperdal Risperdal Consta</td>
</tr>
<tr>
<td></td>
<td><strong>Sulpiride</strong> Dogmatil</td>
</tr>
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<td></td>
<td><strong>Ziprasidone</strong> Zeldox</td>
</tr>
<tr>
<td></td>
<td><strong>Zuclopenthixol</strong> Clopixol</td>
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