Pharmacotherapy in schizophrenia and other psychotic disorders

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- Pharmacological treatment—are effective for reducing the impact of psychotic symptoms, as well as related symptoms of agitation and aggression.
- In many patients, these symptoms can be completely eliminated.
- **Negative symptoms and cognitive dysfunction** are only very inadequately treated with currently available antipsychotics.

- **HISTORY**

- patients were frequently hospitalized for long periods of time.
- Sedating agents such as bromides and barbiturates
- physical treatments such as hydrotherapy and wet sheet packs were also used for their calming effects.

- sleep treatment with barbiturates
- Insulin coma treatment
- Prefrontal lobotomy was proposed as a treatment for serious mental illnesses by Moniz in 1935.
- Drugs such as camphor and pentylenetetrazol (Metrazol) were used initially to induce seizures.
- electroconvulsive therapy (ECT)

- Reserpine, the most potent of the rauwolfia alkaloids
- The discovery of chlorpromazine in the early 1950s may be the most important single contribution to the treatment of a psychiatric illness.

- **PHASES OF TREATMENT IN SCHIZOPHRENIA**

The acute stage

- characterized by positive psychotic symptoms and related agitation/aggression that require immediate clinical attention.
- Treatment during this phase focuses on alleviating the most severe psychotic symptoms.
- Lasts from 4 to 8 weeks

Stabilization phase

- patients remain at risk for relapse if treatment is interrupted or if the patients are exposed to stress.
- During this phase, treatment focuses on consolidating therapeutic gains, with similar treatments as those used in the acute stage.
- last as long as 6 months following recovery from acute symptoms.

The stable or maintenance phase

- To prevent psychotic relapse or exacerbation and to assist patients in improving their level of functioning.
- minimization of negative symptoms and cognitive dysfunction
- Negative symptoms and cognitive disturbances have been associated even more with functional impairment than positive symptoms.

- pooling large amounts of data suggests that 15 to 25 percent in a year will experience a relapse while receiving medications and 50 to 75 percent will relapse without medications.
- Other evidence indicates that patients who experience relapses while they are receiving an antipsychotic have milder episodes than patients who relapse on no medication.

- a subgroup of up to one in six patients may not respond to the next antipsychotic trial as well anymore as they did before the relapse.

- It is important to recognize that although many such patients achieve remission, recovery (which includes sustained, relatively normal social and vocational adjustment) is far less common.
- It has been well established that even patients who have had only one episode have a four in five chance of relapsing at least once over the next 5 years, and that stopping medication is the most significant risk factor.

- Although published guidelines do not make definitive recommendations about the duration of maintenance treatment following the first episode, recent data suggest that 1 or 2 years might not be adequate.
- It is generally recommended that multiepisode patients receive maintenance treatment for at least 5 years.

- many experts would recommend pharmacotherapy on an “indefinite” or “for the foreseeable future” basis.
- The first 3 to 6 months following an acute episode or relapse is a period of particular vulnerability.
- With short lengths of hospital stay, adequate linkages with ambulatory programs are critical to ensure continuity of care.

- After stabilization for 6 months, gradual dosage reduction may be attempted.
- Average estimates suggest that more than 40 to 50 percent of patients become at least partially noncompliant within 1 or 2 years.
- in the patients eligible for long-acting injectable treatment, these are associated with significantly less hospitalizations than when the patient was prescribed oral antipsychotics.

- **FIRST EPISODE SCHIZOPHRENIA**

- More treatment responsive
- require lower antipsychotic doses (approximately 50%)
- More sensitive to side effects
- often have a difficult time accepting their illness
- At high risk for nonadherence, relapse, psychosocial deterioration, and suicidality.

- As in chronic-stage illness, antipsychotic treatment is the cornerstone of management, multidisciplinary interventions, focusing on engagement, treatment continuation, relapse prevention, physical health, and functional recovery are paramount.

EFFECTIVENESS OF ANTIPSYCHOTIC MEDICATIONS

- About 70 percent of patients treated with an antipsychotic achieved relative remission or substantial improvement.
- Placebo about 25 percent

Assessment

- Blood tests for complete blood cell count (CBC), electrolytes, fasting glucose, hemoglobin A1C, lipid profile, liver, renal, and thyroid function should be ordered.
- pregnancy tests in women, as well as human immunodeficiency virus (HIV) and syphilis tests when relevant.
- The presence of movement disorders, particularly preexisting tardive dyskinesia (TD)

Selection of an Antipsychotic Drug

- antipsychotics can be categorized into two main groups:
- the older conventional antipsychotics, which have also been called first-generation antipsychotics (FGAs) or dopamine receptor antagonists
- newer drugs, which have been called second-generation antipsychotics (SGAs) or serotonin-dopamine antagonists.

- The FGAs are further categorized as being low, mid, or high potency
- the higher potency drugs having more specificity and greater affinity for D2 receptors and a greater tendency to cause EPS.
- Lower potency drugs are less likely to cause EPS, but tend to have more effects on other neurotransmitter receptors and are thus more
- likely to cause postural hypotension, sedation, weight gain, and anticholinergic effects.

- The SGAs are further categorized as D2 partial agonists and D2-serotonin 2a antagonists

Comparisons of Antipsychotics

- all available antipsychotics appear to be similarly effective, at least at a group level, but with substantial differences in adverse effects.
- The exception is clozapine, which has been consistently shown to be more effective than other medications for individuals who have symptoms that persist despite adequate treatment with other antipsychotics, at least when clozapine is adequately dosed.

- olanzapine, and risperidone have been shown in some meta-analyses to produce greater symptom response than antipsychotics other than clozapine.
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Long-Acting Injectable Antipsychotics

- Nonadherence to antipsychotics is common and one of the most relevant and preventable risk factors for insufficient response and relapse, long-acting injectable formulations of antipsychotics have been developed
- long-acting injectable antipsychotics are helpful for continuation and maintenance treatment, but not necessarily for rapid acute treatment.

Starting Antipsychotics

- Prior to starting an antipsychotic, clinicians should describe to patients themedication that is being prescribed, its target symptoms, and its possible side effects, particularly those that are common and unpleasant when adrug is first started (e.g., muscle stiffness, sedation, and akathisia).
- it is frequently helpful to involve one or more family members in decision making about drug treatment.

more recent studies and meta-analyses have found that in a 4- to 6-week treatment course, the greatest reduction in symptoms occurs within the first 1 to 2 weeks.

It has also been found that little or no response during the first week or two (assuming a valid diagnosis, appropriate adherence, and therapeutic dose level) is a powerful predictor of subsequent poor response.

- The recommended dosage range for FGAs is in the range of 300 to 1,000 mg daily of chlorpromazine or the equivalent of other antipsychotics.
- A number of dosage comparison studies have failed to support the routine use of higher doses.
- Large multicenter trials indicate that risperidone is most effective at 4 to 8 mg daily . Higher doses may lead to EPS without an advantage in increased effectiveness.

- A reasonable practice would be to manage patients with schizophrenia with 4 mg of risperidone and increase the dose if they fail to respond after 4 to 6 weeks.
- Olanzapine is usually effective in the range of 10 to 20 mg daily , although a number of case reports describe individuals who demonstrated optimal responses at doses of 25 mg and higher.

- there is no evidence that doses of aripiprazole greater than 30 mg daily are more effective than the recommended range of 10 to 30 mg daily

- The dose of an antipsychotic that is likely to be effective is the dose that occupies approximately 60 to 70 percent of D2 receptors measured in the striatum.
- improvement in psychotic symptoms can begin to occur within the first 24 hours of treatment, particularly with the use of short-acting intramuscular antipsychotics.

- **Managing Agitation in Acute Psychosis**

- Agitation in acute schizophrenia can result from disturbing psychotic symptoms, such as frightening delusions or suspiciousness, or from other causes, including drug abuse or withdrawal, or akathisia.
- Patients with akathisia can appear agitated when they experience a subjective feeling of motor restlessness.

- In case of agitation a dose increase of the antipsychotic should be beneficial, whereas in the case of akathisia, the symptoms would worsen.
- Benzodiazepine treatment can improve both agitation and akathisia.

- Antipsychotics and benzodiazepines can result in relatively rapid calming when psychotic patients are agitated.
- An advantage of an antipsychotic is that a single intramuscular injection of haloperidol, fluphenazine, olanzapine, aripiprazole, or ziprasidone will often result in calming without an excess of sedation.

- Intramuscular ziprasidone, aripiprazole, and olanzapine are similar to their oral counterparts in not causing substantial EPS during acute treatment.
- Rapidly dissolving oral formulation of olanzapine, risperidone, or aripiprazole may also be helpful as an alternative to an intramuscular injection, at least in order to ensure that the patient has ingested the medication fully.

- Lorazepam (Ativan) has the advantage of reliable absorption when it is administered either orally or intramuscularly.
- The combination of lorazepam with an antipsychotic
- Due to the sedating properties of short-acting injectable olanzapine that may depress respiratory drive, it should not be combined with benzodiazepines within a 2-hour window prior or after its administration.

- **MANAGING SIDE EFFECTS**

- A common form of EPS is akathisia, a side effect consisting of a subjective feeling of restlessness with or without restless movements, usually in the legs or feet.
- Researchers have estimated that 25 to 75 percent of patients treated with a high-potency FGAs will experience akathisia.

- The partial D2 agonists aripiprazole can lead to early restlessness that may not be true akathisia, but rather due to early stimulatory effects that are minimized or controlled by switching slowly from a full D2 blocker or a sedating or anticholinergic antipsychotic to aripiprazole, using a lower starting dose or cotreating temporarily with a benzodiazepine or antihistamine.

- movement-related side effects that may be peak concentration related can be minimized when administering the antipsychotic in the evening, having the peak level occur during sleep.

Antipsychotic-induced parkinsonism

- affects about 30 percent of patients who are chronically treated with FGAs.
- The first evidence of drug-induced parkinsonism may be a diminished arm swing or decreased facial expressiveness.
- Akinesia can be subtle and can be mistaken for or exacerbate negative symptoms.

- Risk factors for antipsychotic-induced parkinsonism:
- increasing age and dose
- FGA use
- a history of parkinsonism
- underlying basal ganglia damage.

EPS and alternatives

- reducing the dose of the antipsychotic (which is most commonly an FGA)
- adding an antiparkinson medication
- changing the patient to an SGA that is less likely to cause EPS.
- The most effective antiparkinson medications are the anticholinergic antiparkinson drugs

EPS and alternatives

- Prophylactic antiparkinson medications may also be indicated when high potency drugs are prescribed for young men who tend to have an increased vulnerability for developing dystonias.
- need for chronic anticholinergic treatment should be reevaluated as indicated above.

- **Tardive Dyskinesia**

Definition

- According to (DSM-5), the abnormal movements should be present for at least 4 weeks, and patients should have been exposed to an antipsychotic for at least 3 months (at least one month in the elderly).
- The onset of the abnormal movements should occur either while the patient is receiving an antipsychotic or within 4 weeks of discontinuing an oral or 8 weeks after the withdrawal of a depot antipsychotic.

Prevalence

- Prevalence surveys indicate that 20 to 30 percent of patients who are chronically treated with an FGA will exhibit symptoms of TD.
- Three to 5 percent of young patients receiving an FGA develop TD each year.

Risk Factors

- These results were somewhat expected in that early occurring EPS are a significant risk factor for TD.
- Patients with organic mental illness and affective disorders may also be more vulnerable to TD than those with schizophrenia.

recommendations for preventing and managing TD.

- (1) establishing objective evidence that
- antipsychotic medications are effective for an individual
- (2) utilizing the lowest effective dose of antipsychotic
- (3) prescribing cautiously with children, elderly patients, and patients with mood disorders
- (4) examining patients on a regular basis for evidence of TD

recommendations for preventing and managing TD.

- (5) when TD is diagnosed, consider alternatives to the antipsychotic being used, obtain informed consent, and also consider dosage reduction
- (6) if the TD worsens, consider a number of options, including discontinuing the antipsychotic or switching to a different drug. Clozapine has been shown to be effective in reducing severe TD or tardive dystonia.

- All FGAs as well as risperidone and paliperidone elevate prolactin levels, which can result in galactorrhea and irregular menses.
- suppression in gonadotropin-releasing hormone
- libido and sexual functioning
- decreases in bone density and lead to osteoporosis.

- Clozapine and quetiapine do not appear to elevate prolactin above normal levels, while the partial D2 agonists, aripiprazole, brexpiprazole and cariprazine may reduce prolactin levels.
- when patients demonstrate side effects related to prolactin, such as galactorrhea, menstrual disturbances or sexual side effects, changing patients to a prolactin-sparing agent may be effective.

- **Health Monitoring in Patients Receiving Antipsychotics**

- Routine cardiometabolic monitoring:
- body weight, blood pressure and fasting glucose, and lipids with or without fasting or random hemoglobin A1C at baseline, 3 months and annually after antipsychotic initiation.
- More frequent assessments are recommended if significant weight gain occurs.

- **STRATEGIES FOR POOR RESPONDERS**

- When patients with acute schizophrenia are administered an antipsychotic medication, approximately 50 percent will improve to the extent that they will achieve a complete remission of positive symptoms or experience only mild symptoms.
- The remaining 50 percent of patients will improve, but will still demonstrate variable levels of positive symptoms that are resistant to the medications.

- Before deciding that a particular antipsychotic is not working adequately for a patient, it is important to ensure that the diagnosis is correct, to rule out substance related or medical reasons, and ensure that the patient has been adherent to the medication regimen and that they received an adequate trial of the medication.
- A 6-week trial on an adequate dose of an antipsychotic represents a reasonable trial for most patients.

- If patients demonstrate even a mild amount of improvement during this period, it may be reasonable to wait before changing a medication, for 3 to 6 months.
- However, early lack of at least minimal improvement (i.e., within the first 2 weeks) seems to identify a subgroup of patients who achieve a lower level of response even after 3 months of subsequent treatment.

- There is substantial evidence indicating that clozapine is effective for patients who respond poorly to other antipsychotics.
- A number of meta-analyses have been conducted supporting clozapine's superiority in patients with refractory symptoms, especially when clozapine was adequately dosed (>400 mg).

- Whether patients failing SGAs should have at least one trial of an FGA prior to clozapine is unclear, but since partial and covert nonadherence is a common cause of treatment “resistance,” a trial with a long-acting injectable antipsychotic may be considered prior to switching a patient to clozapine.

- In recent years, there has been an increase in the use of antipsychotic polypharmacy.
- Other “augmentation” strategies for the treatment of positive symptoms with benzodiazepines, lithium, antiepileptics, and β-blockers have been studied to some extent and controlled trials and meta-analyses are generally negative.

- The use of adjunctive medications to treat symptoms of affective disturbance, anxiety, agitation, and so forth may be more appropriate.
- ECT can also be considered as a treatment of last resort for refractory individuals, even in those not adequately responding to clozapine.

- If the patient is responding poorly, many clinicians will consider raising the dose above the usual therapeutic level.
- Nearly all studies found that higher doses were not associated with greater improvement than conventional doses. This suggests that changing to another drug is more likely to be helpful than changing to a high dose since many adverse effects may be dose related.

- Studies suggest that a poor response to one FGA is likely to be followed by a poor response to another.
- This has led many clinicians to change to an SGA in the hope that a somewhat different profile of receptor interactions may lead to better response.

- **Duration of antipsychotic therapy**

- — For patients with known or suspected schizophrenia who have recovered from an acute first psychotic episode, we recommend continuing antipsychotics for at least two to three years.
- Whether to continue beyond this interval depends on the course and individual features.

- For those with a first episode of psychosis, we base the decision to continue antipsychotic therapy on the symptom intensity, level of psychiatric disruption, response to medications, and support. For those who had psychosis that was extremely disruptive, difficult to control, or accompanied by violence or suicidal ideation, we favor continuing antipsychotic therapy indefinitely.

- Otherwise, if it seems that potential relapses can be readily controlled, we explore the possibility of discontinuing medications after two to three years.

- For those who have had multiple episodes of psychosis in the past, we generally recommend continuing antipsychotic therapy indefinitely.
- However, in patients whose recurrent psychosis has been mild with clear warning signs, a trial of antipsychotic discontinuation may be reasonable

Treatment-resistant schizophrenia

- — Patients with schizophrenia who do not benefit adequately from two or more trials of standard antipsychotic medications despite typically therapeutic doses and treatment durations (eg, six weeks) are considered to have treatment-resistant schizophrenia.
- We usually evaluate these patients for clozapine eligibility.
- However, due to its potential toxicity, it is reserved for treatment-refractory cases or cases with high risk for suicide.

- **SUICIDAL BEHAVIOR**

- Approximately 20 to 40 percent of patients make suicide attempts and 5 to 10 percent succeed.
- Suicidal behavior appears to be an independent domain from psychosis; however, depression and comorbid substance abuse increase the risk.
- Based on a large-scale study of clozapine in patients at risk for suicide, clozapine received an indication for the prevention of suicidal behavior.

- **NEGATIVE, MOOD, AND COGNITIVE SYMPTOMS**

- Negative symptoms and cognitive impairments are associated with a substantial amount of the social and vocational disability in schizophrenia.
- This observation has resulted in a reappraisal of the goals of treatment, placing a greater emphasis on treatment strategies for decreasing the severity of these impairments.

- Negative and cognitive symptoms can be classified as being either primary, which is related to the illness, or secondary negative symptoms, which is that they are related to non-illness related factors.
- secondary negative symptoms that can be addressed directly include depression, psychotic symptoms of suspiciousness or paranoia, social anxiety, EPS, sedation, sleep apnea, chronic pain or environmental deprivation.

- The management of secondary negative symptoms begins with the management of the condition that caused these symptoms. For depression, this may include the addition of an antidepressant medication;
- If the previously mentioned causes of secondary negative symptoms have been ruled out, the patient is likely to be demonstrating a type of enduring primary negative symptom.

- it is probably reasonable for clinicians to consider changing to an SGA for patients with substantial negative symptoms in an attempt to minimize any that are secondary to EPS.
- Several meta-analyses have indicated that antidepressant augmentation of antipsychotics may improve negative symptoms, but whether the improvement pertains predominantly to primary or secondary negative symptoms remains unclear.

- Patients with schizophrenia frequently suffer from impairments in memory, attention, and information processing.
- As with negative symptoms, cognitive impairments can also be secondary to other causes, including depression, psychotic symptoms of thought disorganization or hallucinations, substance abuse, side effects of antipsychotics, such as EPS, sedation, side effects of anticholinergic antiparkinson medications used to treat EPS, or sleep apnea.

- Addressing these factors, including decreasing the use of anticholinergic medication by changing to drugs that do not require antiparkinson medications, particularly SGAs, may be helpful.
- However, cognition was carefully monitored in the CATIE study and did not differ meaningfully among the FGA, perphenazine, and the SGAs.