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Schizophrenia, Part II: Treatment

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*This CE article is a continuation of the previously published CE article entitled "Schizophrenia, Part I: Etiology and Pathophysiology" (**www.inetce.com**, Volume 3, Number 8, December 1999). This article will serve to complete the discussion of schizophrenia by focusing on treatment.*

LEARNING OBJECTIVES

After completing this continuing education program, the pharmacist should be able to:

1. Discuss the goals for treatment of schizophrenia.
2. Identify the differences between typical and atypical antipsychotic agents.
3. Discuss the pharmacologic mechanisms of action for antipsychotics.
4. Describe the adverse effects associated with schizophrenia pharmacotherapy.
5. Describe various treatment regimens in different patient populations

ABSTRACT: Schizophrenia is a chronic disorder and the most commonly diagnosed psychosis. In the United States, there are over 3 million current cases with an estimated 100,000 new cases diagnosed each year. The drugs used to treat schizophrenia are commonly called antipsychotics and were formally known as neuroleptics or major tranquilizers. For many years, the treatment of schizophrenia relied on therapeutic agents that displayed serious adverse effects (extrapyramidal and anticholinergic effects). One of the most serious of these effects is tardive dyskinesia, a potentially irreversible disorder characterized by involutary, abnormal movements. In the past, treatment with typical antipsychotics was ineffective in a significant proportion of schizophrenics. Typical antipsychotic agents tend to be more effective in reduction of the positive symptoms than the negative symptoms of schizophrenia. Atypical agents are now the first-line therapy for schizophrenia, which are attributable to their efficacy in ameliorating both positive and negative symptoms and reducing the incidence of serious adverse effects. Both the increased efficacy and reduced adverse effects are the result of greater selectivity for antagonism of dopamine receptors in specific regions of the brain and their ability to modulate dopaminergic neurotransmission by blockade of a subset of serotonin receptors.

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TREATMENT OF SCHIZOPHRENIA

Goals of Therapy

The treatment of schizophrenia is palliative rather than curative. In the past, the general inefficacy and adverse effects of the typical agents limited the goal of therapy to a partial relief of symptoms. The advent of newer, atypical agents with more favorable adverse effect profiles has made the goal of complete symptom remission a real possibility. While it should not be expected that treatment will relieve all of the associated symptoms or that the patient will return to a pre-disease level of functioning, the use of atypical antipsychotics may lead to a remission of symptoms with fewer serious side effects. The long-term goals of therapy include remission and prevention of relapse.

Nonpharmacologic Therapy

Although the mainstay of treatment is the use of pharmacologic agents, a number of non-pharmacologic treatments are used to improve the symptoms of the patient. These include psychosocial rehabilitation programs involving education, supportive housing, teaching basic living skills, social skills training, and work programs. Family involvement in the care of the patient has been shown to decrease rehospitalizations and improve functioning.[1]

Pharmacologic Therapy

The agents used to treat schizophrenia were formerly called neuroleptics because of a propensity to induce neurologic adverse effects. They were also classified as major tranquilizers in order to differentiate them from anxiolytics, which were known as minor tranquilizers. They are now known as antipsychotics. In addition to their use in the treatment of schizophrenia, they are indicated for other psychoses. Antipsychotics are further classified as either typical or atypical depending on the mechanisms by which they affect responses to neurotransmitters and their ability to affect both the positive and negative symptoms of schizophrenia. The atypical agents are currently considered first-line therapy because of their ability to treat negative symptoms with lower incidence of extrapyramidal effects.[2,3,4] Olanzapine, quetiapine, and risperidone are considered to be the safest of the atypical agents; generally, patients should be tried on all of these agents before a trial of clozapine. A suggested treatment algorithm is shown in Figure 1.[4,5] The atypical agent ziprasidone was recently approved, and may also fit into the algorithm, but at this time clinical evidence supporting its inclusion is limited.

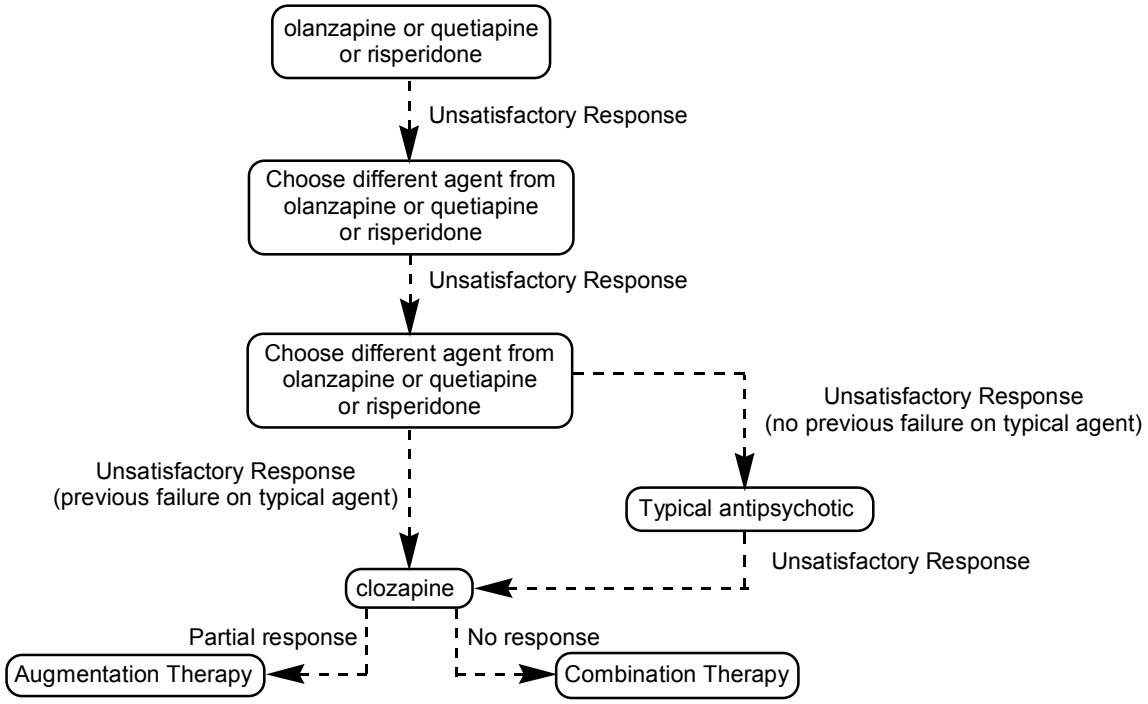


Figure 1. Pharmacotherapy Algorithm for Schizophrenia

Initial Treatment

The goals for the first 7 days should be reduction of anxiety, agitation, combativeness, aggression, and hostility.[6] A normalization of sleeping and eating patterns is also desired. The dosage ranges for a number of antipsychotic agents are given in Table 1 and the average dose is typically in the middle of the range.[7] Atypical agents have been shown to be as effective as typical agents in controlling acute schizophrenia.[8,9] Agitated patients are frequently treated with rapid neuroleptization. This is the use of high-dose, high-potency agents such as haloperidol. A more rational therapeutic approach is the addition of a benzodiazepine (lorazepam 2 mg) to the usual dose of the antipsychotic agent.[6] This approach has been shown to be more effective with a lowered incidence of serious adverse effects.[2]

Generic Name	Trade Name	Usual Dose Range (mg/day)	Recommended Maximum Dose (mg/day)
Typical Agents			
Chlorpromazine	Thorazine	100-800	2000
Thioridazine	Mellaril	100-800	800
Mesoridazine	Serentil	50-400	500
Trifluperazine	Stelazine	5-40	80
Perphenazine	Trilafon	10-64	64
Fluphenazine	Prolixin, Permitil	2-20	40
Thiothixene	Navane	4-40	60
Loxapine	Loxitane	10-80	250
Haloperidol	Haldol	2-20	100
Molindone	Moban	10-100	225
Atypical Agents			
Clozapine	Clozaril	50-500	900
Olanzapine	Zyprexa	10-20	20
Quetiapine	Seroquel	250-500	800
Risperidone	Risperdal	2-8	16
Ziprasidone	Geodon	40-160	160

Table 1. Dosing Information for Antipsychotic Agents

Stabilization Therapy

Improvement is usually a slow process requiring 6 to 8 weeks and titration of the dose is reasonable if the patient has no side effects. An adequate trial of a new medication should last at least 6 weeks at therapeutic dosage, and if no improvement is seen, then the practitioner should evaluate a number of factors including diagnosis, compliance, potential that the patient is treatment resistant, and current response compared with past response before considering the next stage of therapy.[2,4]

Maintenance Therapy

Proper maintenance therapy is important in prevention of relapse. The average relapse rate for patients receiving drug therapy is 20% as opposed to 60%-80% with placebo.[10] Medication should be continued for at least 12 months following remission for schizophrenic patients after their first psychotic episode.[10] Maintenance for patients with multiple acute episodes is less defined. In patients exhibiting multiple acute episodes,

5 years of maintenance therapy should be considered. If lifetime therapy is necessary because of repeated psychotic decompensations or the potential for violence or suicide, the lowest effective dose should be used.[10]

Antipsychotics should be tapered slowly over 1 to 2 weeks before discontinuation or medication switching to minimize withdrawal symptoms.[6] These symptoms most likely occur because of rebound cholinergic effects and include rebound parkinsonism, akathisia, tremor, headaches,

abdominal cramps, nausea, vomiting, diarrhea, insomnia, nightmares, restlessness, salivation, sweating. The low-potency typical agents and clozapine may require a longer tapering period.[6]

Switching From Typical to Atypical Agents

There are a number of reasons to switch from typical to atypical agents. Patients to be considered for switching include those who still experience significant positive or negative symptoms during therapy, those who experience significant adverse effects (extrapyramidal effects, amenorrhea, galactorrhea), and those who experience relapse despite good compliance.[11] Patients should be counseled on the benefits and potential risks before medication changes.[12]

There are some patients who are not good candidates for medication switching. These include those who pose a danger to themselves or others if symptoms exacerbate, those who have been stable for less than 3 to 6 months, those who have been previously noncompliant and are on depot forms, or those who need an injectable dosage form.[9] Patients should not be forced to switch medications against their will.

The best time to switch patients is following a relapse or hospitalization.[9] The old medication should be tapered and overlapped with the new agent for a 1 to 2 week period to prevent withdrawal symptoms. If withdrawal symptoms occur, then the overlap period should be extended.[4]

Treatment-resistant Patients

Although this type of patient is not officially defined, it commonly refers to a patient that has not adequately responded to drug therapy. It can be more rigidly defined as a patient who did not respond to a trial of 3 different antipsychotic medications.[13] Ten percent to 30% of patients have been shown to be treatment resistant to typical antipsychotic agents.[14,15] There is some evidence that atypical agents may show some benefit in these patients, but only clozapine has been shown to be effective in large, randomized clinical trials with treatment-resistant patients.[13] Improvement in these patients may be gradual with up to 60% showing improvement when clozapine is used for 6 months.[16]

Noncompliance

Noncompliance is a significant problem in patients being treated with antipsychotic agents.[6] Reasons for noncompliance include denial of illness, lack of insight, delusions of allergy to the medications, adverse effects, cost of medication, social stigma associated with the illness, and cognitive deficits (failure to remember to take the medication).[2] Concomitant substance abuse is a strong predictor of noncompliance.[17] Methods to improve patient compliance include family involvement, patient education, and teaching patients how to self-medicate while institutionalized.[2,18]

Patients who are unreliable in taking oral medications may benefit from depot agents. The reason for noncompliance, however, should be determined before depot therapy is initiated. If the patient is noncompliant because of adverse effects, then a medication with a different adverse effect profile should be considered. Depot medication is not recommended for patients who do not consent to treatment.[6]

Conversion to a depot form should follow stabilization on oral forms of the same agent or at least a short trial to determine the incidence of adverse effects. One simple oral to depot conversion for fluphenazine is the Stimmel method.[19] This method uses 1.2 times the oral daily dose for stabilized patients. This amount is rounded up to the

nearest 12.5 mg interval and administered in weekly doses for the first 4 to 6 weeks. Following this initial period, the fluphenazine may be administered every 2 to 3 weeks. For more acutely ill patients, 1.6 times the oral daily dose should be administered.

Haloperidol depot typically requires 10 to 15 times the oral daily dose. The calculated dose is rounded up to the nearest 50 mg interval and administered monthly with oral dosing overlapping for the first month. Alternatively, a method developed by Ereshefsky in which 20 times the oral daily dose was divided into 100-200 mg doses and given every 3 to 7 days until the entire calculated dose was administered does not require oral overlapping and resulted in a lower relapse rate.[20]

Relapse

Relapse (acute schizophrenic episode) is an expected occurrence, so monitoring of patients is very important.[21] Monitoring can be performed using diagnostic rating scales, and should occur at regular intervals.[2] Early identification of relapse is important so medication adjustments can be made to prevent full relapse and possible hospitalization.

Augmentation Therapy

This strategy employs non-antipsychotic agents to supplement the effect of antipsychotic therapy. It is generally only used in treatment-resistant patients. If this method is effective, improvement is seen early in therapy. If a response is not observed within a few days, then the augmentation agent should be discontinued.[6] Typical agents used for augmentation include lithium, selective serotonin reuptake inhibitors, propranolol, and benzodiazepines.[6,15,22]

Combination Therapy

This strategy employs 2 different antipsychotic agents. The recommended combinations are 2 atypical agents or 1 typical agent/1 atypical agent.[6] Therapy should be used only for treatment-resistant patients and should not continue longer than 12 weeks, since no supporting evidence currently exists demonstrating benefit for this regimen.[6]

Pharmacology

As was discussed in Part I of this series, the pathophysiology of schizophrenia is controversial, and may involve many factors.[21] Common to most theories of schizophrenia is the involvement of the dopamine system.[23] It is not known, however, if the problem is with the synthesis, degradation, release, reuptake, binding to the receptor, or the second messenger system involved with dopamine receptors.

Currently, 5 different dopamine receptor subtypes have been described.[23] They are classified into 2 families (D_1-like or D_2-like) based on their effect on cAMP levels. The D_1 receptor increases cAMP by activation of adenylyl cyclase, and is located mainly in the putamen, nucleus accumbens, and olfactory tubercle. The D_5 receptor also increases cAMP and is found in the hippocampus and hypothalamus. The therapeutic potency for antipsychotic agents does not correlate with their binding affinity for the D_1 receptor.

The D_2 receptor decreases cAMP by inhibition of adenylyl cyclase and is found in the highest concentrations both pre- and post-synaptically in the caudate-putamen, nucleus accumbens, and olfactory tubercle. The D_3 receptor also is believed to decrease cAMP and is found in the frontal cortex, medulla, and midbrain. D_4 receptors also

decrease cAMP but are not well studied at this time. Unlike D_1 receptors, the binding affinity of typical antipsychotic agents for D_2 receptors does correlate with their potency and is believed to be the mechanism of action for these agents. Newer, atypical agents, however, are not potent antagonists of the D_2 receptor, which suggests that the activity of these agents is attributable to additional mechanisms. Two accepted mechanisms for the efficacy of atypical antipsychotic agents are the following:

- Specificity for antagonism of D_2 receptors in the limbic system. This specificity for receptors in the limbic area is believed to contribute to the lack of extrapyramidal effects. These movement disorders are believed to be caused by blocking D_2 receptors in the striatal region and treating negative symptoms, which are believed to occur because of hypodopaminergic activity in the mesocortical region.[6,9,24]

- Antagonism of 5-HT_2 receptors on dopamine neurons in the mesocortical area. This action prevents the release of dopamine from these neurons, which is thought to contribute to negative symptom improvement.[6,9,24]

Agents Used In the Treatment of Schizophrenia

Prior to the discovery of typical antipsychotic agents, the common practice was institutionalization for schizophrenic patients. The use of these first-generation antipsychotics led to a national trend in deinstitutionalization of many schizophrenics. For many years, the mainstay of schizophrenia treatment was these typical antipsychotics. But, the introduction of the atypicals has reduced the role of these agents to second-line therapy. The similarities between structural classes have allowed the clinician to become familiar with a single drug in each structural group and develop a workable understanding of these agents.

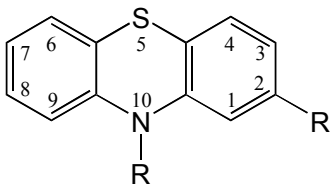
Typical Antipsychotics

The typical antipsychotics show equal efficacy when used in equipotent doses. This allows the selection of agent to be based on adverse effect profile and previous response of the patient or a closely related family member who has taken the drug. In general, the incidence of specific types of adverse effects can be generalized based on the relative potency of the agent. Low-potency agents (e.g., thioridazine) are less specific for D_2 receptors and produce significant effects, which are attributable to blockade of histaminic (sedation), muscarinic (urinary retention, blurred vision, constipation, dry mouth), and α_1-adrenergic receptors (orthostatic hypotension, reflex tachycardia). High-potency agents (e.g., haloperidol) predominantly produce extrapyramidal symptoms because of significant D_2 receptor blockade. The adverse effects of typical antipsychotics are summarized in Table 2.[6]

Phenothiazine Derivatives

These agents are based on the tricyclic phenothiazine structure shown below.

The potency and adverse effects of these agents differ based on the substituent found at the 2-position and also on the composition of the side chain at the 10-position. The functionality in the side chain is used to further classify these agents as agents with aliphatic, piperidine, or piperazine side chains.



The agents with an aliphatic side chain include chlorpromazine (Thorazine®) and trifluprom azine (Vesprin®). Chlorpromazine was the first phenothiazine used to treat psychosis. It also has activity as an antiemetic. This group of agents produces significant sedation and hypotension. Anticholinergic effects are also common. Extrapyramidal side effects (EPS) are moderate. As with all phenothiazines, potentiation of other CNS depressants (sedatives, ethanol, and anesthetics) may occur.

The agents with a piperidine side chain include thioridazine (Mellaril®) and mesoridazine (Serentil®). These agents are equivalent in potency to the aliphatic side chain group. They have a low incidence of EPS, possibly because of their high anticholinergic activity. They also produce significant sedation and hypotension. Antiemetic activity is reduced compared with the aliphatic side chain group. Thioridazine has been reported to produce pigmentary retinopathy at daily doses in excess of 800 mg, and this should be considered the strict upper limit for therapy. This effect is not seen with mesoridazine.

The agents with a piperazine side chain include prochlorperazine (Compazine®), trifluoperazine (Stelazine®), perphenazine (Trilafon®), fluphenazine (Permitil®, Prolixin®), and acetophenazine (Tindal®). This group of agents is characterized by high potency, high incidence of EPS and low sedation, hypotension, and anticholinergic effects. Prochlorperazine, because of the high EPS, is typically used as an antiemetic rather than an antipsychotic. Fluphenazine is available as a depot form, which is advantageous in non-compliant patients.

Ring Analogs of Phenothiazines

Thioxanthenes

This group is composed of chlorprothixene (Taractan®) and thiothixene (Navane®). They are closely related to the previously described phenothiazine structure with the exception of a carbon in place of the nitrogen at the 10-position. These agents are more potent than structurally equivalent phenothiazines. They have a high incidence of EPS possibly attributable to a low anticholinergic effect. Sedation is low and orthostatic hypotension is moderate with these agents.

Dibenzoxapines

Loxapine (Loxitane®) is the only clinically relevant member of this group. It is similar in structure to the phenothiazines except the middle ring is a 7-membered heterocycle. It is as potent as the piperazine side chain phenothiazines. Loxapine has moderate incidence of EPS but low sedation, hypotension, and anticholinergic effects.

A number of other structural classes exhibit antipsychotic activity but are not closely related to the phenothiazines. These currently available agents are generally more potent than phenothiazines.

Phenylbutylpiperadines

Haloperidol (Haldol®) is a potent agent with high EPS owing to potent striatal dopamine block with almost no compensatory anticholinergic effects. It is a rapid acting antipsychotic with low incidence of hypotension and sedation. One advantage for this agent is its availability as a depot form for treatment of non-compliant patients.

Pimozide (Orap®) is the most potent antipsychotic available. Its use is limited by

high incidence of EPS. Anticholinergic effects and sedation are moderate and hypotension is low. It is only indicated in the United States for treatment of Tourette's syndrome in patients not responding to standard therapy.[25]

Dihydroindolones

Molindone (Moban®) is a moderately potent agent. It has a moderate incidence of EPS and sedation. Hypotension and anticholinergic effects are low. This agent is unique in that it has been shown to decrease appetite and may be useful for the treatment of obese patients.[26]

	Equivalent Dose (mg)	Sedation	Orthostatic Hypotension	Anticholinergic Effects	Extrapyramidal Symptoms
Phenothiazines					
Aliphatic Side Chain					
Chlorpromazine	100	H	H	M	M
Promazine	200	M	M	H	M
Trifluprомazine	25	H	M	H	M
Piperidine Side Chain					
Thioridazine	100	H	H	H	L
Mesoridazine	50	H	M	H	L
Piperazine Side Chain					
Fluphenazine	2	L	L	L	H
Perphenazine	10	M	L	L	M
Trifluoperazine	5	L	L	L	H
Thioxanthenes					
Thiothixene	4	L	M	L	H
Dibenzoxazepines					
Loxapine	15	L	L	L	M
Phenylbutyl-piperadines					
Haloperidol	2	L	L	L	H
Pimozide	0.3 – 0.5	M	L	M	H
Dihydroindolones					
Molindone	10	M	L	L	M

H = high incidence of effect, M = moderate incidence of effect, L = low incidence of effect

Table 2. Comparison of Potency and Incidence of Adverse Effects for some Typical Antipsychotic Agents

Atypical Agents

These agents are classified as atypical because of absent or low incidence of EPS and an ability to treat negative symptoms. These agents act antagonistically on several neurotransmitter receptors including dopamine (D_1, D_2, D_4, and D_5), serotonin (5-HT_2, 5-HT_6, and 5-HT_7), α_1-adrenergic, histaminic (H_1), and muscarinic.[24,27,28,29] Unlike the typical agents whose antipsychotic activity is related to affinity at the D_2 receptor, these agents have a higher affinity for the 5-HT_2 receptor compared with the D_2 receptor. This increased antiserotonergic effect is partly responsible for the weight gain seen with these agents. The diverse interactions of these agents give rise to varying adverse effects and drug-drug interaction profiles. These profiles are typically the basis for choosing one agent over another, as they are, with the exception of clozapine and ziprasidone, interchangeable. These 2 agents are exceptions owing to a significant risk of agranulocytosis (clozapine) and a lack of clinical information (ziprasidone). The atypicals are structurally classified as either dibenzapines or benzisoxazoles.

Dibenzapines

Clozapine (Clozaril®) is the prototypical atypical agent. It is usually reserved for patients that do not respond to other atypicals or to typical antipsychotics. The risk of agranulocytosis with clozapine is significant, and patients that do receive this agent must have a baseline white blood count (WBC) and differential before treatment and weekly WBC counts throughout treatment and for 4 weeks following discontinuation.[25] A comparison of common adverse effects for the atypical agents is given in Table 3.[6]

Olanzapine (Zyprexa®) is a first-line agent for treatment of schizophrenia. It has a very low incidence of EPS. Anticholinergic effects and sedation are prominent while hypotension is moderate. This agent also has a moderate incidence of weight gain associated with it.

Quetiapine (Seroquel®) is another first-line agent. Sedation and weight gain are less prominent than with olanzapine. Hypotension is moderate, and this agent does not interact with muscarinic receptors, thus no anticholinergic effects.

Benzisoxazoles

Risperidone (Risperdal®) is the third first-line agent for treatment of schizophrenia. It has a low incidence of sedation, orthostatic hypotension, and weight gain. It does not interact with muscarinic receptors so no anticholinergic effects are seen. At low doses, incidence of EPS is low, but with higher doses the incidence is similar to typical agents. Some patients may experience a prolongation of the QT/QT_c interval, but the clinical significance of this prolongation has not been established.[25]

Ziprasidone (Geodon®) is a relatively new antipsychotic agent. The major consideration for this agent is a greater capacity to prolong the QT/QT_c interval compared with most other antipsychotics. This prolongation has not been shown to induce cardiac arrhythmias, but other agents that prolong the QT interval have been shown to cause torsade de pointes.[25,29]

	Sedation	Orthostatic Hypotension	Anticholinergic Effects	Extrapyramidal Symptoms	Weight Gain
Clozapine	H	M	H	L	M
Olanzapine	H	M	H	L	M
Quetiapine	M	M	N	L	L
Risperidone	L	L	N	L	L
Ziprasidone	L	L	L	L	N

H = high incidence, M = moderate incidence, L = low incidence, N = no effect

Table 3. Comparison of the Incidence of Adverse Effects for Atypical Antipsychotic Agents

Adverse effects

The diversity of location and function of the D_2 receptor are shown in Table 4.[6] This variety of function makes it difficult to selectively relieve the symptoms of schizophrenia without incidence of adverse effects. In addition to interaction with dopamine receptors, the antipsychotic agents interact with a number of other neurotransmitter receptors to produce a wide variety of undesirable effects.

Tract	Innervation	Function	Antagonist Effect
Nigrostriatal	Caudate nucleus and putamen	Extrapyramidal system and movement	Movement disorders
Mesolimbic	Limbic areas	Arousal, memory, stimulus processing, and motivational behavior	Relief of psychosis and positive symptoms of schizophrenia
Mesocortical	Frontal and prefrontal lobe cortex	Cognition, communication, and social function	Potentially increases the negative symptoms of schizophrenia
Tuberoinfundibular	Pituitary gland	Regulation of prolactin release	Increased prolactin

Table 4. Location and Function of Dopaminergic Receptors and Effect of Antagonists

Central Nervous System Effects

These effects are commonly referred to as the extrapyramidal side effects (EPS) and are much more common with typical agents. The effects include the following:

Dystonia

This condition is defined as a state of abnormal tonicity.[30] It is commonly described as a severe muscle spasm, and can be frightening and painful for the patient. The onset is usually seen in the first 3 days after administration.[31] Dystonia can affect a number of areas including the tongue (dysphagia and glossospasm), neck (torticollis and retrocollis), trunk (hyperextension), face (grimace), eyes (blepharospasm and oculogyric crisis), jaw (trismus), and may be life threatening

(pharyngeal-laryngeal).[9] The exact mechanism is unknown, but may involve increased release of dopamine or heightened sensitivity of dopamine receptors attributable to blockade.[30] Young males are at highest risk for dystonia. High-potency agents also increase risk.[2] If treatment is necessary, a variety of options are available. IV or IM anticholinergics (benzotropine) or IM diphenhydramine are effective.[9] Alternative treatment includes benzodiazepines.[6] Discontinuation of antipsychotic therapy is not usually necessary. Relief is normally seen within 5 minutes if treatment is administered IV and 15 to 20 minutes if given IM.[9] Propylaxis with anticholinergics is not generally recommended except in young males taking high-potency typical agents and in patients with a previous history of dystonia.[2]

Pseudoparkinsonism

This condition is similar to idiopathic parkinsonism. The symptoms may include any of the following: akinesia, bradykinesia, or other decreased motor activity, "pill rolling" tremor that is more noticeable at rest, cogwheel rigidity, postural abnormalities (stooped posture), or a shuffling gait.[32] Anticholinergic symptoms may also be present that include seborrhea, drooling (sialorrhea), and increased sweating (hyperhidrosis).[30] The mechanism for parkinsonism is a deficiency of dopamine.[30,32] Onset is usually within 1 to 2 weeks after initiation of therapy. The incidence ranges from 15% to 36% depending on the typical antipsychotic employed.[6] High-potency agents can produce akinesia alone in approximately 60% of patients.[6] Additional risk factors include increased age (> 40 years) and female sex.[6] Treatment with anticholinergic agents is generally effective for relief of symptoms in 3 to 4 days, but longer treatment ($\leq$ 2 weeks) is generally necessary for complete resolution.[30,32] Discontinuation of the antipsychotic is generally not necessary. The dopaminergic agent amantadine has also been shown to be effective for treatment with lower effect on memory function than anticholinergics. Long-term treatment of pseudoparkinsonism is controversial, and attempts should be made to taper therapy after 3 to 4 months.[30] Propylaxis against pseudoparkinsonism is not generally recommended.[30]

Akathisia

This condition is characterized by motor restlessness. It is typically diagnosed following patient complaints of inner restless or a compulsion to remain in motion combined with objective symptoms of pacing, shifting, shuffling, or tapping of the feet. The onset generally occurs later than pseudoparkinsonism symptoms. This condition occurs in 20% to 40% of patients on high-potency typical agents.[30] The pathophysiology is unknown but two theories are used to explain it.[30] The first is that a dopamine blockade in the mesocortical region leads to increased locomotor activity. The second states that a dopamine blockade causes dysregulation of the noradrenergic tracts to the limbic system. Treatment may involve switching to an atypical agent.[33] β-blockers appear to be the most effective adjunct therapy for this condition, but benzodiazepines have also been used.[30,33]

Tardive Dyskinesia (TD)

This condition is characterized by rhythmic, persistent, and involuntary movements. The onset is late compared with initiation of therapy and is usually insidious. The traditional description of TD is orofacial movements.[32] These signs are usually the first detectable symptoms and include mild

tongue movements. This progresses to more pronounced signs including tongue thrusting, twisting, and fly catching behavior. Facial movements involve the lips (smacking, puckering, sucking), facial muscles (tics, grimace, puffing of cheeks, arching of brows), and eyes (frequent blinking, upward deviation).[34] These symptoms are especially serious if they interfere with chewing, swallowing, or speaking; weight loss is a common effect. The extremities and trunk may also be involved.[35] Unusual posturing, pelvic thrusting, axial hyperkinesias, jerking, rocking, and swaying are sometimes observed. The orofacial symptoms are more common in older patients, while the trunk movements are more common in young patients.[6] Stress may worsen the movements. Sedation typically decreases movements and they disappear when sleeping.

The pathophysiology of TD is complex, and many theories have been proposed to explain it.[6,36] These include the traditional theory that postsynaptic dopamine receptor blockade leads to disuse denervation. This theory is frequently considered with a cholinergic dysfunction owing to dopamine/acetylcholine imbalance. These theories might explain why the atypical agents seldom produce TD, since they have less affinity for dopamine receptors. Another explanation for TD is that the metabolism of dopamine increases, leading to an increase in free radical formation that results in damage to the neurons. This theory is supported since antioxidants such as alpha-tocopherols have shown some benefit in patients with TD.[35]

Risk factors for tardive dyskinesia include increased age, diabetes mellitus, mood disorders, and possibly female sex.[36] The most significant risks, however, are the duration of therapy, daily dosage, and total cumulative dose.[36] Dosage reduction may have a significant effect if the patient can tolerate the smaller dose without the return of symptoms.

There are no standard criteria for diagnosis, but evaluation can be made using rating scales. Two of these include the Abnormal Involuntary Movement Scale (AIMS) and the Dyskinesia Identification System: Condensed User Scale (DISCUS), but neither is diagnostic when used alone.[37,38] These evaluations are significant because prevention of TD is important because of the difficulty in treating the symptoms. The incidence of TD with typical agents is highly variable.[36] One study showed an incidence of 4% per year of drug treatment for the first 4 years of treatment.[39] The significantly lowered incidence of TD is a major advantage for atypical agents and is a reason that they are first-line therapy.

Early signs of TD may be reversed but if left untreated they may become irreversible even on discontinuation of the antipsychotic. There are no approved agents for treatment, but a number of agents have been used that represent remedies for the pathophysiology theories (Vitamin E, benzodiazepines, baclofen, propranolol).[36,40] Another possible remedy is to switch antipsychotic agents. If the patient is taking a typical agent, then a switch to an atypical agent may provide some benefit. Clozapine has not been reported to cause TD and is a recommended agent in patients with moderate to severe symptoms. It has been shown in controlled trials to reduce involuntary, abnormal movements by 50%.[36]

Other CNS Effects

Sedation

The antihistaminic and antiadrenergic effects of these agents most likely cause sedation. It usually occurs early in treatment and may decrease over time even if left untreated. Administration of the dose at bedtime may significantly reduce daytime sedation and improve sleep.

Seizures

γ-Aminobutyric acid (GABA) depletion by antipsychotics lowers the seizure threshold and leads to an increased risk of drug-induced seizures.[6] The risk is further increased by a preexisting seizure disorder, previous history of drug-induced seizures, CNS pathology or head trauma, or abnormal EEG.[6] The occurrence of an isolated seizure may be treated with a decreased dosage, but anticonvulsants are not recommended.[6] The agents with the lowest seizure risk are atypical agents (with the exception of clozapine), haloperidol, thioridazine, fluphenazine, and molindone.[41] The highest risk agents are chlorpromazine and clozapine followed by trifluperazine and perphenazine.[41]

Thermoregulation

Adjustment of the body temperature to ambient temperature (poikilothermia) can be a serious effect in extremes of temperature.[42] In hot weather, hyperprexia is a concern, and may be aggravated by the inhibition of sweating caused by anticholinergic effects. In colder environments, hypothermia is a concern, especially in elderly patients. These effects occur more often with low-potency typical agents and with atypicals that have higher anticholinergic activity.[6]

Neuroleptic Malignant Syndrome (NMS)

This effect occurs in less than 1% of patients and may be seen with both typical and atypical agents.[16,43] The onset of symptoms is variable in relation to initiation of therapy, but the condition develops rapidly. The mechanism is unknown, but may involve the disruption of central thermoregulatory controls or an excess production of heat caused by skeletal muscle contraction. Symptoms include elevated body temperature (may reach 106°F), altered level of consciousness, muscle rigidity, and autonomic dysfunction.[6] A number of treatments is used including bromocriptine, amantadine, and the muscle relaxant dantrolene, but the most effective treatment is the rapid discontinuation of antipsychotic therapy.[44] Symptom recognition along with supportive therapies (antipyretics, cooling blankets, fluids and electrolytes, and ventilation) has significantly reduced the mortality associated with NMS. Mortality that was as high as 20% has been reduced to 4%.[6,43]

Cardiovascular Effects

Orthostatic Hypotension

This effect is defined as a drop in systolic pressure of greater than 20 mm of Hg.[6] It is caused by blockade of α_1-adrenergic receptors that inhibit reflex vasoconstriction when the patient rises to a sitting or standing position. Patients may experience light-headedness and fainting. Mild cases can be resolved by educating the patient concerning slow changes in postural position or support hose. Most patients develop tolerance to the effect in 2 to 3 months, but for those that do not develop tolerance, lowered doses or changing agents may be necessary. Higher-potency agents tend to have less effect. Severe hypotensive episodes should be treated by placing the patient in the Trendelenburg position and administering IV fluids.[6] If the condition is not satisfactorily resolved, then pressor agents may be necessary, but only selective α-

agonists (phenylephrine, metaraminol) should be used.[23] Epinephrine also has β-adrenergic agonist activity and may result in further lowering of the pressure.

Electrocardiogram (ECG) Changes

These effects are generally clinically insignificant in healthy patients and include increased heart rate (sinus tachycardia from anticholinergic effect or reflex tachycardia from α-adrenergic antagonism), flattened T waves, ST segment depression, and prolongation of QT and PR intervals. In patients with pre-existing heart conditions or older than 40 years, more caution is necessary. Ziprasidone does produce greater QT prolongation, but the clinical significance is not clear at this time.[29]

Endocrine Effects

Hyperprolactinemia

This condition is relatively common, especially with high-potency typical agents or risperidone, and is attributable to dopamine blockade in the hypothalamus. This condition may produce menstrual irregularities or amenorrhea. Gynecomastia is seen in males and galactorrhea is seen in both sexes. Tolerance does not usually develop, and switching therapy to olanzapine or quetiapine, which has no effect on prolactin levels, is the most rational treatment option.[45]

Weight Gain

Many factors are involved including diet, activity levels, and consumption of improper foods attributable to poor self-care. The atypical agents more commonly cause this effect, and significant weight gain has been seen with clozapine and olanzapine.[46] Ziprasidone does not appear to have this effect.[29] Patients should be educated about the possibility of weight gain, proper nutrition, and exercise.

Glucose Regulation

There is mounting evidence that the atypical antipsychotics may interfere with glucose regulation and metabolism. Case reports have indicated that some patients treated with clozapine and olanzapine may develop diabetic ketoacidosis.[47] Although the risk appears to be small, patients may need to be monitored for metabolic abnormalities.

Hematologic Effects

Transient leukopenia is common with antipsychotic therapy but usually does not progress to clinical significance.[48] If the leukopenia is persistent or severe, then the antipsychotic should be discontinued and WBC counts should be monitored closely.

Agranulocytosis is the most dangerous hematologic effect. It occurs with piperazine side-chain phenothiazines but is most prominent with clozapine. The incidence is $\leq 1\%$.[49] Increasing age and the female sex are the greatest risk factors.[50] The greatest risk for occurrence is between months 1 and 6 of treatment.[50] The product labeling of clozapine mandates WBC count monitoring during therapy and for one month following discontinuation.[25] This effect is idiosyncratic and appears to be unrelated to dose. It may appear as a local infection with sore throat, leukoplakia, and ulcerations of the pharynx. If the total WBC count is less than $2000/mm^3$ or the absolute neutrophile count (ANC) is less than $1000/mm^3$, the agent should be discontinued. Filgrastim (Neupogen®) has been used to decrease morbidity.[51]

Hepatic Effects

Elevated aminotransferases and alkaline phosphatase are commonly reported and may not produce clinical symptoms.[52] This elevation occurs most often in patients under 50 years and is not dose related. Mild elevations should be followed, and if

aminotransferases rise to >3 times normal levels, then the antipsychotic should be switched to a structurally unrelated agent.[6] The potential for these hepatic effects may require special attention in patients with a history of alcohol abuse.

Cholestatic jaundice occurs rarely with phenothiazine treatment. This effect is, most likely, attributable to a hypersensitivity reaction, and occurs within the first 2 weeks of therapy.[52] Resolution typically occurs without residual liver damage upon discontinuation. Therapy should be resumed as late as possible using a non-phenothiazine agent.[6]

Ophthalmologic Effects

The anticholinergic effects of antipsychotic agents may produce a lack of accommodation. This effect is usually temporary, but severe cases may be treated with ophthalmic pilocarpine drops.[53] This anticholinergic effect may also exacerbate existing narrow-angle glaucoma, and antipsychotics should be used with caution in susceptible patients.[53]

Lens and cornea opacity resulting from deposition of drug may occur with chronic phenothiazine use. This effect does not usually affect visual acuity, but eye examinations are recommended in patients receiving long-term phenothiazine treatment.

The most severe ophthalmologic effect, retinitis pigmentosis, may occur with daily doses of thioridazine greater than 800 mg.[53] It is cause by deposition of melanin, and may lead to permanent visual impairment.

Animal studies have linked quetiapine to increased cataract formation.[54] This effect has not been reported in humans, however, and patients receiving this agent should have baseline and periodic eye examinations.

Genitourinary Effects

The anticholinergic effects of antipsychotics may produce urinary hesitancy and retention. Men with benign prostatic hyperplasia are especially affected.[55] Some patients, especially older females, may experience urinary incontinence.[56] The cause of incontinence is not well understood but is probably unrelated to urinary retention.

A more troubling problem that frequently affects compliance is the sexual dysfunction related to antipsychotic therapy. The anticholinergic effects of these agents have been proposed to cause erectile dysfunction in males and decreased libido and anorgasmia in females.[6] The α-adrenergic blockade is believed to be responsible for the priapism and delayed ejaculation seen in males.[2] It is also possible that these effects are related to a decreased testosterone level related to the hyperprolactinemia.[57] This effect may contribute to the decreased libido experienced by male patients. A reasonable treatment for sexual dysfunction is switching to an atypical agent with lowered α-adrenergic and anticholinergic effects (olanzapine or quetiapine).[6] These agents also tend to have less effect on prolactin levels.

Dermatologic Effects

Contact dermatitis may occur in patients, and is usually relieved by quickly swallowing the liquid dose.[6] It may also occur in caregivers who prepare liquid solutions, so caution should be used when handling these preparations.

Allergic reactions are rare and usually occur within 2 months of therapy initiation.[6] Common symptoms of an allergy are

maculopapular, erythematous, and pruritic rashes. The reaction should be treated with drug discontinuation and topical steroids.

Phenothiazines, especially chlorpromazine, absorb UV light and form free radicals, which can damage the skin and induce photosensitivity.[6,42] Exposure to sunlight should be limited if receiving these agents, and patients should be educated on using sunblock and wearing protective clothing and sunglasses.[42] These agents may also produce a bluish-gray discoloration of areas exposed to sunlight.[6]

Sudden Death Syndrome

The cause of this rare effect is not known. A widely accepted theory is that ventricular arrhythmias worsen to cause fibrillation and death.[6] Another theory is that laryngeal/pharyngeal dystonia leads to hypoxia and death.[6] This condition is also known as obstructive asphyxia or "café coronary." A number of other drug- and nondrug- related proposals has been made to explain this problem.[58]

Miscellaneous Adverse Effects

Sialorrhea is commonly associated with clozapine use, and can be especially troubling during sleep.[25] Clonidine and benztropine are potentially effective therapeutic options.[59]

Special Populations

Pregnancy and Lactation

The safety of these agents has not been established. They are secreted in breast milk, but this is not a contraindication for their use.[25]

Elderly Populations

These patients are especially sensitive to anticholinergic effects of drugs. Caution should be used with low-potency typical agents. As with all populations, atypical agents are recommended first-line therapy.

Drug Interactions

Most of the drug interactions involving antipsychotics are minor. Some severe interactions related to metabolism are seen and have been previously reviewed.[25]

Overdose Toxicity

The therapeutic index is high for antipsychotic agents, and clinically significant overdoses are rare.[23] Mild intoxication results in sedation, hypotension, and miosis. Severe intoxication may result in agitation and delirium, which progresses to motor retardation, seizures, cardiac arrhythmias, respiratory arrest, coma, and death. Treatment of severe intoxication includes supportive measures, gastric lavage, and activated charcoal.[6] Induction of emesis is inhibited because of the antiemetic effect of many antipsychotics, and dialysis is ineffective owing to drug-protein binding.[6]

CONCLUSION

In the past, because of the lack of efficacy and adverse effect profiles of the typical antipsychotic agents, partial symptom relief was commonly all that could be expected. With the advent of newer, atypical antipsychotics having higher efficacy and lowered adverse effects, complete symptom remission has become a reality. The overall result is that a patient suffering from a schizophrenic illness now has a much greater likelihood of becoming a functioning person who is able to work, participate in family life, and make a positive contribution to society.

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