SCIENTIFIC SECTION

Review Article

Pharmacologic features and effects of neuroleptics

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Neuroleptic drugs reduce the severity and prevent the recurrence of symptoms of schizophrenia. Recent studies indicate that these drugs probably produce their antipsychotic effects by blocking dopamine receptors in the brain, although they also block acetylcholine and norepinephrine receptors. The potency of commercially available neuroleptics in blocking dopamine receptors varies widely, being related to the compound's lipid solubility.

Neuroleptics predispose the patient to short-term and long-term medical hazards that must be weighed against the benefits of reduced symptom intensity, shortened psychotic episodes and lessened likelihood of recurrence of acute schizophrenic episodes. The side effects associated with short-term therapy are either extremely rare or are treatable by dose change, medication change or the use of additional drugs. In long-term therapy the risks are more problematic in that they are sometimes irreversible. These include tardive dyskinesia, skin discoloration and corneal deposits. The clinician must consider the pattern and severity of each patient's present and past psychotic episodes before deciding whether maintenance therapy with neuroleptics is justified. If it is, doses should be re-evaluated frequently and kept as low as possible. Concomitant administration of anticholinergic agents should be avoided if possible. Most important, the long-term administration of neuroleptics should be prescribed only for patients with schizophrenia and not for those with conditions that respond to other treatments.

Les neuroleptiques réduisent la gravité des symptômes schizophréniques et ils en préviennent les récidives. Des études récentes indiquent que ces médicaments exercent probablement leurs effets antipsychotiques par un blocage des récepteurs dopaminergiques du cerveau, bien qu'ils bloquent aussi les récepteurs de l'acétylcholine et de la norépinéphrine. L'activité bloquante des neuroleptiques du commerce sur les récepteurs dopaminergiques varie considérablement et elle est fonction de leur liposolubilité.

Les neuroleptiques prédisposent les patients, à court et à long terme, à des risques médicaux qui doivent être pesés en fonction des bénéfices escomptés qui sont une réduction de l'intensité des symptômes, une réduction de la durée des épisodes psychotiques et une baisse des possibilités de récidive des accès de schizophrénie aiguë. Les réactions indésirables lors d'un traitement à court terme sont ou bien extrêmement rares ou traitables par une modification de la dose, un changement de médication ou l'emploi de médicaments additionnels. Lors d'un traitement au long cours les risques sont plus préoccupants car ils sont parfois irréversibles. Ceux-ci comprennent les dyskinésies tardives, les colorations anormales de la peau et les dépôts cornéens. Avant de décider du bien-fondé de poursuivre un traitement neuroleptique d'entretien le clinicien doit considérer l'évolution caractéristique et la gravité des accès psychotiques présents et passés de chaque patient. Quand le traitement d'entretien est indiqué les doses doivent être réévaluées fréquemment et gardées au plus bas niveau possible. L'administration concomitante d'un anticholinergique doit être évitée si possible. Plus important encore, l'administration au long cours de neuroleptiques doit être réservée aux patients souffrant de schizophrénie et non prescrite pour des affections qui répondent à d'autres traitements.

Antipsychotic agents, or neuroleptics, were once referred to as "major tranquillizers", an unfortunate misnomer because it implied a nonspecific tranquillizing action. This implication led to the misuse of these potent drugs for conditions that appeared, clinically, to require tranquillization: anxiety, insomnia, agitated depression, the hyperkinetic syndrome or mania, aggressive behaviour or the effects of withdrawal from various substances. In 1969 Kline[1] listed over 30 conditions for which phenothiazines, the earliest synthesized neuroleptics, had been used in the years 1950 through 1967.

Far from being nonspecific "tranquillizers", all neuroleptics are thought to exert their antipsychotic effect by a selective action on dopamine-mediated pathways in the limbic and striatal regions of the

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brain.[2-4] These agents should be used only for psychotic conditions, particularly schizophrenia, in which these pathways are believed to be dysfunctional.[5]

The short-term use of neuroleptics is safe and effective for acute agitation, hypomania, impulsivity and aggressive behaviour, as well as for intractable vomiting and hiccoughs. However, the long-term prescription of neuroleptics for chronic anxiety, insomnia and agitated depression, although commonplace, is unjustified. Even at low doses,[6] neuroleptics taken for long periods cause chronic blockade of the dopamine receptor, which may lead to supersensitivity related to "chemical denervation" in the nigrostriatal pathways.[7] The eventual result may be tardive dyskinesia, a condition so called because it does not usually appear until the patient has had several years of neuroleptic therapy. The symptoms of tardive dyskinesia include purposeless movements of lips, tongue, jaw, facial muscles and eyelids, choreoathetoid movements of the arms and legs and, less commonly, torsive movements of the trunk. In older patients the dyskinesia may be irreversible.[8] Because of this association of neuroleptics with tardive dyskinesia long-term prescription of the various neuroleptic agents should be reserved for schizophrenic conditions.[9]

Pharmacokinetic features of neuroleptics

Chlorpromazine is the prototype and most extensively studied of the neuroleptics. It is almost completely absorbed from the gastrointestinal tract but is biotransformed into more than 165 metabolites, some of which are psychopharmacologically inactive.[10] Although most of the metabolites are strongly bound to plasma proteins, the unbound portion passes through the blood–brain barrier and achieves a concentration in the brain that is five times that in the blood. Following oral intake blood levels of neuroleptics peak within 1½ to 3 hours. Neuroleptics are stored in adipose tissue, and after the end of long-term treatment their metabolites can be measured in the blood for as long as 6 months.[11]

When haloperidol is administered intramuscularly in emergency situations it is totally absorbed in 20 minutes, but when it is administered orally its bioavailability is so reduced that an intake of 20 mg is required to equal the effect of 5 mg given intramuscularly.[10]

Accurate measurement of blood levels of neuroleptics has been impossible because of the presence of active and inactive metabolites. Currently dopamine-receptor assay techniques are being developed to aid clinicians in evaluating the patient's response.[12] These new techniques may yield a better understanding of neuroleptic nonresponse and lead to more effective therapy and prophylaxis.

Mode of action

The three-dimensional structure of neuroleptics may explain their selective blocking action on dopamine receptors. All these drugs are able to adopt a conformation that overlaps that of dopamine;[13] thus, they compete with dopamine for binding at dopamine receptor sites on nerve cells. Because of structural variations, several of the neuroleptics occupy other receptors as well. For example, spiroperidol (not currently used in North America) occupies serotonin receptors,[14] and flupenthixol has a high affinity for dopamine-sensitive adenylate cyclase, which is distinct from the dopamine receptor.[13] Some neuroleptics also occupy α-adrenergic and muscarinic cholinergic receptor sites in the brain, which accounts for many of their side effects. Affinity for the dopamine receptor, however, is common to all neuroleptics and is proportional to the dose used to control psychotic symptoms.[3]

Therapeutic doses of neuroleptics differ because of varying lipid solubility.[11] For instance, trifluoperazine is 10 times as fat soluble as chlorpromazine and therefore dissolves 10 times more readily in the lipid cell membrane. For this reason it binds to the membrane's neuroleptic receptor at plasma levels 10 times lower than that of chlorpromazine.

The nerve fibres affected by the antipsychotic action of neuroleptics are probably the mesocortical and mesolimbic dopaminergic neurons.[15]

Schizophrenia and the therapeutic effects of neuroleptics

Diagnosis of schizophrenia

Because of their many side effects, neuroleptics should be reserved for the treatment of schizophrenia. However, it is not easy to diagnose this condition. Symptoms come and go and their intensity fluctuates. Perhaps the most pathognomonic sign, when present, is a fragmented, overinclusive style of thinking that manifests itself in the patient's speech. Even experienced clinicians, however, cannot make a firm diagnosis of schizophrenia on the basis of symptoms and signs alone. Corroboration is needed from details of the patient's life history and from the response to treatment (Table I).

Early response

Initially neuroleptics induce sedation. This is a beneficial effect since acutely ill patients may have suffered several days of terror and insomnia before receiving any treatment. However, although sedation may be medically indicated, individuals who believe they are in imminent danger (as acutely ill schizophrenic patients often do) may consider it essential to keep awake and vigilant, and may not welcome the sedative effect, especially if they feel they are unpro-

Table I—Factors to assess in the diagnosis of schizophrenia

Symptoms and signs
Family history
Personality before illness
Age at onset of illness
Precipitating factors
Response to neuroleptics
Recurrence of illness
Chronicity of illness
Functional impairment

tected. Such patients usually feel more protected in a hospital, and for this reason it is usually necessary that they be admitted to hospital during an initial episode of schizophrenic illness.

As their terror abates, patients should become less suspicious and less hostile. Their idiosyncratic mannerisms should lessen and they should become more approachable. Patients who respond adequately to neuroleptics usually show these psychologic changes in the first 5 days of their treatment.

Distorted perceptions should begin to wane within 2 weeks. Distorted beliefs that are based on altered perceptions, however, may never fully disappear: patients may no longer hear voices whispering in their room but may continue to believe that in the past undercover agents had deliberately installed electronic equipment to keep them under surveillance.

Difficulties with thinking and with emotional response may take 2 months to dissipate. Improvements associated with neuroleptic therapy occur most rapidly in the first 2 months and continue at a slower pace for approximately 6 months.

A feeling of dysphoria often remains with patients after the acute stage of their illness is over. Neuroleptics do not relieve this problem, and patients may feel that these drugs make it worse. This is possible. In part, the dysphoria may be a symptom associated with the patient's convalescence and may simply need time to abate. In addition, these empty feelings — lack of energy, lack of initiative, lack of ambition, interpersonal withdrawal — may be "deficit" symptoms of schizophrenia that are not altered by neuroleptics.[10] But, in part, the dysphoria may also be a side effect of neuroleptics. Whether this is the case or not, neuroleptic therapy cannot be stopped at this point because of the 70% risk that schizophrenia will recur within a year if this is done.[15,16]

Effects of maintenance therapy

Over 100 controlled studies[15] have shown that maintenance therapy with neuroleptics is effective in preventing schizophrenic relapse.[12] This therapy reduces the readmission rate threefold.[17] In those who do have a relapse while taking neuroleptics in maintenance doses, further recurrences may be prevented by raising the dose or by ensuring that the patient is absorbing the drug adequately or is complying with the therapy as recommended.

On the other hand, there are risks involved in long-term maintenance therapy with neuroleptics, and some individuals appear to make the same or even better progress without drugs.[18] At present it is impossible to predict who these individuals will be; they are not necessarily those who show mental reintegration most quickly and completely after the psychotic episodes.[19] Because of this unpredictability, the decision to stop maintenance therapy with neuroleptics should be made with caution. It is currently considered advisable to give maintenance neuroleptic therapy for 2 years after the acute illness. By that time the patient and the physician should know and trust one another. The dose of the neuroleptic can then be gradually reduced, with intermittent attempts at withdrawing the drug for short intervals ("drug holidays"). During this time the physician should regularly and frequently review the patient's symptoms and interpersonal behaviour and adjust the neuroleptic dose accordingly.

Side effects of neuroleptics

Dopamine blockade

Neuroleptic-induced tardive dyskinesia is probably an outcome of the supersensitivity related to the "chemical denervation" that results from long-term dopaminergic blockade.[7] This same blockade of dopamine receptors, which, when it occurs in the limbic region, is presumed to be responsible for the antipsychotic action of neuroleptics, also occurs in the nigrostriatal pathways of the basal ganglia and mimics the effects of Parkinson's disease, a condition that results from the degeneration of presynaptic dopaminergic neurons. Acute dystonias (torticollis and oculogyric crises), akathisia (motor restlessness) and the parkinsonian syndrome (akinesia, rigidity and tremor) can occur. Anticholinergic drugs given once or twice a day (in a daily total dose of 2 to 10 mg) will control these symptoms. The acute dystonias usually respond to 2 mg of benztropine given intramuscularly. The use of anticholinergic drugs can usually be stopped after 3 months without a return of symptoms,[20] although some researchers have found that the need for these drugs is continuous in patients with chronic schizophrenia who are receiving long-term neuroleptic therapy.[21] In the long-term maintenance treatment of schizophrenia, clinicians should, whenever possible, give neuroleptics in doses that are sufficiently low that the concomitant administration of anticholinergics is not necessary.

Neuroleptic blockade of the dopaminergic tuberoinfundibular system suppresses the inhibition of prolactin secretion, thereby enhancing prolactin production, with ensuing breast swelling. However, fewer than 3% of women treated with neuroleptics complain of this symptom. Neuroleptics also block the secretion of follicle stimulating hormone and luteinizing hormone. This can lead to both anovulation and amenorrhea. Some women, however, may continue to ovulate. A gain in body weight is a common side effect of neuroleptics. It may be due to the patient's relative inactivity, fluid retention and increased appetite; the last is thought to be mediated by dopaminergic blockade of hypothalamic neurons. For such patients an energy-restricted diet and an increase in the amount of exercise they take are indicated.

Alpha-adrenergic blockade

Postural hypotension, mydriasis, skin flushing, cardiac conduction abnormalities and ventricular arrhythmias can result from neuroleptic administration. The main cause of the cardiac disorders appears to be prolonged cardiac repolarization due to α-adrenergic receptor blockade. Sedation and inhibition of ejaculation of semen are also thought to be consequences of α-adrenergic blockade. These symptoms are seen most

often in patients taking the high-dose neuroleptics, which block both dopamine and α-adrenergic receptors at roughly equal concentrations. Haloperidol, in contrast, will only block α-adrenergic receptors at a concentration 25 times as high as its dopaminergic-blocking concentration.[11]

Norepinephrine is the agent of choice for treating acute neuroleptic-induced hypotension.[10]

Cholinergic blockade

Although most neuroleptics block muscarinic cholinergic receptors, they require very high concentrations to do so. The exception is thioridazine, which blocks these receptors at relatively low concentrations. Anticholinergic effects include dry mouth, constipation, urinary retention, blurred vision, miosis, reduced gastric motility, mental confusion, tachycardia, increased intraocular pressure and sexual impotence.

These effects are, of course, increased by the use of anticholinergic drugs. However, because the effects usually disappear within 8 hours, giving the anticholinergic agent only at bedtime may solve the problem.[10] Fecal impaction and urinary retention must be watched for in elderly patients.

Increased fluid intake, a diet high in roughage and the use of sugarless lozenges may reduce some of the distress of anticholinergic effects, and tolerance does develop.

Miscellaneous side effects

Neuroleptics reduce the seizure threshold in a manner that seems to be dose-related. Photosensitivity is a problem in 4% of patients, especially those taking chlorpromazine. These patients must be warned to use sunscreen lotions and to avoid prolonged exposure to sunlight, or permanent skin discoloration may occur. Long-term administration of neuroleptics can cause corneal and lens opacities that, fortunately, do not interfere with vision. Skin rashes may also occur as a result of drug allergy. However, as cross-sensitivity between neuroleptics is rare, when a patient is allergic to one of these drugs another can be tried. Thioridazine has been implicated in irreversible retinitis pigmentosa. Agranulocytosis has occurred in the first 2 months of treatment in 1 in 5 million patients, and hypersensitivity-induced obstructive jaundice, usually in the first month of treatment, has occurred in 1 in 1000 patients.[10]

Choice of a specific neuroleptic

Neuroleptics appear to all have the same mode of action and to be equally efficacious.[3] Despite this, some individuals respond to one drug but not to another. It was once thought advisable to prescribe the more sedating, high-dose, low-potency neuroleptics, such as chlorpromazine, to excited patients and the more energizing, low-dose, high-potency neuroleptics, such as fluphenazine, to withdrawn patients (Fig. 1). Physicians now acknowledge that symptoms tend to be fluid in schizophrenia and that it is best to treat the individual and not the symptoms. The choice of a neuroleptic is now more likely to depend on the past response of the patient, or of a member of the patient's family, to a particular drug, on the patient's vulnerability to specific side effects, which vary considerably from drug to drug, and on the patient's ability to absorb drugs taken by mouth or to adhere to an oral regimen. The cost of the drugs, which varies considerably, must also be taken into account.

During the acute phase of schizophrenia, when large doses of neuroleptics may be necessary, the use of low-dose, high-potency drugs — those of low cardiovascular toxicity — is advisable, especially for older patients. For maintenance pharmacotherapy, when less neuroleptic effect is required, the use of high-dose, low-potency drugs — those that produce parkinsonism less readily — is less likely to necessitate anticholinergic therapy or to lead to tardive dyskinesia.[22]

Depot neuroleptics

Depot neuroleptics (fluphenazine enanthate, fluphenazine decanoate, pipotiazine, flupenthixol decanoate and fluspirilene) are given from once a week to once a month intramuscularly. They are beneficial for patients who, for whatever reason, cannot take medication orally. However, because depot neuroleptics are high-potency drugs, they may produce extrapyramidal reactions that may be hard to control. It is usually necessary to give anticholinergics as well. The use of

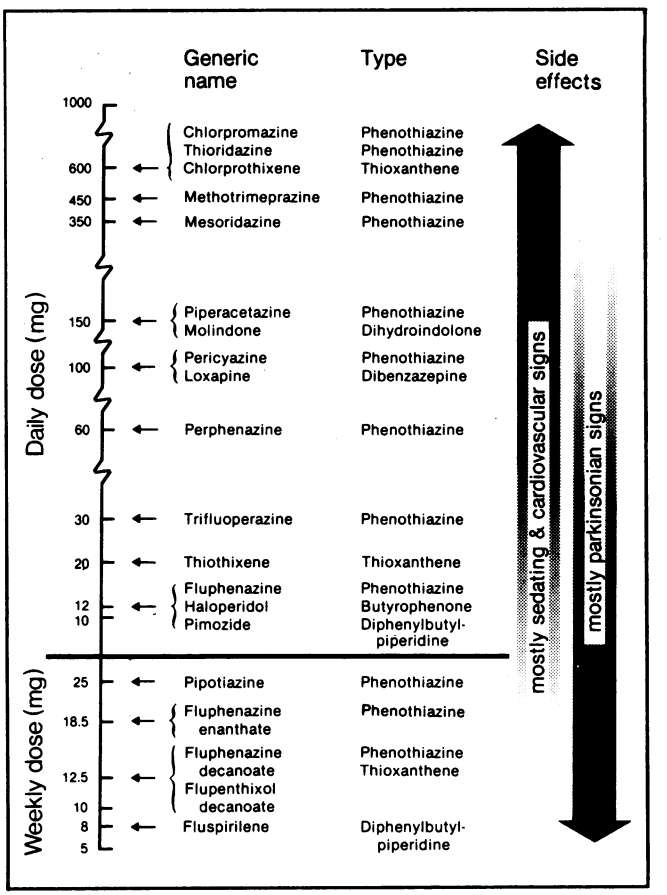

FIG. 1—Approximate dose of neuroleptics for adults, arranged from the high-dose, low-potency agents to the low-dose, high-potency agents. These doses may vary from as little as half to as much as twice those shown.

depot drugs leads to tardive dyskinesia more often than therapy with low-potency neuroleptics that are taken orally.[22] Patients who can be relied on to take their oral medication probably should not be given depot neuroleptics.

Drug combinations

As neuroleptic and antidepressant drugs both have anticholinergic properties, an unwanted anticholinergic effect results when these drugs are taken in combination, especially in patients taking anticholinergic agents as well. In addition, neuroleptics (particularly phenothiazines) and antidepressants appear to be synergistic in their toxic effects on the cardiovascular system.[23] In practice it is rarely necessary to prescribe neuroleptics and antidepressants together. Patients who drink alcohol while taking neuroleptics are predisposed to acute dystonias.[24] When antacids and anticholinergic agents are taken with neuroleptics the absorption of the neuroleptics is reduced.[25] Prepackaged combination drugs should be avoided.

Failure to respond

Failure to respond may mean that the patient is not taking the drug, is not taking a large enough dose or is not absorbing the drug. If the dose is adequate and compliance has been ensured, a different neuroleptic should be tried. The therapeutic approach for nonresponse should be to shift from the high-dose, low-potency drugs to the low-dose, high-potency drugs or from one class (for example, phenothiazines) to another (for example, butyrophenones). It is important to remember that optimal dosages vary widely among patients.

Dosage

In the acute stage of schizophrenia

The appropriate initial dose of a neuroleptic will depend on the degree of the patient's disorganization and agitation as well as on age, body build and past and present medical history, including any known history of a previous drug response. The initial dose can be higher for patients in hospital than for outpatients. The range of doses that are therapeutic seems to be wider for women than for men; women often respond well to low doses, yet can tolerate higher doses better than men.[26]

Haloperidol is an especially useful drug in emergency care. It can be administered intramuscularly — 10 mg immediately and 5 mg every 30 minutes up to a daily dose of 125 mg — until the patient's symptoms are controlled. As it has relatively little α-adrenergic blocking effect, there is a minimal risk of hypotension, a side effect that can be a problem when high-dose, low-potency drugs are used intramuscularly. An additional advantage of haloperidol is that it can be given orally in an odorless, tasteless concentrate that achieves peak levels in the blood within 2 hours.[10] Intramuscular fluphenazine has recently become available for use in emergency care as well.

The usual dose range of chlorpromazine for acute schizophrenia is 300 to 1400 mg. The initial dose should be divided and given two or three times a day because single large doses can cause profound hypotensive effects, especially in the elderly.

For maintenance therapy

After the acute phase the patient's clinical improvement and the presence of side effects signal the need for dose reduction. It is inadvisable for a reduction in dose to coincide with the patient's discharge from hospital. Nor should dose reduction be attempted if the patient is experiencing any major stress, such as starting a new job, moving away from home or returning to school. At these times the patient needs to be protected against the extra stress. Dose reductions should be made slowly and gradually during nonstressful periods, with the full understanding and cooperation of the patient and the family. Patients must understand that neuroleptics have a prophylactic action even when symptoms are absent (i.e., that taking them is like brushing your teeth every day to prevent cavities), and that they have a stress-screening action (i.e., that taking them is like wearing hockey equipment to protect yourself from injury). Patients must also learn to distinguish between signs of impending psychosis (irritability, insomnia, mood lability) and symptoms that indicate that their illness is recurring (hallucinations, delusions), postpsychotic dysphoria (emptiness, anergia), acute neuroleptic side effects (parkinsonism), anticholinergic side effects (mental confusion, blurred vision) and anticholinergic withdrawal effects (nausea, vomiting, headache).

In choosing the type and dose of neuroleptic for maintenance management, physicians should be guided as much by the need to ease side effects as by the wish to reduce the severity of psychotic symptoms. Some patients tolerate psychotic symptoms better than neuroleptic-induced side effects. For instance, they can learn to live with the sensation of being watched if they feel strong and limber enough to be able to act if a threat materializes. Neuroleptics that induce weakness and stiffness, even though they reduce the being-watched sensation, may make the patient feel worse rather than better.

To prevent tardive dyskinesia the clinician should:

- Prescribe long-term neuroleptic treatment only for schizophrenic patients who will not respond to other treatment.
- Give low doses of the neuroleptic for maintenance treatment.
- Avoid the long-term administration of anticholinergic agents.
- Avoid high-potency drugs for long-term treatment.
- Arrange frequent drug holidays. This is a controversial recommendation[27] but does make theoretical sense; during a lengthy period without neuroleptic treatment the patient's supersensitivity may be reversed.
- Be aware that although on the one hand the risk of tardive dyskinesia is greatest in the older patient, on the other hand many patients over 40 years of

age no longer require maintenance therapy with neuroleptics. Often their illness has abated and they are able to recognize signs of potential danger without continuing to take medication.

Neuroleptic-induced tardive dyskinesia becomes temporarily worse if an anticholinergic is given or if the dose of the neuroleptic is decreased or the drug is withdrawn. Nevertheless, patients with tardive dyskinesia should have a trial of neuroleptic withdrawal, and every attempt should be made to manage the illness without neuroleptic treatment. If this proves impossible the opposite strategy, raising the neuroleptic dose, will block the supersensitive receptors and mask the tardive dyskinesia as well as control the psychosis. For very ill patients this seems to be the only possible course of action, even though it involves the patient in a vicious cycle, masking and aggravating the dyskinesia at the same time. With regard to aggravating psychotic symptoms by the long-term use of neuroleptics, it has been suggested that a supersensitivity psychosis due to chemical denervation in the mesolimbic region may ensue, although this remains to be demonstrated.[28] None of the modes of treating tardive dyskinesia with other drugs now being tried is predictably successful, although many are being investigated.[29]

Conclusion

All neuroleptics are equally effective in blocking dopamine receptors, but they have widely differing potency. The higher the lipid solubility of the neuroleptic, the lower the dose the patient will require.

In short-term therapy the side effects of different neuroleptics depend on their relative ability to block receptors for dopamine, acetylcholine and norepinephrine, and the choice of a neuroleptic depends in part on the patient's ability to tolerate the side effects specific to that drug.

In long-term therapy side effects due to the chronic blockade of dopamine receptors cause complications. The long-term use of neuroleptics should be restricted to the treatment of schizophrenia, and doses should frequently be re-evaluated and kept as low as possible. The concomitant administration of anticholinergic drugs should be avoided if possible.

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Generic names of the drugs discussed and brand names for those drugs that are generally available in Canada

Chlorpromazine: Chlorprom, Chlor-Promanyl, Largactil
Thioridazine: Mellaril, Novoridazine, Thioril
Chlorprothixene: Tarasan
Methotrimeprazine: Nozinan
Mesoridazine: Serentil
Piperacetazine: Quide
Molindone: Moban
Pericyazine: Neuleptil
Loxapine: Loxapac
Perphenazine: Phenazine, Trilafon
Trifluoperazine: Novoflurazine, Solazine, Stelazine, Terfluzine, Triflurin
Thiothixene: Navane
Fluphenazine enanthate: Moditen
Haloperidol: Apo-Haloperidol, Haldol
Pimozide: Orap
Pipotiazine: Piportil
Fluphenazine decanoate: Modecate
Flupenthixol decanoate
Fluspirilene: Imap

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