An Overview of Side Effects Caused by Typical Antipsychotics

George W. Arana, M.D.

Typical antipsychotics often combine efficacy in treating antipsychotic illnesses with a side effect profile that can affect every system of the body and range from the annoying—photosensitivity and jaundice, for example—to the disabling—seizures and blindness, among others—to the potentially fatal—agranulocytosis and neuroleptic malignant syndrome. The side effects of conventional antipsychotics are associated with effects at CNS transmission and receptor sites and appear in relation to dose levels and potency of the drug. Characteristics of patients—including gender, age, and comorbid medical illness—can make them more or less susceptible to particular antipsychotic side effects. Side effects influence patient quality of life and affect patient compliance with medications. This article will consider the physiologic systems affected by conventional neuroleptics, the sexual and reproductive side effects of typical antipsychotics, and the central nervous side effects of the conventional neuroleptics in the light of these concerns. *(J Clin Psychiatry 2000;61[suppl 8]:5–11)*

Typical antipsychotics have been a potent weapon in the psychiatrist's armamentarium against psychotic illnesses, but the side effect profile of these medications is troubling. Adverse events can affect every system of the body and range from the annoying—photosensitivity and jaundice, for example—to the disabling—seizures and blindness, among others—to the potentially fatal—agranulocytosis and neuroleptic malignant syndrome. The side effects of conventional antipsychotics are associated with effects at CNS transmission and receptor sites and appear in relation to dose levels and potency of the drug. Patient characteristics—including gender, age, and comorbid illness—can influence susceptibility to particular antipsychotic side effects. Side effects affect subjective and objective assessments of patient quality of life, influencing patient compliance with medication.

Most physiologic systems are adversely affected by typical antipsychotics. In particular, those side effects affect the CNS, including movement disorders, sedation, and seizures, and certain other side effects can be particularly troublesome for patients such as those affecting sexual and reproductive function.

From the Department of Psychiatry, Medical University of South Carolina, Ralph H. Johnson VA Medical Center, Charleston.

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Reprint requests to: George W. Arana, M.D., Director, Mental Health Service, Ralph H. Johnson VAMC, 109 Bee Street, Charleston, SC 29401.

PHYSIOLOGIC REACTIONS

The physiologic systems affected by typical neuroleptics provide an apt system for organizing side effects (Table 1).

Autonomic and Cardiovascular

Potentially the most dangerous side effects of typical antipsychotics are the autonomic and cardiovascular effects, which can include ileus, falls, arrhythmias, and seizures. Cardiac effects may be direct or follow from hypotension and anticholinergic-induced tachycardia that indirectly affect the cardiovascular system. Postural hypotension, possibly related to α-adrenergic blockade or Ca++ channel blockade, can be a serious problem in elderly patients who are treated with low-potency antipsychotics. This side effect also may contribute to hip fractures when low-potency antipsychotics are used in geriatric populations. Patients sometimes develop tolerance to orthostasis; gradually increasing the dose may reduce the risk of hypotension. Less dangerous but troublesome anticholinergic effects include dry mouth, constipation, and tachycardia. These are usually benign but may sometimes be clinically significant, as, for example, in a patient with a compromised cardiovascular system.

In addition to the autonomic and cardiovascular effects of conventional antipsychotics, quinidine-like changes can be observed on electrocardiographs in some patients.[1] These quinidine-like effects include QT prolongation, abnormal T-wave morphology, and widening of the QRS complex. Patients receiving antipsychotic medications are at particular risk for torsade de pointes arrhythmia,[2] which

Table 1. Physiologic Systems Affected by Typical Antipsychotic Compounds

System	Effect	Danger	Compound
Autonomic and cardiovascular	Anticholinergic: xerostomia, constipation	Ileus, falls, arrhythmias	High risk: low potency, eg, thioridazine, chlorpromazine; low-medium risk: medium potency, eg, perphenazine, thiothixene, loxapine, trifluoperazine
	α-Adrenergic: postural hypotension, orthostasis		
	Ca++ channel blockade: retrograde ejaculation; postural hypotension	Falls, arrhythmias	Thioridazine, mesoridazine, and others
	Quinidine-like: t-wave flat/increased QR interval	Arrhythmias	Most
	Tolerance, probably to anticholinergic effect	Withdrawal, seizures	All, mostly low potency, increased anticholinergic
Endocrinologic	Hyperprolactinemia: amenorrhea, galactorrhea, gynecomastia, impotence	Pituitary adenoma	All
Metabolic	Weight gain: > 5 kg gain within 2 mo in average patient	Obesity	All
	Temperature dysregulation: hyperpyrexia, hypopyrexia	Heat stroke, hypothermia	All
Hematologic	Leukocytosis and leukopenia: transient high or low white cell count; usually within 3–6 wk of starting treatment	Agranulocytosis (1/10,000 pt)	All
Hepatic	Liver function test elevation: transient, soon after initiating treatment	None	All
	Jaundice (cholestatic-like): early in treatment idiosyncratic fever, right upper quadrant pain, chills	None	All
Allergic	Maculopapular rash, erythema multiforme, generalized urticaria	Angioedema; exfoliative dermatitis	All
Dermatologic	Photosensitivity: skin hyperpigmentation	None	High doses, chronic use, mostly chlorpromazine
Ophthalmologic	Corneal/lenticular changes: granular deposits not impairing vision	None	Chlorpromazine, trifluoperazine, perphenazine, thioridazine, fluphenazine, chlorprothixene
	Acute angle-closure glaucoma: can be treated and not contraindication	Blindness	All
	Pigmentary retinopathy	Blindness	> 800 mg/d thioridazine; occasionally chlorpromazine

is potentially lethal due to sudden onset of action, difficulty in treating, and potential to convert to a life-threatening ventricular fibrillation. Standard antiarrhythmic agents that cause QT prolongation cannot be used because the prolonged QT interval sets the stage for this disorder. Torsade de pointes can be treated with isoproterenol or cardiac pacing. Clinicians should be aware of this risk, which may develop with many commonly used antipsychotics, including thioridazine, pimozide, haloperidol, and chlorpromazine.

Endocrinologic and Metabolic

Neuroleptic side effects affecting the endocrinologic system—amenorrhea, galactorrhea, gynecomastia, and impotence—arise from hyperprolactinemia, which has been considered an unavoidable side effect in most patients treated with therapeutic doses of traditional antipsychotics and may even be a clinical marker of response. Marken et al.[3] suggested that typical neuroleptics may block dopamine receptors in the pituitary prolactin-secreting cells, preventing dopamine-induced reduction of prolactin release. The resulting hyperprolactinemia can result in amenorrhea in women and impotence in men. Windgassen et al.[4] found a prevalence rate of 19% for galactorrhea in 150 neuroleptic-treated schizophrenic patients. Hamner and Arana[5] studied the available literature and identified risk factors for galactorrhea as use of a depot antipsychotic, traditional antipsychotic therapy (especially long-term), prior pregnancy, use of oral contraceptives, and a history of antipsychotic-induced galactorrhea. Sustained prolactin elevations are less likely to occur with the use of atypical antipsychotics, so atypicals are treatment options in patients with neuroleptic-induced hyperprolactinemia.

Hyperprolactinemia is defined as a prolactin level above 20 μg/L, but clinically significant symptoms are unlikely to occur until the level reaches 30 to 60 μg/L or higher. Thus, hyperprolactinemia alone is not a reason to prescribe therapeutic interventions unless adverse effects are troublesome for the patient. Education and reassurance may allay concerns about symptoms such as galactorrhea. If symptoms become clinically significant and the patient is unable to reduce the dose of or change antipsychotics, treatment with an agent such as bromocriptine, which lowers prolactin levels, may be tried. In rare cases, hyperprolactinemia is a sign of pituitary adenoma.

A weight gain of more than 5 kg within 2 months is an adverse event of antipsychotics acting on the metabolic system in many patients. When chlorpromazine was introduced, the large majority of patients gained considerable amounts of weight, and similar problems have occurred to varying degrees with all antipsychotics. Excessive weight gain places the antipsychotic-treated patient at risk for the obesity-associated illnesses that affect the general population such as non–insulin dependent diabetes mellitus and cardiovascular disease. Weight gain is also often a factor in noncompliance with treatment. Since weight gain is likely to be a concern for most patients taking antipsychotic agents, it is important to stress behavioral and educational strategies to help prevent weight increases.

Other metabolic side effects of neuroleptics include hyperpyrexia and hypopyrexia. The slight temperature decrease in most antipsychotic-treated patients is unlikely to be clinically significant. Heat stroke was more likely to be problematic in the days before air conditioning became common.

Hematologic and Hepatic

Neuroleptic side effects affecting the hematologic system include leukocytosis and leukopenia, which usually occur within the first 3 to 6 weeks after antipsychotic treatment is started. Although agranulocytosis, a potentially fatal adverse affect, has been most frequently linked with the first atypical antipsychotic clozapine, it can also occur with any of the typical antipsychotics.

Liver function abnormalities during antipsychotic treatment have been noted as long as antipsychotics have been in use, but are seldom a reason for drug discontinuation. Mild-to-moderate increases in transaminase enzyme levels are sometimes discovered in routine laboratory analyses, usually early in treatment; these increases are unlikely to result in serious liver damage. Some patients experience cholestatic-like jaundice with idiosyncratic fever, abdominal pain, and chills early in treatment. Cholestasis affects 1% to 2% of patients who take chlorpromazine, independent of dose, and often during the first 4 weeks of treatment[1]; it has also been reported with haloperidol.[6] Antipsychotic treatment should be discontinued and a thorough hepatic evaluation performed in patients who are symptomatic or who have large elevations in liver enzyme levels.

Allergic, Dermatologic, and Ophthalmologic

Allergic side effects include maculopapular rash, erythema multiforme, and generalized urticaria. Urticaria is among the most common allergic reactions to the administration of psychotropic medications. Photocontact urticaria has been observed during chlorpromazine treatment,[7] but allergic reactions can occur with all typical agents. The most serious allergic adverse effects are angioedema and exfoliative dermatitis.

Antipsychotic adverse events affecting the dermatologic system include photosensitivity and skin hyperpigmentation. If the photosensitivity is an allergic reaction, it should occur after an incubation period and should be correlated with dose. Patients should be warned about this possible side effect so they can take precautions by avoiding exposure and using sun blocks. Skin hyperpigmentation seems to occur mainly in patients treated chronically with high doses of chlorpromazine.[1] Pathophysiologic mechanisms that may be responsible for this include an inflammatory response to chlorpromazine that causes increased melanin deposition or melanin acting as a scavenger of purple- to blue-colored free radicals formed by ultraviolet light acting on chlorpromazine.

Ophthalmologic side effects, which sometimes involve cutaneous structures or pigmentary changes, are often considered to be related to the dermatologic effects, although the pathophysiologic mechanisms may differ. Ocular effects range from the inconvenient corneal/lenticular changes to the vision-threatening acute angle-closure glaucoma and pigmentary retinopathy. Acute angle-closure glaucoma, which occurs when pupils are dilated in patients with physiologically narrow anterior chamber angles, is a greater risk for patients taking medications with strong anticholinergic effects.[8] Symptoms include blurred vision, pain, lacrimation, lid edema, and such systemic effects as nausea and vomiting. To prevent permanent loss of vision from increased intraocular pressure, either surgical intervention or treatment with topical anticholinesterase and parasympathomimetic drugs must be immediate. Since acute angle-closure glaucoma can be treated, it is not a contraindication for antipsychotic use. Pigmentary retinopathy is most likely in patients taking more than 800 mg/day of thioridazine, but has been reported with lower doses of other antipsychotics.[9] It occurs when pigment is deposited, spreading from the periphery to the central retina. Patients first lose peripheral vision, then night vision decreases, and scotoma may develop; eventually blindness can follow. Visual acuity may improve if pigmentary retinopathy is discovered early and antipsychotic therapy is stopped, but the pigmentary changes are thought to be permanent and may progress even after treatment discontinuation. To minimize ophthalmologic side effects, patients who are being treated with typical antipsychotics should be encouraged to seek routine eye care and asked regularly about vision changes.

SEXUAL AND REPRODUCTIVE SIDE EFFECTS

All traditional antipsychotic medications have been associated with sexual dysfunction (Table 2). Men may experience ejaculatory disturbances related to Ca++ channel blockade and/or adrenergic effects. Impotence, decreased libido, and changes in the quality of orgasm may be due to reduced testosterone or hyperprolactinemia. Women may experience orgasmic dysfunction and reduced libido possibly due to α-adrenergic activity and/or Ca++ channel blockade.

Prolonged erection, which can lead to priapism, is possibly related to the α-adrenergic activity. About 20% of all cases of medication-induced priapism are attributed to conventional antipsychotics, but priapism has not been related to dose, length of treatment, or potency of the antipsychotic.[10] Priapism should be treated as a urologic emergency since effective treatment within the first 4 to 6 hours should minimize the need for invasive procedures and the possibility of permanent impotence.

Although sexual side effects can make conventional antipsychotics intolerable to many patients, clinicians of-

Table 2. Sexual and Reproductive Side Effects of Typical Antipsychotic Compounds

Classification	Effect	Danger	Compound
Sexual dysfunction			
Men	Ejaculatory disturbances: Ca++ channel blockade and/or adrenergic effects	None	Chlorpromazine, chlorprothixene, fluphenazine, haloperidol, mesoridazine, thiothixene, thioridazine, trifluoperazine
	Impotence, decreased libido, change in quality of orgasm: reduced testosterone or hyperprolactinemia	None	Chlorpromazine, fluphenazine decanoate, haloperidol, pimozide, thioridazine, thiothixene
	Prolonged erection: possible α-adrenergic activity	Priapism	Chlorpromazine, fluphenazine, haloperidol, mesoridazine, molindone, perphenazine, thioridazine, thiothixene
Women	Orgasmic dysfunction, reduced libido: possible α-adrenergic and/or Ca++ channel blockade	None	Fluphenazine, mesoridazine, thioridazine, trifluoperazine
Teratogenicity	First-trimester exposure: nonspecific congenital defects; minimize with low-dose, high-potency agent	Birth defects	All
Risk to neonates	Neonatal hepatic dysfunction, anticholinergic side effects, extrapyramidal side effects	Complicated childbirth	All
Breastfeeding	Drugs secreted in milk may cause neurologic and other side effects	None	Chlorpromazine, trifluoperazine, prochlorperazine, thioridazine, haloperidol, mesoridazine

ten fail to ask about sexual function and patients do not report sexual problems voluntarily. Aizenberg et al.[11] studied 122 male patients—20 drug-free schizophrenic patients, 51 neuroleptic-treated patients, and 51 healthy controls—to quantitatively and qualitatively assess sexual function with a detailed structured interview. The researchers found that, although a high frequency of sexual dysfunction was reported by both schizophrenic groups of patients, impairments in arousal (erection) and orgasm during sex were reported mainly by the treated patients, who also disclosed dissatisfaction with their sexual function. The authors noted that, while neuroleptic treatment was associated with restoration of desire in schizophrenic patients, it can lead to problems with erection, orgasm, and sexual satisfaction.

Teratogenicity, risk to neonates, and risk from ingesting breast milk are also concerns with the typical antipsychotics, which cross the placenta and are secreted in breast milk. First-trimester exposure should be avoided when possible to avoid nonspecific congenital defects. The risk can be minimized with the use of a low-dose, high-potency agent. In neonates whose mothers were treated with conventional antipsychotics, the risk can include hepatic dysfunction, anticholinergic side effects, and extrapyramidal side effects. Handal et al.[12] reported on a 2-week-old girl with symptoms resembling those of tardive dyskinesia. Her mother had received perphenazine decanoate during the second and third trimesters of pregnancy.

Typical antipsychotics ingested by breastfeeding mothers can be secreted in milk and cause neurologic and other side effects in infants. Yoshida et al.[13] studied 12 mothers who were prescribed haloperidol, chlorpromazine, or trifluoperazine and breast-fed their infants. Clinical and developmental evaluations of the infants continued until they were 30 months old. Eighteen bottle-fed infants whose mothers also took antipsychotics or mood-stabilizing medications served as controls. Infants were found to be ingesting up to 3% of the maternal daily dose per kg body weight. Although 2 infants had plasma concentrations of haloperidol at the adult level, adverse events were not found. However, 3 other breastfed infants showed a decline in developmental scores between first and second assessments. The researchers advised caution if breastfeeding mothers take neuroleptic drugs at the upper end of the recommended range.

CNS SIDE EFFECTS

The CNS side effects of antipsychotics include movement disorders such as tardive dyskinesia and acute extrapyramidal symptoms (EPS), akathisia, akinesia, and dystonia; the neuroleptic malignant syndrome, which may be a variant of acute EPS; seizures; and sedation and other cognitive effects (Table 3). Most patients who receive conventional antipsychotics experience movement disorders, which not only can be troublesome to patients but also concern caregivers. The neuroleptic malignant syndrome is particularly worrisome because of its potential for morbidity and mortality. Some physicians limit the use of antipsychotic medications because of the risk of seizures, which are generally manageable with dose and drug adjustments. Sedation and other cognitive effects often bother patients and may limit compliance.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome of choreoathetotic movements that occurs after the chronic use of antipsychotic medications, is one of the most troubling side effects arising from conventional neuroleptic use, in part because it is disfiguring and contributes to the stigma of schizophrenia. Elderly patients, women, and people with diabetes seem to present the greatest risk for the development of tardive dyskinesia, which can be irreversible and may interfere with the normal activities of daily living. The overall incidence rate ranges from 32% after 5 years of neuroleptic exposure to 68% after 25 years of exposure.[14] Tardive dyskinesia may develop in as many as 53% of elderly patients after 3 years of cumulative exposure to

Table 3. CNS Side Effects of Typical Antipsychotic Compounds[a]

Effect	Key Features	Comments
Tardive dyskinesia (TD)	Irreversible in many patients; interferes with ADL; disfiguring, contributes to stigma	Risk of TD vs cost reduction will be focus of debate over use of atypical antipsychotics
Acute extrapyramidal symptoms	Very uncomfortable for patients; can mask clinical depression; interfere with writing and ADL	Anticholinergics are quite effective
Akathisia	Very uncomfortable for patients; can resemble psychotic agitation, anxiety; often leads to increased dosing	β-Blockers, anticholinergics, benzodiazepines are effective; twice as likely to develop in women
Akinesia	Mimics negative symptoms of schizophrenia or psychomotor retardation of depression	MAO-B promising for treatment
Dystonia	Laryngeal spasm is life-threatening; frightening to patients; interferes with compliance; rare after 1 wk of treatment	Most common in younger men; prophylaxis and acute treatment methods are effective
Neuroleptic malignant syndrome	Life-threatening (about 15% mortality); unpredictable, occurs in 0.01%–1% of psychiatric admissions; reduces option to use high doses	Early recognition is key; mortality rate decreased from 75% before 1970 to 15% in 1990
Seizures	All drugs reduce seizure threshold; an early complication of treatment; manageable with dose-drug manipulation	Risk factors include preexisting seizures, CNS pathology, abnormal EEG, rapid increase of dosage
Sedation	Interferes with rehabilitation; mistaken for contrary behavior	Likely effect of histamine blockade
Cognitive impairment	No significant positive or negative effects on memory; may interfere with attention or response time	Apparent cognitive impairment probably EPS-related

[a]Abbreviations: ADL = activities of daily living; EPS = extrapyramidal symptoms; MAO = monoamine oxidase.

typical antipsychotics.[15] Medication should be changed whenever signs of tardive dyskinesia are observed.

Clinicians sometimes try to avoid the use of conventional antipsychotics because of concern about the legal liability of tardive dyskinesia. Since the risk of tardive dyskinesia increases in proportion to the length of treatment, and there are emerging data that indicate a lower incidence of treatment-emergent tardive dyskinesia with the use of the more expensive atypical antipsychotics,[16] the risk of tardive dyskinesia versus cost of treatment is likely to become an issue in medication selection over the next several years.

Acute Extrapyramidal Symptoms

The incidence of acute EPS—akathisia, akinesia, and dystonia—associated with traditional antipsychotics varies, but most researchers agree that neuroleptic-induced EPS occur in 50% to 75% of patients who take typical antipsychotics.[17] For the typical neuroleptics, EPS can be placed on a scale of potency. High-potency drugs can be administered at lower doses and are associated with higher rates of EPS but less sedation, hypotension, and anticholinergic effects. Low-potency drugs are associated with fewer EPS but higher rates of sedation, hypotension, and anticholinergic effects.[1]

Routine monitoring for EPS is essential, and scales such as the Simpson-Angus Neurologic Rating Scale, the Extrapyramidal Symptom Rating Scale, and the Barnes Rating Scale for Drug-Induced Akathisia offer the best tools for documenting and objectively quantifying longitudinal changes. Patients should be assessed for the presence of EPS when treatment with conventional antipsychotics begins and regularly thereafter.

Akathisia. About 25% of patients treated with a conventional neuroleptic will develop akathisia, a side effect characterized by a sense of inner restlessness and a compulsion to move accompanied by restless motion.[18] This symptom is probably the most intolerable of those that develop early in treatment. Fidgety motion of the legs when sitting and inability to stand in one place are the most common observable symptoms. Patients might complain of feeling restless, tense, jittery, or anxious.

Akathisia, which can resemble psychotic agitation, is associated with higher doses of medication, and may coexist with other EPS. Women are twice as likely as men to experience akathisia. While some investigators have noted that akathisia occurs more often when high-potency antipsychotics are used, Sachdev and Kruk[19] did not find this factor significant. The most effective treatment for akathisia is a decrease in the dose of antipsychotic or the use of a β-adrenergic blocking agent. Anticholinergic agents and benzodiazepines are also effective. Atypical antipsychotics, which generally have less risk of acute EPS, may be a reasonable alternative for patients who cannot tolerate akathisia.

Akinesia. Over 50% of patients treated with conventional antipsychotics may experience akinesia, and 90% of the cases are reported within 3 months of starting treatment.[20] Akinesia, which mimics the negative symptoms of schizophrenia or the psychomotor retardation of depression, involves (1) slowed motor activity with difficulty initiating and sustaining behaviors, (2) anhedonia with depressed mood and flattened affect, and (3) cognitive impairment. Thus, distinguishing akinesia from negative symptomatology or depression can be difficult, but has obvious implications in terms of treatment. The rela-

tionship between akinesia and negative symptoms is complex and gives rise to the difficulty in distinguishing between primary and secondary negative symptoms.

Prophylactic antiparkinsonian agents for akinesia are not recommended, although monoamine oxidase inhibitor-B has shown promise for treatment. As with akathisia, akinesia should be treated by lowering the antipsychotic dose, if possible, or changing neuroleptics. If neither strategy is successful, antiparkinsonian treatment should be tried.

Dystonia. Dystonia is another disturbing side effect of typical neuroleptic therapy, which usually occurs during the first week of treatment or shortly after a dose increase. The involuntary contractions or muscle spasms, which are frightening to patients, may occur within hours of initiating treatment; the laryngeal spasm can be life-threatening. During contraction, the affected body part may appear to move in a moderately slow, writhing fashion. A sustained contraction may stop temporarily before starting again. Other problems, such as temporomandibular joint dislocation, may develop secondary to the muscle spasms. The pain, surprise, and bizarre quality of acute dystonia may cause future noncompliance.

Dystonic reactions generally respond rapidly to anticholinergic medications such as benztropine, and prophylactic anticholinergic treatment is useful for patients at high risk such as young men who are receiving high-potency antipsychotics.[1] When my colleagues and I[21] reviewed data from 9 studies that compared the incidence of drug-induced acute dystonia with and without the concomitant anticholinergic therapy, we found that the rate of dystonia was decreased almost 2-fold in those taking concomitant anticholinergics.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS), like agranulocytosis, is a potentially fatal side effect of neuroleptic treatment characterized by hyperthermia, severe EPS, autonomic nervous system instability, and clouding of consciousness. The incidence of NMS ranges from 0.01% to 1%,[22] and the risk is increased in agitated men who have received intramuscular injections of antipsychotic medications in high and rapidly escalating doses. Early detection and appropriate interventions are important in ameliorating the course and outcome of NMS; the mortality rate from NMS has decreased from 75% before 1970 to 15% in 1990.

Multiple factors probably contribute to the occurrence of NMS. The fact that patients can be rechallenged with antipsychotic medications without a recurrence of NMS[23] means some factors, e.g., comorbid medical conditions, dehydration, agitation, must be transient.

Seizures

Typical antipsychotics in general reduce the seizure threshold, making seizures a potential early complication of antipsychotic treatment. The practical risk of seizures, which occur in 0.5% to 0.9% of patients taking conventional antipsychotics,[1] is low. Rapid upward titration is a risk factor for seizures, which can generally be managed with dose and drug adjustments. Other risk factors include a history of seizures, CNS pathology, and abnormal electroencephalograph results. Since seizures can be minimized through careful medication selection, dosage reduction, and use of anticonvulsants, the occurrence of seizures is not a contraindication to treatment.

Sedation

Conventional antipsychotics are sedating, a likely effect of histamine blockade. While sedation may seem beneficial initially in the treatment of highly agitated psychotic patients, over the long term, it is often mistaken for contrary behavior and interferes with rehabilitation. In general, high-milligram, low-potency antipsychotics produce more sedation than low-milligram, high-potency agents. Sedation can be difficult to distinguish from the mental slowing of cognitive impairment.

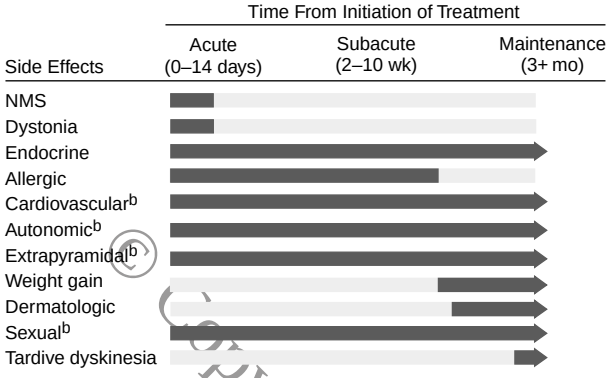
Cognitive Impairment

The effects of conventional neuroleptics on cognition are not well understood. Reviews of the literature reveal contradictory findings. Cassens et al.,[24] for example, reported that the acute administration of conventional antipsychotics impairs performance on some, but not all, tasks requiring vigilance and attention and on some tasks requiring motor behavior. The effects of conventional antipsychotics on cognition are confounded by the fact that many antipsychotic-treated patients are also taking anticholinergic medication. Spohn and Strauss[25] found neuroleptic therapy was associated with limited normalization on many psychological measures, whereas anticholinergics were associated with disruption of memory. Apparent cognitive impairment, thus, may be related to the administration of anticholinergic medication or with EPS-like akinesia that cause cognitive dulling. Jeste et al.,[26] in a review of human and animal studies of adverse neurobiological effects arising from long-term use of typical neuroleptics, noted that persistent cognitive impairment associated with long-term use has not been well documented.

IMPACT OF SIDE EFFECTS ON QUALITY OF LIFE

All of these side effects affect the patient's quality of life and contribute to noncompliance. Awad and Hogan[27] reported that subjective response to neuroleptics can predict compliance, therapeutic outcome, and suicidal behavior. While conventional neuroleptics are effective in the treatment of psychotic illness, they have adverse side effect profiles that can affect every physiologic system. Some of these effects such as dystonia and allergic reac-

Figure 1. Side Effects That Impact Quality of Life[a]



[a]Abbreviation: NMS = neuroleptic malignant syndrome.
[b]Many can be medically managed.

tions occur within the first few days of starting treatment while others such as tardive dyskinesia may not emerge for months or years (Figure 1). Many of these adverse effects, such as cardiovascular and extrapyramidal symptoms, can be managed medically.

Side effects influence the patient's daily life in a variety of ways that extend from the merely annoying to the life threatening. There is a wide variability in the susceptibility of patients for the develoment of the side effects reviewed in this article. Side effects are evident both in the subjective and objective assessments of patient quality of life, sometimes influencing patient compliance with medication. Hence, the clinicians must carefully consider the impact of side effects when a conventional neuroleptic is prescribed.

Drug names: benztropine (Cogentin and others), bromocriptine (Parlodel), chlorpromazine (Thorazine and others), chlorprothixene (Taractan), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), isoproterenol (Isuprel hydrochloride), loxapine (Loxitane), mesoridazine (Serentil), molindone (Moban), perphenazine (Trilafon), pimozide (Orap), prochlorperazine (Compazine), thioridazine (Mellaril and others), thiothixene (Navane), and trifluoperazine (Stelazine).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented herein that is outside U.S. Food and Drug Administration–approved labeling.

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