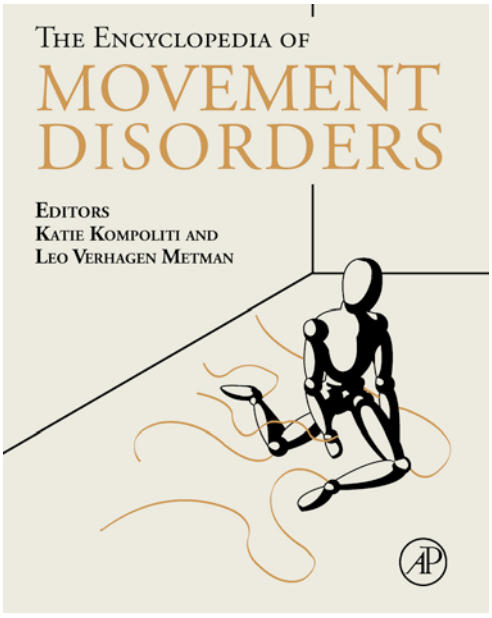
Provided for non-commercial research and educational use.
Not for reproduction, distribution or commercial use.

This article was originally published in Encyclopedia of Movement Disorders, published by Elsevier. The attached copy is provided by Elsevier for the author's benefit and for the benefit of the author's institution. It may be used for non-commercial research and educational use, including (without limitation) use in instruction at your institution, distribution to specific colleagues who you know, and providing a copy to your institution's administrator.



All other uses, reproduction and distribution, including (without limitation) commercial reprints, selling or licensing of copies or access, or posting on open internet sites, personal or institution websites or repositories, are prohibited. For exception, permission may be sought for such use through Elsevier's permissions site at:

http://www.elsevier.com/locate/permissionusematerial

Howard A K and Zurowski M (2010) Neuroleptics and Movement Disorders. In: Kompoliti K, and Verhagen Metman L (eds.) *Encyclopedia of Movement Disorders*, vol. 2, pp. 282-291 Oxford: Academic Press.

Author's personal copy

Kulkarni SK and Naidu PS (2003) Pathophysiology and drug therapy of tardive dyskinesia: Current concepts and future perspectives. *Drugs of Today* 39: 19–49.
Lifshitz K, O'Keeffe RT, Lee KL, et al. (1991) Effect of extended depot fluphenazine treatment and withdrawal on social and other behaviors of *Cebus apella* monkeys. *Psychopharmacology* 105: 492–500.
Linn GS (2004) Neuroleptic-induced acute dystonia and tardive dyskinesia in primates. In: LeDoux M (ed.) *Animal Models of Movement Disorders*, pp. 725–733. Burlington: Elsevier.
Linn GS, Negi SS, Gerum SV, and Javitt DC (2003) Reversal of phencyclidine-induced prepulse inhibition deficits by clozapine in monkeys. *Psychopharmacology* 169: 234–239.
Linn GS, O'Keeffe RT, Lifshitz K, Lee K, and Camp-Lifshitz J (2001) Increased incidence of dyskinesias and other behavioral effects of re-exposure to neuroleptic treatment in social colonies of *Cebus apella* monkeys. *Psychopharmacology* 153: 285–294.
Meltzer HY, Matsubara S, and Lee JC (1989) Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin pKi values. *Journal of Pharmacology and Experimental Therapeutics* 251: 238–246.
Werge T, Elbaek Z, Andersen MB, Lundbaek JA, and Rasmussen HB (2003) *Cebus apella*, a nonhuman primate highly susceptible to neuroleptic side effects, carries the GLY9 dopamine receptor D3 associated with tardive dyskinesia in humans. *The Pharmacogenetics Journal* 3: 97–100.

Neuroleptics and Movement Disorders

A K Howard, University of British Columbia Hospital, Vancouver, BC, Canada
M Zurowski, University of Toronto, Toronto, ON, Canada

© 2010 Elsevier Ltd. All rights reserved.

Glossary

Agonist – A molecule that binds to a receptor and stimulates the signaling processes associated with the receptor.
Agranulocytosis – A potentially serious condition characterized by an absence of white blood cells exposing an individual to infection risk.
Antagonist – A molecule that binds to a receptor and neutralizes the periodic signaling processes associated with the receptor without affecting the constitutive activity of the receptor.
Atypical – A reference to the characteristic of a neuroleptic to attenuate psychosis without producing motor side effects.
Delusions – False, fixed irrational beliefs out of keeping with the person's educational, cultural, and social background.
Extrapyramidal symptoms – A group of side effects to neuroleptics consisting of, but not limited to, dystonia, parkinsonism, akathisia, and tardive dyskinesia.
First generation antipsychotics (FGAs) – The initial group of antipsychotic drugs based on the original pharmacological mechanism; also referred to as typical or conventional antipsychotics.
Hallucinations – Perceptions in any sensory modality occurring in the absence of an external stimulus.
Inverse agonist – A molecule that binds to a receptor and inhibits the signaling processes associated with the receptor if signaling is constitutively active.
Mesolimbic pathway – The dopamine pathway from the ventral tegmental area of the midbrain to the nucleus accumbens or ventral striatum involved in antipsychotic treatment response among other functions.
Metabolic syndrome – A collection of symptoms including obesity, hypertension, glucose intolerance, and dyslipidemia, which increase the risk of coronary artery disease and stroke, caused by the weight gain associated with second generation antipsychotics.
Neuroleptics – The class of psychotropic medications efficacious as antipsychotics.
Nigrostriatal pathway – The dopamine pathway from substantia nigra to the dorsal striatum affected in Parkinson's disease.
Partial agonist – A molecule that binds to a receptor and stimulates the signaling processes associated with the receptor to a lesser degree than a full agonist.
Phenothiazines – One of the major antipsychotic families that includes the agent chlorpromazine.
Second generation antipsychotics (SGAs) – A more recent group of antipsychotic drugs based on a transition to a different pharmacological mechanism; also referred to as atypical or novel antipsychotics, they are purported to carry less risk of neurological adverse effects.

Definition and History

Neuroleptics comprise a large, diverse group of medications known for their ability to attenuate hallucinations and delusions, the core symptoms of psychosis. The term

Author's personal copy

Table 1 Neuroleptics listed by class and generation

First generation
Phenothiazines
Acetophenazine
Butaperazine
Carphenazine
Chlorproethazine
Chlorpromazine[a]
Cyamemazine
Dixyrazine
Fluphenazine[b]
Mesoridazine[c]
Methotrimeprazine
Perazine
Pericyazine
Perphenazine
Piperacetazine
Pipotiazine[d]
Prochlorperazine
Promazine
Propericiazine
Sulforidazine
Thiopropazate
Thioproperazine
Trifluoperazine[e]
Triflupromazine
Nonphenothiazines
Benperidol
Bromperidol
Chlorprothixene
Clocapramine
Clopenthixol
Clothiapine
Droperidol[f]
Fluanisone
Flupenthixol[b,g]
Fluspirilene
Haloperidol[b,h]
Loxapine[i]
Melperone
Molindone[j]
Moperone
Mosapramine
Nemonapride
Oxypertine
Penfluridol
Pimozide[k]
Pipamperone
Sulpiride
Sultopride
Thiothixene
Tiapride
Timiperone
Trifluperidol
Zuclopenthixol[l]
Second generation
Amisulpride
Asenapine
Bifeprunox
Clozapine[m]
Iloperidone
Mazapertine
Olanzapine[n]
Paliperidone
Perospirone
Quetiapine[o]
Risperidone[b, p]
Sertindole
Ziprasidone[q]
Zotepine
Aripiprazole[r]

[a]Example of aliphatic phenothiazine.
[b]Oral and depot (long-acting intramuscular) formulations.
[c]Example of piperidine phenothiazine.
[d]Depot formulation only.
[e]Example of piperazine phenothiazine.
[f]Parenteral form only.
[g]Example of thioxanthene.
[h]Example of butyrophenone.
[i]Example of dibenzoxazepine.
[j]Example of dihydroindolone.
[k]Example of diphenylbutylpiperidine.
[l]Oral and short-acting and long-acting depot formulations.
[m]Example of dibenzodiazepine.
[n]Example of thienobenzodiazepine.
[o]Example of dibenzothiazepine.
[p]Example of benzisoxazole.
[q]Example of benzothiazolylpiperazine.
[r]Example of dihydrocarbostyril, aripiprazole is considered to be the next generation of antipsychotics due to its novel partial dopamine agonist pharmacology.

neuroleptic is Greek meaning 'to take hold of the nerves.' This refers to the absence of movement induced in experimental animals by early antipsychotics that was akin to the loss of dopamine neurons in Parkinson's disease. Historically, the therapeutic efficacy of these agents was believed to correlate with their capacity to produce psychomotor slowing and a calm emotional indifference. This led to their anachronistic classification as major tranquilizers. Most neuroleptics are antipsychotic agents although metoclopramide is one example of a drug in the neuroleptic class used primarily as an antiemetic. There are currently close to seventy antipsychotics from over a dozen chemical families prescribed around the world. These are listed in **Table 1**. The most clinically useful categorization divides them into two groups: (1) the conventional, typical, or first generation antipsychotics (FGAs) that are more likely to cause motor side effects, and (2) the novel, atypical, or second generation antipsychotics (SGAs) that are less prone to do so.

Neuroleptics trace their origin to the manufacturing of dyes in England in the nineteenth century. In 1856, Perkin devised mauve, which led to Caro's development of methylene blue, a phenothiazine derivative. Ehrlich, a German bacteriologist credited with discovering the biotherapeutic effects of these dyes, recognized in 1891 that methylene blue could treat symptoms of malaria.

Author's personal copy

However, quinine proved more effective for this purpose. In World War II, with access to quinine limited, unsuccessful attempts were made by Gilman and others to manipulate the phenothiazine ring to produce alternative antimalarial compounds.

Serendipitously, French scientists chose to evaluate the phenothiazines for their antihistaminergic effects. Laborit, an anesthesiologist, found that promethazine's long duration of action could potentiate the effects of other anesthetics, allowing for lower dosages. In 1950, chlorpromazine demonstrated the same quality as well as calming and antiemetic properties in animals. The following year, Laborit and Huguenard noted that chlorpromazine quieted patients preoperatively without inducing coma, and they supplied it to two groups of Parisian psychiatrists led by Hamon and Delay. The first patient, a 57 year old laborer admitted to the Val de Grace Hospital for erratic, grandiose, and assaultive behavior, responded dramatically. Chlorpromazine was released in 1952 with open-label studies and a 1960 controlled trial in the United States confirming its efficacy. It replaced reserpine, a plant derivative that had been used as an antihypertensive in the late 1940s and subsequently as an antipsychotic due to its tranquilizing properties.

The magnitude of the discovery of chlorpromazine's antipsychotic therapeutic benefit cannot be understated. Worldwide inpatient populations decreased significantly. Theories of mental illness were powerfully influenced and treatments transformed from restrictive to compassionate. The locus of care changed from asylum to community. The risks of more invasive biological therapies were avoided, and the physical and mental wellbeing of countless ill patients was improved.

In the 1960s, when reserpine was found to deplete biogenic amines such as dopamine, norepinephrine, and serotonin, the dopamine hypothesis of schizophrenia and the monoamine hypothesis of depression emerged. Although overly simplistic, these theories remain the cornerstones of our pathophysiologic understanding of these psychiatric disorders. Carlsson and Linquist supported the dopamine hypothesis further by attributing to dopamine antagonism – the ability of nonreserpine neuroleptics to reduce amphetamine-induced psychomotor agitation in animals and to cause extrapyramidal symptoms in humans.

The psychopharmacological revolution continued with the proliferation of phenothiazine-related compounds, although chlorpromazine remained the most prescribed antipsychotic through the 1960s and 1970s. They eventually became known as low-potency neuroleptics because they required high doses for antipsychotic efficacy. Soon high-potency agents, which at small doses reduced stimulant-related hyperkinetic behavior in rodents, were synthesized. However, these new compounds were found to dramatically increase the incidence of extrapyramidal symptoms to as many as one in three patients in 1958, the year haloperidol was introduced. The following year, Sigwald reported the first case of antipsychotic-induced tardive dyskinesia.

The motor side effects of high-potency antipsychotics drove scientists, in particular German and Swiss psychiatrists, to search for atypical compounds. Clozapine, the antipsychotic least susceptible to motor complications, was synthesized in 1959 but could not be used until the late 1970s or marketed until the late 1980s due to its infrequent but life-threatening risk of agranulocytosis. In 1990, clozapine was finally released to the United States market and, shortly thereafter, its limited liability for extrapyramidal symptoms and tardive dyskinesia and its efficacy in treatment-refractory patients were uncovered. Riding on the coat tails of clozapine's success, risperidone was approved and marketed using its claim of atypical features in 1994, then olanzapine in 1996, quetiapine and sertindole in 1997, and ziprasidone, aripiprazole, and others more recently. The significant morbidity due to the metabolic syndrome of obesity, hypertension, dyslipidemia, and glucose intolerance from these agents, and their overstated therapeutic benefits continue to motivate the search for more suitable compounds.

Pharmacology

Pharmacokinetics

To maximize absorption, orally administered neuroleptics are given with food. Age, gender, drug interactions affecting protein binding or cytochrome P450 activity, hepatic or renal impairment, and caffeine and nicotine consumption affect plasma concentrations.

The half-life of the various neuroleptics ranges although most are given once daily. Peak levels are established within 4 h if given orally. In acute settings, intramuscular delivery is preferable. Bioavailability can also be augmented with short-acting (2–3 days) and long-acting (2–4 weeks) depot intramuscular formulations. Parenteral administration of certain agents is appropriate for acute monitored medical settings.

Pharmacodynamics

Chlorpromazine was marketed outside the United States as Largactil, a name reflecting its large number of actions in the central nervous system. In general, neuroleptics claim a vast array of neurotransmitter receptor affinities. Those that are quantifiable are listed in **Table 2**. Each medication is characterized by unique pharmacodynamics and receptor affinities, particularly in the dopamine, serotonin, and acetylcholine systems.

Author's personal copy

Table 2 Receptor systems affected by neuroleptics and their postulated effects

Dopamine D_1 blockade: antipsychotic
Dopamine D_2 blockade: antipsychotic; parkinsonism and motor side effects; hyperprolactinemia
Dopamine D_3 blockade: antipsychotic
Dopamine D_4 blockade: antipsychotic
Dopamine partial agonism: antipsychotic; attenuation of motor side effects and hyperprolactinemia
Dopamine reuptake inhibition: antidepressant; antiparkinsonian; psychomotor acceleration
Histamine$_1$ blockade: antiemetic; sedation; hypotension; weight gain; potentiation of other CNS drugs
Muscarinic M_1 blockade: attentuation of parkinsonism, dystonia, and akathisia; dry mucous membranes; blurred vision; constipation; urinary retention and incontinence; sinus tachycardia; ECG changes; memory disturbances; sexual dysfunction; potentiation of other anticholinergics
Norepinephrine reuptake inhibition: antidepressant
α_1 Norepinephrine blockade – postural hypotension, dizziness, reflex tachycardia, sedation, hypersalivation, urinary incontinence; potentiates other alpha blockers
α_2 Norepinephrine blockade – sexual dysfunction; may antagonize antihypertensives and increase cholinergic activity
Serotonin (5-HT$_1$) blockade (A, D): antidepressant; anxiolytic; inhibition of impulsivity
Serotonin (5-HT$_2$) blockade (A, C): antidepressant; anxiolytic; attenuation of motor side effects; hypotension sedation; weight gain; sexual dysfunction
Serotonin (5-HT$_{3,6,7}$) blockade: undefined
Serotonin reuptake inhibition: antidepressant

As early experimenters surmised, a reduction in postsynaptic dopamine activity by D_2 receptor binding predicts the efficacy of antipsychotics. All compounds share this mechanism. PET studies in schizophrenia confirm an increased release of dopamine and increased baseline D_2 receptor occupancy in the striatum of psychotic individuals. When an antipsychotic reaches 48% D_2 receptor occupancy, dopamine activity begins to normalize. D_2 blockade in the mesolimbic pathway, specifically the ventral striatum, correlates with antipsychotic efficacy, whereas blockade in the dorsal striatum, leading to low endogenous dopamine activity and consequently increased acetylcholine, is associated with extrapyramidal symptoms. D_2 blockade in the tuberoinfundibular pathway causes hyperprolactinemia as dopamine inhibits prolactin release. An antipsychotic effect is also postulated to occur by modulation of D_1, D_3, and D_4 receptor activity. Serotonergic blockade produces anxiolytic and mood-enhancing effects and antihistaminergic activity sedation. Other receptor affinities result in untoward effects. The search for pharmacodynamic factors that explain atypicality, the mitigated risk of motor complications with certain antipsychotics, has resulted in a number of possibilities described below.

Variability in D_2 blockade

The magnitude of D_2 blockade does not differentiate the agents that are more or less likely to cause motor side effects. Studies of D_2 striatal receptor occupancy leave little margin for error suggesting that a therapeutic antipsychotic effect occurs between 60 and 70% occupancy and extrapyramidal symptoms between 74 and 82%. At higher doses, the SGAs begin to resemble FGAs. It was therefore considered that at certain doses, the SGAs might fall within the therapeutic window of ~70% occupancy, but studies tend to show similar peak occupancy levels as conventional agents and, in fact, occupancy measurements of newer atypical agents are reported to reach as high as 90%. An alternative explanation is that minimal motor side effects may be attributable to neuroanatomical selectivity of D_2 receptor blockade. SGAs have lower striatal:cortical D_2-binding ratios compared to FGAs and greater preference for A_{10} mesolimbic dopamine neurons over A_9 nigrostriatal neurons. This is complicated by a drug's capacity to penetrate the blood–brain barrier that also determines its variable effects in various dopamine pathways.

A range in D_2 receptor affinity can also distinguish FGAs from SGAs. Physiological dopamine transmission occurs in phasic bursts in response to task requirements or stress-induced demands. Medications that block these receptors more permanently have a greater impact on these functions. Some SGAs have been found to have lower affinities for the D_2 receptor with quetiapine and clozapine having particularly fast dissociation rates. Following recognition of the receptor and alteration of the associated signaling system, these compounds quickly detach. In vitro studies of the dissociation coefficient, K_d, predict motor side effects clinically. The rapid psychiatric relapses seen when patients discontinue these compounds may also relate to an accelerated physiological displacement of these drugs by endogenous dopamine. While rapid dissociation is a characteristic of some SGAs, others have slower dissociation coefficients. It is possible that D_2 receptor affinity is affected by binding at other receptors.

Serotonin–dopamine blockade

Serotonin modulates presynaptic dopamine release from axon terminals to varying degrees depending on the pathway involved. In the nigrostriatal and tuberoinfundibular pathways, dopamine may be released by 5-HT$_{2A}$

Author's personal copy

antagonism, a common SGA characteristic, thus limiting motor side effects and hyperprolactinemia. Alternatively, when 5-HT_{2A} antagonism occurs in the mesocortical and mesolimbic pathways, the efficacy of the therapeutic dopamine blockade may be complemented. However, serotonin antagonism is not the critical defining feature of atypicality. Some conventional neuroleptics that commonly produce motor side effects are also serotonin antagonists. Some SGAs that produce few motor side effects have minimal serotonin blockade. The likelihood of avoiding neurological complications does not correlate with the 5-HT_{2A}/D_2 binding affinity ratios for some SGAs. At higher doses, even SGAs with serotonin blockade become increasingly liable to produce extrapyramidal symptoms. Finally, PET studies confirm that even in the presence of serotonergic blockade, there is high striatal D_2 blockade.

Dopamine partial agonism

In 1993, haloperidol was shown to stimulate the release of prolactin in vivo in the absence of dopamine. Previously thought to act as an antagonist at the dopamine receptor by neutralizing periodic receptor activity, this demonstrated that its mode of action was actually that of an inverse agonist, inhibiting all signaling activity. A number of in vitro tests confirmed this as the mechanism of many neuroleptics of both generations. Partial agonists at the D_2 and D_3 receptors inhibit excessive dopamine activity by ensuring high occupancy but low efficacy. This low-level stimulation of postsynaptic receptors also prevents the dopamine tone of the synapse from declining excessively. The end result is moderate antipsychotic efficacy with minimal motor side effects and hyperprolactinemia. However, this mechanism of action is claimed only by the most recent antipsychotics, and therefore cannot fully explain the atypical effects of SGAs.

Other explanations of atypicality

It is unlikely that one hypothesis explains atypical antipsychotic activity. High intrinsic muscarinic and histaminergic blockade are also considered protective against motor side effects. Other theories put forth include: a discrepancy between the effects of FGAs and SGAs on different signaling pathways such as G proteins; modulation of ligand-gated ion channels by atypical antipsychotics; and neuronal and glial cell proliferation as an intrinsic mechanism of some antipsychotics but not others.

Indications

Psychiatric

The primary indications for the use of antipsychotic agents are psychiatric. FGAs and SGAs are the standards of care in schizophrenia, mood disorders especially bipolar affective disorder and unipolar depression with psychotic features. They are also effective in attenuating the psychosis accompanying schizoaffective disorder, delusional disorder, dementia, substance abuse, neurological conditions such as epilepsy, and organic brain syndromes such as acute intermittent porphyria. Certain agents are approved for refractory generalized anxiety disorder. Low-dose SGAs improve the behavioral disturbances associated with autism and pervasive developmental disorders. Off label uses include: aggression, hostility, and impulsivity in neuropsychiatric illness such as traumatic brain injury; refractory OCD, depression, and posttraumatic stress disorder (PTSD); trichotillomania; assaultive and self-mutilatory behavior; personality disorders; insomnia; substance use disorders; anorexia nervosa; and disruptive behavior disorders and comorbid attention deficit/hyperactivity disorder in children.

Neurological

Migraine headaches

Included in the many off-label strategies for the abortive treatment of acute migraine are antipsychotics from either the first or second generation.

Movement disorders

Chronic tic disorders respond favorably to neuroleptic treatment. Pimozide and haloperidol are approved medications in Tourette's syndrome, but many other FGAs and SGAs are commonly used. Antipsychotics, particularly clozapine, are also prescribed off label to suppress ballismus, essential tremor, akinetic disorders, chorea, blepharospasm, Meige syndrome, and tardive dyskinesia.

Psychosis, tremor, and dyskinesias in Parkinson's disease

Few pharmacological options exist for patients with Parkinson's disease functionally compromised by hallucinations or delusions. First generation antipsychotics, risperidone, olanzapine, and aripiprazole have all been reported to worsen parkinsonism. The effects of ziprasidone remain unclear. Quetiapine is favored for its ease of use despite complaints of sedation and postural hypotension. In open label and prospective studies in the Parkinson's population, it is modestly effective as an antipsychotic at an average dose of 50 mg day^{-1}. Controlled studies, however, do not demonstrate this effect. In fact, clozapine is the only agent successful in treating psychosis in Parkinson's disease in double-blind controlled trials. Despite this evidence as well as reports of improvement in tremor and dyskinesias, clozapine, even at a low dose of 25–37.5 mg day^{-1}, introduces the risk of agranulocytosis although no deaths have been reported in this population. As a result, weekly monitoring of complete blood count with differential for 6–12

Author's personal copy

months is required then monthly monitoring if no abnormalities are detected. Patients also struggle with the side effects of sedation and exacerbations in drooling and postural dizziness.

Psychosis and chorea in Huntington's disease

Conventional agents have for some time been part of the pharmacological armamentarium for suppressing choreiform movements in early Huntington's disease. Once gait disturbance and postural instability are marked, the parkinsonism and other motor side effects which often accompany long-standing antipsychotic use can put patients at increased risk of falls. SGAs may be useful at this stage. For patients who also suffer from psychosis, usually presenting as delusions, clinical experience supports the use of FGAs early in the course of disease and SGAs, specifically quetiapine and clozapine, at later stages.

Dementia

Antipsychotic agents are given off-label for the behavioral and psychological symptoms of dementia. Treatments are exclusively short-term due to a black box warning by the FDA following the discovery of higher mortality and stroke risk associated with chronic use of antipsychotics in the elderly. Visual hallucinations in dementia with Lewy bodies are treated with quetiapine or clozapine when cholinesterase inhibitors are ineffective or contraindicated.

Other Uses

Antipsychotics are also prescribed to reduce nausea and vomiting, to relieve intractable hiccups or pruritus especially when associated with neurodermatitis, and to serve as adjunctive anaesthesia or tetanus therapy.

Contraindications

From the available data, no conclusions can be drawn about the risk/benefit profile of the majority of antipsychotics in breast-feeding or pregnancy, with the exception of clozapine, which can be potentially life threatening in the infant, and olanzapine, which poses an increased risk of motor side effects in breast-fed babies. While they are not clearly teratogenic as a class, antipsychotics should be avoided in pregnancy, particularly in the first trimester. Moderate to high doses in the last trimester produce extrapyramidal symptoms and temperature regulation difficulties in the newborn.

Caution should be exercised in patients with extensive heart, lung, liver, and kidney disease, glaucoma, prostatic enlargement, or a QTc interval > 450 ms.

Side Effects

While each antipsychotic has a unique side effect profile, overall tolerability does not seem to differ between FGAs and SGAs. More patients discontinue treatment with the FGAs due to extrapyramidal symptoms and the requirement for anticholinergic agents. Greater weight gain is observed with the SGAs. Table 3 lists reported adverse effects of antipsychotics. Further discussion of some psychiatric, neurological, and endocrine complications follows.

Psychiatric

Sedation, particularly in children and adolescents, is the most common psychiatric side effect of neuroleptics. Although it often attenuates over time, sedation impairs cognition and decreases function even when the agent is prescribed at bedtime. De novo depression and panic attacks, the provocation of mania, and the exacerbation of aggression, agitation, and insomnia are all linked to antipsychotic use. Cognitive impairment occurs with agents with anticholinergic properties, although as a class antipsychotics are less likely than the illnesses they treat to cause cognitive dysfunction. Discontinuation symptoms such as restlessness, insomnia, nausea, vomiting, tachycardia, diaphoresis, akathisia, extrapyramidal symptoms, and florid psychosis have long been described with sudden cessation of treatment. These phenomena are mediated by rebound from blockade of multiple receptors and can be difficult to distinguish from relapse. Longer tapers or the addition of anticonvulsants and benzodiazepines while tapering are prophylactic.

Neurological

Although attempts to avoid extrapyramidal symptoms are extensive, these side effects are habitually missed on clinical examination. While FGAs pose a higher risk, SGAs are still associated. Baseline assessment for movement disorders prior to antipsychotic initiation with repeat examination twice yearly is minimum standard of care.

Acute dystonia

Attributed to strong D_2 blockade, acute and painful prolonged spasms are commonly localized to the neck although involvement of the tongue, trunk, and limbs is also reported. Oculogyric crises, opisthotonus, and laryngospasm are fortunately rare. Usually occurring in the first week of treatment, with drug initiation or escalation, dystonia is treated with parenteral benztropine, diphenhydramine, or lorazepam, but may recur necessitating an antipsychotic dose reduction or daily oral anticholinergics. Risk factors include male gender, African–American

Author's personal copy

Table 3 Adverse effects of antipsychotics

Nervous system
Agitation
Discontinuation symptoms
Extrapyramidal symptoms (parkinsonism, dystonia, akathisia, tremor[a], myoclonus[a], Pisa syndrome[a], perioral tremor/rabbit syndrome[a])
Insomnia
Sedation
Seizures
Tardive symptoms (dyskinesia, dystonia, parkinsonism[a], akathisia[a], ballismus[a], tics[a], vomiting[a], temperature dysregulation[a])
Anxiety[a]
Cognitive impairment[a]
Depression[a]
Headache[a]
Neuroleptic malignant syndrome[a]
Pain, myalgias, or paraesthesiae[a]
Stroke[a]
Head and Neck
Blurry vision
Cataracts
Epistaxis[a]
Lenticular pigmentation[a]
Pigmentary retinopathy[a]
Rhinitis[a]
Cardiovascular
ECG changes: prolonged PR, QRS, or QTc
Hypotension[b]
Tachycardia
Cardiomyopathy[c]
Cardiac conduction abnormalities including *torsades de pointes*[d]
Edema[a]
Respiratory
Hypoventilation[c]
Pulmonary thromboembolism[c]
Gastrointestinal
Constipation
Dry mouth
Sialorrhea
Transient liver enzyme elevation
Cholestatic jaundice[a]
Diarrhea[a]
Dyspepsia[a]
Dysphagia[a]
Glossitis[a]
Pancreatitis[c]
Reflux esophagitis[a]
Insterstitial nephritis[a]
Genitourinary
Sexual dysfunction
Urinary incontinence
Urinary retention
Priapism[a]
Dermatological
Photosensitivity
Altered skin pigmentation[a]
Flushing of the skin[a]
Rash[a]
Endocrine
Hyperprolactinemia
Galactorrhea and breast engorgement
Hypogonadism
Menstrual irregularities
Osteopenia/osteoporosis[e]
Sexual dysfunction
Temperature dysregulation[a]
Weight gain
Diabetes
Gall bladder disease
Hyperlipidemia
Hypertension
Osteoarthritis
Hypothyroidism[a]
SIADH[c]
Hematological
Agranulocytosis[a]
Eosinophilia[a]
Exacerbation of thromobocytopenia[a]
Transient neutropenia[a]
Uric acidemia[a]

[a]Incidence $< 2\%$.
[b]Worse with rapid dose increases and higher doses.
[c]Case reports only.
[d]Malignant arrhythmias rare; avoid doses of pimozide > 20 mg, thioridazine > 800 mg, and higher doses of ziprasidone.
[e]Monitoring of bone loss recommended in female patients with hyperprolactinemia.

ethnicity, young age, treatment naïveté, thyroid and parathyroid irregularities, and recent cocaine use.

Parkinsonism

Correlating with nigrostriatal dopamine reduction, antipsychotic-induced parkinsonism emerges in a typical although more symmetrical fashion after several weeks of treatment. Risk factors include older age, female gender, comorbid neurological disorders, and high doses of FGAs. The differential diagnosis includes negative symptoms of schizophrenia, depression, and idiopathic Parkinson's disease. Parkinsonism is expected to resolve after drug tapering and discontinuation, but may take up to 6 months. In those cases that persist longer with parkinsonian signs, the diagnosis of Parkinson's disease, unveiled by neuroleptic exposure, is likely.

Akathisia

In up to 20% of patients started on neuroleptics, a dose-related subjective sense of unease, restlessness, and dysphoria develops in the first few weeks. The clinician observes repetitive movements of the lower limbs, pacing, and rocking. Psychomotor agitation, anxiety, drug seeking, and withdrawal may confound the recognition of akathisia. Associated with the elderly, women, mood and anxiety disorders, concurrent treatment with selective serotonin reuptake inhibitors (SSRIs), excess caffeine intake, and low iron, akathisia may attenuate with

Author's personal copy

β-blockers or benzodiazepines but tends to persist for at least the first several months of treatment and is a common contributor to noncompliance, insomnia, violence, and suicide. Akathisia can also be a part of a tardive syndrome, starting after months of therapy (see later text).

Tardive dyskinesia

Although an upregulation or supersensitivity of postsynaptic D_2 receptors has been proposed, the exact mechanism of tardive dyskinesia is poorly understood. After several months or years of treatment in younger adults, or weeks in the elderly, often when an antipsychotic is tapered or discontinued, patients begin to display orofacial choreoathetosis, chewing or jaw clenching, protruding the tongue, grimacing, frowning, pursing, smacking, or puckering the lips, and blinking. Involvement of the limbs, trunk, neck, and diaphragm, with grunting, are seen. Movements are difficult to suppress and potentially embarrassing, although there is often a lack of awareness. Worsened by stress and the use of anticholinergics, tardive dyskinesia is absent in sleep. The differential diagnosis includes dyskinesias that can occur spontaneously in neuroleptic-naïve patients, Huntington's, and Tourette's. The movements persist in 75% of patients after 5 years and worsen with ongoing treatment, limiting adherence to medications, quality of life, and health status. Risk factors include previous extrapyramidal symptoms, diabetes, older age, mood disorders, cognitive impairment, and female gender in some reports. Concomitant lithium therapy may be protective. There is little rigorous data on exact incidence and prevalence. Conservative estimates suggest a rate of 5–8% per year for FGAs and 1–3% in SGAs in adults, and 5–30% per year in those over 45 years old depending on the agent used and population sampled. Children experience tardive dyskinesia at a rate of 0.4%, but they are often exposed to lower doses for shorter durations. Treatment efficacy is lacking and options include switching to clozapine, reintroducing the causative agent, and slowly tapering it, or starting tetrabenazine. Vitamin E or B_6, clonazepam, clonidine, and anticonvulsants are minimally effective. Deep brain stimulation remains experimental.

Other tardive phenomena

Delayed onset dystonias associated with prolonged use of FGAs and SGAs require distinction from Wilson's disease and idiopathic dystonia. Treatment with anticholinergics, clozapine, tetrabenazine, or BoTox is modestly effective. Tardive dyskinesia may coexist. Tardive parkinsonism, akathisia, ballismus, Tourette's, vomiting, and hypothalamic syndrome (sense of cold accompanied by polydipsia) are rare.

Other movement disorders

Rabbit syndrome or a rhythmic, fine, perioral tremor occurs in association with neuroleptics. Female gender, age, and previous brain injury predispose. This facial tremor is thought to be a manifestation of drug-induced parkinsonism. Movements tend to respond to a reduction in therapy, cessation of antipsychotics, or introduction of anticholinergics. Less commonly, Pisa syndrome or persistent lateral flexion of the trunk to one side may begin after months of treatment. The predisposed demographic and treatment are similar to rabbit syndrome. Exacerbation of tic disorders, de novo cataplexy, and myoclonus are also reported.

Other neurological complications

Generalized tonic–clonic seizures occur with an incidence rate as high as 10% in children and 4% in adults, especially with polypharmacy. Headaches are infrequent with most agents. Stroke and TIA are three times more common in demented elderly patients on antipsychotics compared to placebo.

Neuroleptic malignant syndrome

An emergent condition characterized by varying combinations of hyperthermia, diaphoresis, muscle rigidity, elevated serum creatinine kinase, altered level of consciousness, labile blood pressure, tachycardia, and hypersalivation, NMS is associated with a 25% mortality rate. A precipitous decrease in dopamine levels in the striatum and hypothalamus is responsible. Not only occurring with FGAs and SGAs when rapidly increased or initiated, but also with metoclopramide and withdrawal of dopamine replacement therapy, it must be differentiated from heat stroke, catatonia, serotonin syndrome, delirium tremens, toxidromes, and thyrotoxicosis. Risk factors include male gender, young age, associated brain injury or illness, mood disorder, and dehydration. Treatment consists of rehydration, preventing myoglobinuria and renal failure, and cooling. Dantrolene up to 10 mg kg^{-1} or until rectal temperature normalizes, bromocriptine, reinstatement of levodopa, and steroid pulse therapy are all useful.

Endocrine

Metabolic syndrome

Weight gain due to some FGAs and most SGAs is a serious cause of morbidity and a leading contributor to medication nonadherence. On average, one-half of patients taking neuroleptics gain 20% of their body weight increasing their probability of developing the metabolic syndrome, which involves hypertension, dyslipidemia, glucose intolerance, and subsequent coronary artery and cerebrovascular disease. Risk factors include females, children, adolescents, and patients experiencing their initial episode of schizophrenia, although this may be due to SGAs being first-line agents in these populations. Compounds with greater histaminergic, serotonergic, and alpha blockade are often implicated. Strict monitoring of

Author's personal copy

weight, diet, exercise, blood pressure, lipids, and glucose levels is encouraged. Strategies for pharmacological intervention are not yet well elucidated.

Interactions

Pharmacodynamic

The increasingly common practice of combining antipsychotics magnifies the risks of excessive D_2 antagonism with associated neurological complications and NMS, and serotonin and anticholinergic toxicity. Antipsychotics produce additive: hypotension with antihypertensives and monoamine oxidase inhibitors; motor side effects with SSRIs, cholinesterase inhibitors, lithium, and metoclopramide; hyperprolactinemia with some oral contraceptive pills; and sedation with benzodiazepines.

Pharmacokinetic

The most likely etiology for any drug interaction with antipsychotics derives from the inhibition or induction of hepatic cytochrome P450 1A2, 2D6, and 3A4 subtypes. Tegretol is a potent inducer of 1A2 and 3A4 lowering FGAs and SGAs to undetectable levels. Smoking induces 1A2, so altered smoking status, including abstinence in hospital, affects antipsychotic levels. Various genetic polymorphisms of the 2D6 enzyme, although present in a minority of individuals, lead to increases or decreases in activity, necessitating dose changes. Many antipsychotics are 2D6 inhibitors, so cautious use of other 2D6 substrates is necessary. Side effects to medications may be additive like the combined lowering of seizure threshold by lithium and clozapine. Interactions such as cardiotoxic levels of pimozide due to impaired clearance by clarithromycin, and decreases in the INR due to induction in warfarin metabolism by quetiapine, are of adequate frequency and severity to demand careful consideration prior to introducing neuroleptics.

Dosing

Principles

Antipsychotic prescribing involves: an estimate of the drug's starting dosage and potency based on its D_2 affinity with 2–10 mg day^{-1} of haloperidol equivalence; individualized dosing based on symptom severity, comorbidity, age, potential drug interactions including nicotine and caffeine intake, side effect profile, dosing schedule, and personal and family history of prior response to a particular compound; choice of appropriate route of administration based on the acuity of the setting, the duration of treatment, and the expectation of compliance; lowering doses for chronic maintenance therapy; gradual titration over at least 2–4 weeks with increases of every five half-lives; and adjusting the dose based on response and not drug level.

Switching

After several weeks, if lack of response is attributable to medication choice, switching antipsychotics is advised. Symptoms, side effects, and quality of life measures improve with a change from FGAs to SGAs. Olanzapine and clozapine are considerations for improved efficacy. Switches from one SGA to another or to the FGAs can optimize triglyceride levels and weight. Switching strategies should consider the relevant pharmacology of the involved agents and the risks of rebound and additive effects.

See also: Acetylcholine; Akathisia; Anticholinergics and Movement Disorders; Antidepressants and Movement Disorders; Benzodiazepines and Movement Disorders; Beta-blockers and Movement Disorders; Botulinum Toxin; Central Nervous System Stimulants and Movement Disorders; Cholinesterase Inhibitors in Parkinson's Disease; Chorea; Choreiform Disorders; Deep Brain stimulation; Dementia with Lewy Bodies; Dopamine; Dopamine Receptors; Dopaminergic Agonists in Parkinson's Disease; Drug-induced Movement Disorders; Dyskinesias; Dystonia, Drug-induced (Acute); Gait Disturbances in Parkinsonism; Hallucinations and Movement Disorders; Hemiballismus; Huntington's Disease; Levodopa; Locus Coeruleus and Norepinephrine; Myoclonus; Neuroleptic-induced Nonhuman Primate Models of EPS and TD; Nicotine; Obsessive-Compulsive Disorder; Parkinson's Disease: Definition, Diagnosis, and Management; Pisa Syndrome; Psychosis in Parkinsonism; Rabbit Syndrome; Serotonin and Tryptophan; Serotonin Syndrome; Tardive Dystonia; Tardive Syndromes; Tourette Syndrome; Tremor, Essential (Syndromes); Tremor: Drug-induced; Wilson's Disease.

Further Reading

Bezchlibnyk-Butler KZ, Jeffries JJ, and Virani AS (eds.) (2007) *Clinical Handbook of Psychotropic Drugs.* Seattle, WA: Hogrefe & Huber Publishers.

Buckley PF and Correll CU (2008) Strategies for dosing and switching antipsychotics for optimal clinical management. *Journal of Clinical Psychiatry* 69: 4–17.

Chou KL, Borek LL, and Friedman JH (2007) The management of psychosis in movement disorder patients. *Expert Opinion in Pharmacotherapy* 8: 935–943.

Correll CU (2007) Acute and long-term adverse effects of antipsychotics. *CNS Spectrums* 12: 10–14.

Correll CU and Schenk EM (2008) Tardive dyskinesia and new antipsychotics. *Current Opinion in Psychiatry* 21: 151–156.

Cutler A, Ball S, and Stahl SM (2008) Dosing atypical antipsychotics. *CNS Spectrums* 13: 1–14.

Author's personal copy

Haddad PM and Dursun SM (2008) Neurological complications of psychiatric drugs: Clinical features and management. *Human Psychopharmacology* 23: 15–26.
Meyer J (2007) Drug–drug interactions with antipsychotics. *CNS Spectrums* 12: 6–9.
Meyer JM (2007) Antipsychotic safety and efficacy concerns. *Journal of Clinical Psychiatry* 68: 20–26.
Pani L, Pira L, and Marchese G (2007) Antipsychotic efficacy: Relationship to optimal D_2-receptor occupancy. *European Psychiatry* 22: 267–275.
Preskorn SH (2007) The evolution of antipsychotic drug therapy: Reserpine, chlorpromazine, and haloperidol. *Journal of Psychiatric Practice* 13: 253–257.
Shen WW (1999) A history of antipsychotic drug development. *Comprehensive Psychiatry* 40: 407–414.
Stahl SM (2002) Essential Psychopharmacology of Antipsychotics and Mood Stabilizers. Cambridge: Cambridge University Press.
Strange PG (2008) Antipsychotic drug action: Antagonism, inverse agonism or partial agonism. *Trends in Pharmacological Sciences* 29: 314–321.
Tandon R, Belmaker RH, Gattaz WF, et al. (2008) World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophrenia Research* 100: 20–38.

Relevant Websites

http://www.emedicine.com/emerg/topic338.htm – Kathryn Ruth Challoner's article on Toxicity, Neuroleptic Agents (last updated Feb 29, 2008).

Neuronal Ceroid Lipofuscinosis

J D Cooper, Institute of Psychiatry, King's College London, London, UK

© 2010 Elsevier Ltd. All rights reserved.

Glossary

Autosomal recessive – Genetic mutations can be passed on from one generation to the next by different patterns of Mendelian inheritance. In autosomal recessive disorders (like Batten disease), an individual needs to have two mutated copies of the disease-causing gene to be affected. Their parents are both carriers who have one mutated copy of this gene, but are themselves asymptomatic. Each time they reproduce, they have a 25% chance of having an affected child, 50% chance of producing another carrier, and 25% chance of having a completely unaffected child.

Cross-correction – Many of the therapeutic strategies used to combat LSDs depend upon this simple principle, so that an enzyme produced by a cellular subpopulation can be used to treat neighboring deficient cells. Much of the lysosomal enzymes normally made by a cell are secreted into the extracellular space, but will be recaptured and delivered back to the lysosome via binding to mannose-6-phosphate receptors that are present at the plasma membrane of all cells. In LSDs, the missing enzyme is typically delivered by direct enzyme replacement, gene transfer, or the transplant of stemcells. This delivered enzyme is then taken up by deficient cells to 'cross-correct' their functional defect.

Genetically engineered mutant mice – If the disease-causing gene has been identified, it is now relatively routine, to generate a mouse model of this disorder via genetic manipulation. Homologous recombination is used to replace the gene of interest with a construct in which this gene has been altered in some way. This may be to completely disrupt a gene so that no protein is made – a 'knockout' mouse. Alternatively, in a 'knockin' mouse, a particular disease-causing mutation can be introduced into the gene to recreate the human disease. More complicated targeting constructs, allow genes to be switched on or off, either globally or more usually in a particular cell type or tissue.

Lysosomal storage disorder – Lysosomes are acidic organelles that contain over 50 hydrolytic enzymes that degrade a wide variety of substrates. In addition to this classical role as the cell's 'waste-disposal unit,' lysosomes form an important part of the machinery for antigen presentation and are in a key position to influence both endocytosis and exocytosis, and intracellular trafficking. Lysosomal storage disorders (LSDs) are monogenic inherited disorders, each caused by a mutation in a single gene. This may encode one of the lysosomal enzymes, or one of the many lysosomal membrane proteins that regulate the environment within the lysosome. Many LSDs have prominent neurologic and neurodegenerative components, and these are uniformly fatal.