Conventional and Atypical Antipsychotics in the Elderly

A Review

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Abstract and Introduction

Abstract

Psychoses are major mental disorders marked by derangement of personality and loss of contact with reality, and are common in the elderly. Various hypotheses suggest the pivotal role of abnormal neurotransmitter and neuropeptide systems in psychotic patients, the most studied of which are the dopaminergic, serotonergic and glutamatergic systems. In particular, long-term treatment with antagonists at dopamine (D) and serotonin (5-hydroxytryptamine; 5-HT) receptors and agonists at glutamate receptors may improve symptoms. Treatment with antipsychotics is very common in the elderly and often indispensable. However, for successful treatment it is essential to have an adequate multidimensional assessment of the geriatric patient and of his or her polypathology and polypharmacy, together with knowledge of age-dependent pharmacokinetics and pharmacodynamic changes and drug-drug interactions.

Conventional antipsychotics such as haloperidol, chlorpromazine, promazine, tiapride and zuclopenthixol are D_2-receptor antagonists and inhibit dopaminergic neurotransmission in a dose-related manner. They decrease the intensity of all psychotic symptoms, although not necessarily to the same extent and with the same time course. Negative symptoms may persist to a much more striking extent than delusions, hallucinations and thought disorders, and there is a dose-related incidence of extrapyramidal side effects (EPS). Newer antipsychotics, such as clozapine, olanzapine, risperidone, quetiapine and ziprasidone, have a different receptor-binding profile, interacting with both D and 5-HT receptors; they less frequently cause EPS and are better tolerated in the elderly. Their use is advantageous because they are effective both on positive and negative symptoms of schizophrenia and may also be used in the treatment of behavioural disturbances in elderly and/or demented individuals. The use of clozapine is limited by the onset of agranulocytosis, whereas olanzapine, risperidone, quetiapine and, more recently, ziprasidone are widely used, with good results in the above-mentioned diseases.

Introduction

Psychoses are common in the elderly, because they can be either the expression of a disease that had its onset at a young age or the complications of some organic diseases beginning in later life (e.g. dementia).

Psychoses are major mental disorders of organic or emotional origin marked by derangement of personality and loss of contact with reality. They are characterised by a deep division between common events and interior experiences, with delusions or prominent hallucinations occurring in the absence of insight;[1] their prevalence varies from 6% to 10% in the elderly population.[2,3] Various hypotheses suggest the pivotal role of abnormal neurotransmitter and neuropeptide systems in psychotic patients. The most studied are the dopaminergic, serotonergic and glutamatergic systems.[4] In fact, long-term treatment with antagonists at dopamine (D) and serotonin (5-hydroxytryptamine; 5-HT) receptors and agonists at glutamate receptors may improve symptoms. Therefore, pathophysiological studies on dopaminergic, serotonergic and glutamatergic neurotransmission have been the basis of modern pharmacology for psychotic disorders. In particular, we have focused on neurobiological studies that have led to the development of modern antipsychotic drugs.

Neurotransmitter Systems and Psychoses

The Dopamine Hypothesis

The dopamine hypothesis of schizophrenia and psychoses was formulated in the 1950s, when Delay et al.[5] discovered the potential therapeutic effects of chlorpromazine, which has since that time been known as an antihistaminic drug that suppresses hallucinations and delusions in schizophrenic patients. This pharmacological activity was described as neuroleptic action. Later, neurochemical experiments in animal brain and animal behavioural studies led to the recognition of the dopamine antagonist properties of the antipsychotic agents.[6-8] On the other hand, amphetamine, by releasing dopamine from central nerve terminals, could exacerbate psychotic symptoms in patients with schizophrenia.[9,10]

Recently, most attention has been focused on possible mutations or deficits in dopamine receptors. At present, five subtypes of dopamine receptors have been distinguished by gene cloning;[11,12] they are G-protein-coupled receptors, monomers with seven transmembrane domains. Agonist binding evokes the activation of a G-protein that hydrolyses guanosine triphosphate. The G-protein dissociates and activates an effector protein, which is an enzyme or an ion channel that either produces an intracellular second messenger (e.g. cyclic adenosine monophosphate [cAMP], inositol triphosphate or arachidonic acid) or causes ion fluxes.[13,14] Dopamine receptors have been grouped into two main classes: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4).[15] Activation of the former causes an increase in cAMP, whereas activation of the latter causes a decrease in cAMP. D_1 receptors are more abundant in the brain and seem to have a role in actions of dopamine in the control of motor, cognitive and cardiovascular functions.[16,17] However, D_1-receptor antagonists do not show any antipsychotic activity. On the contrary, D_2-receptor antagonists play a key role in the treatment of positive symptoms of psychoses. Excessive blockade of these receptors may cause extrapyramidal symptoms (EPS) and may be involved in the development of tardive dyskinesia.

All the currently known antipsychotics, except the obsolete monoamine depletor reserpine, are D_2 antagonists. Studies on receptor occupancy by positron emission tomography have clearly demonstrated that moderate blockade of central D_2 receptors is adequate for treatment of positive symptoms of psychoses, whereas a high degree of D_2-receptor occupancy gives rise to EPS. In particular, it has been widely shown that striatal D_2-receptor occupancy as measured with [^{123}I]odobenzamide and single photon emission tomography is able to predict the occurrence of EPS in patients treated with antipsychotics.[18] Moreover, it is widely known that the blockade of D_2 receptors in the anterior pituitary gland causes elevation of blood prolactin levels.[19,20] Post-mortem studies on brains of patients affected with schizophrenia have shown elevated levels of striatal D_2 receptors, although it is not entirely clear whether this increase in D_2 receptors is a result of treatment with antipsychotic drugs or is related to the disease process.[21]

D_3 antagonists showed no antipsychotic activity in patients with schizophrenia, nor was any linkage shown between the D_2 and D_3 receptor genes and the onset of schizophrenia.[22] Clozapine, a prototype of the atypical antipsychotics, has a higher affinity for D_4 than for D_2 receptors. In addition, pipamperone, which shows antipsychotic activity, has a 15-fold higher affinity for D_4 than D_2 receptors.[4] Moreover, it has been suggested that D_4 receptors may play a role in the modulation of GABAergic neuronal activity by dopamine.[23] However, a potent and selective D_4 antagonist, L-745870, failed to reveal antipsychotic activity.[23] Table I presents the dopamine receptor subtypes and their main individual features.

The Serotonin Hypothesis

The possible involvement of serotonergic neurotransmission in the onset of psychoses was suggested by the ability of some chlorpromazine-like antipsychotics to antagonise the behavioural effects of the 5-HT-receptor agonist tryptamine in rats, and by the hallucinogenic action of lysergide (lysergic acid diethylamide, LSD), a 5-HT agonist. Later on, some receptor-binding sites for certain antipsychotics were shown to be 5-HT receptors, particularly subtype 5-HT_{2A}. Pipamperone, a butyrophenone showing predominant 5-HT_{2A} antagonist properties, was noted for its anti-agitation and resocialising effects and for its ability to normalise sleep rhythms in psychiatric patients.[24,25] Several years ago, ritanserin, a long-acting 5-HT_{2A} antagonist, was found to attenuate haloperidol-induced EPS, and was shown to be very effective against the negative symptoms of both schizophrenia and dysthymia.[26,27] Later, risperidone, an atypical antipsychotic showing very potent 5-HT_{2A} antagonism with a weaker D_2 antagonism, was developed.[28-30] It is successfully used in treating the positive and negative symptoms of schizophrenia, in both the young and the elderly. Moreover, it enhances cognition and has fewer adverse effects than the conventional antipsychotics;[31-33] its action suggests that negative symptoms may derive from the overactivation of excitatory 5-HT_{2A} receptors. This receptor subtype seems to be the most important serotonin receptor, since all the newer antipsychotics are relatively potent 5-HT_{2A} antagonists and are more potent antagonists at 5-HT_{2A} than at D_2 receptors.[34-37]

The localisation of 5-HT_{2A} receptors in mammalian brain has been extensively studied by means of radioligand autoradiography, *in situ* hybridisation of mRNA and immunocytochemistry. These receptors occur mainly in the telencephalon and much less in the midbrain and hindbrain.[4] Some antipsychotics also show relatively high binding affinity for 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors. Twelve mammalian 5-HT receptors are known; they belong to the superfamily of G-protein-coupled receptors, except the 5-HT_3 receptor, which is a ligand-gated cation channel. Recently, other subtypes have been found, although they are not yet well characterised.

Table II summarises the 5-HT receptor subtypes and their main individual features, as previously reported.[38-40]

The Glutamate Hypothesis

Dysfunction of corticolimbic glutamatergic neurotransmission may contribute to or account for the manifestations of psychoses.[41,42] In fact, glutamatergic neurons represent the primary excitatory afferent and efferent systems innervating the cortex, limbic regions and striatum. A dysfunction of glutamatergic neurotransmission may be relevant in forms of psychosis characterised by negative symptoms and cognitive deficits and deterioration. The postsynaptic actions of glutamate are mediated by a family of glutamate-gated ion channels that permit the influx of sodium and calcium, so depolarising exciting neurons. One of these receptors, the *N*-methyl-D-aspartate (NMDA) receptor, is the site of action of psychotomimetics such as phencyclidine, ketamine and related anaesthetics, which in healthy individuals can reproduce most of the symptomatic features of schizophrenia.

There have been at least three lines of evidence in the development of the hypoglutamatergic hypothesis of schizophrenia and psychoses.

In 1980, Kim et al.[43] proposed the glutamate hypothesis based on their finding that the glutamate levels in cerebrospinal fluid of 20 schizophrenic patients (16 with chronic disease) were about one-half the normal value.[44] They hypothesised primarily impaired function of the glutamatergic neurons in schizophrenia. In addition, Sherman and co-workers[45,46] demonstrated that the release of glutamate was reduced by high K^+ in the synaptosomes of schizophrenic patients and this may support the hypoglutamatergic hypothesis.

Phencyclidine, which has been known as a psychotomimetic street drug since the early 1960s,[47] is reported to block the NMDA ion channel.[48] Unlike amphetamines, phencyclidine exacerbates psychotic symptoms in chronic schizophrenia.[49] In addition, phencyclidine-induced psychosis is regarded as a better pharmacological model of schizophrenia[50-52] than amphetamine-induced psychosis, because this model can mimic not only positive symptoms but also negative ones.[53,54]

Among glutamate receptors, the kainate (KA) receptor was first measured in the post-mortem brains of schizophrenic patients by Nishikawa et al.,[55] who, in 1983, reported increased ^{3}H-KA binding to the putamen and prefrontal cortex areas. A significant increase was found in off-drug psychotic patients compared with healthy controls in these two areas. This biochemical alteration may be related to the impairment of prefrontal cortical function such as certain cognitive functions, alterations in affective and social behaviour, and abnormal eye movements, which are often observed in psychotic patients. The increased KA receptor binding may reflect reduced activity at certain glutamatergic synapses in the CNS.

The 2-amino-3-(3-hydroxy-5-methylisoxazole- 4)-propionic acid (AMPA) receptor was found to be unchanged in some brain areas in patients with schizophrenia and in controls.[56] Although the brain areas analysed were restricted and further studies are required, abnormalities of AMPA receptors in the brain were thought to be minimally involved in the pathophysiology of schizophrenia. Some years ago, ampakines, a family of substances that freely cross the blood-brain barrier and positively modulate AMPA receptors, were developed.[57] They enhance glutamatergic transmission,[58] facilitate long-term potentiation[59] and enhance learning and memory in rodents[60] and humans,[61] suggesting the drugs may improve cognitive dysfunction in patients. Consonant with the general idea of competitive glutamatergic/dopaminergic systems, an ampakine has been shown to reduce the aberrant behaviours induced in rats by methamphetamine,[62] a common and predictive test of antipsychotic drug activity. Some ampakines, such as CX516 and others, hold promise for the treatment of psychoses and seem to improve attention and memory.[63]

Moreover, there are three studies in which the ion channel of the NMDA receptor was assayed. Kornhuber et al.[64] measured NMDA receptors by using ^{3}H-MK-801, an NMDA-receptor antagonist, and found a binding increase in the putamen of the schizophrenic brain. Another study showed an increase in NMDA receptors in three brain areas, the superior temporal cortex, superior parietal cortex and supramarginal cortex, among 13 areas measured.[65] Simpson et al.[51] reported that ^{3}H-trichloropropane binding was bilaterally increased in the orbital frontal cortex of schizophrenic patients. The three studies therefore indicated an increase in NMDA receptors labelled by ^{3}H-ion channel blockers in several areas of schizophrenic brains, the areas differing among the studies.

In one of the studies on the NMDA receptor, Ishimaru et al.[66] found that strychnine-sensitive glycine-binding sites were significantly increased in six of the 16 areas of the schizophrenic cerebral cortex. The authors excluded the effects of long-term treatment with antipsychotic drugs on the binding data from animal experiments. The extent of the increase in ^{3}H-glycine binding is more pronounced and anatomically more widespread than that in ^{3}H-MK-801 binding, investigated in the same brain series.

The significance of the increased ionotropic glutamate, NMDA receptor or glycine-binding sites has not yet been elaborated, but a possible explanation is a postsynaptic compensation for impaired glutamatergic neurotransmission. Similar mechanisms may occur in the brain of psychotic patients during the chronic stage of schizophrenia. Dopaminergic hyperactivity is believed to be a prominent cause of schizophrenia. The release of glutamate may be inhibited by dopamine receptors located on corticostriatal terminals,[67-69] probably acting presynaptically.[70]

Interactions between glutamate and dopamine in the striatum are, however, reciprocal.[70] It has also been shown that glutamate presynaptically stimulates the release of dopamine from the striatum.[71-73] Conversely, the NMDA receptor located on dopaminergic terminals in the cingulate cortex mediates presynaptic inhibition of dopaminergic terminals in the cingulate cortex and along the mesocortical pathway.[74] Deutsch et al.[75] first demonstrated that phencyclidine increased dopamine metabolism in the mesolimbic and mesocortical areas, but did not influence dopamine neurons in the striatum.

As for the subclassification of psychotic disorders, there has been agreement that patients with positive symptoms, such as hallucinations and delusions, are more likely to respond to antipsychotic drugs.[76] It is possible to assume that primarily dopaminergic hyperactivity exists in the brain of such individuals. In patients with antipsychotic drug-refractory negative symptoms, such as flattened affect and social withdrawal, abnormal neurotransmitter substances other than dopamine may be involved, in addition to brain atrophy.[77] One such candidate transmitter is glutamate, and its hypofunction can be hypothesised. Patients with negative symptoms may be subclassified into two groups. One group is core schizophrenic patients, who develop negative symptoms from the beginning of the illness with intellectual and personality deterioration; glutamatergic hypofunction may primarily exist in the brain of such patients. Another group is characterised by shifting from positive to negative symptoms during the course of the beginning of the illness. In other words, patients show positive symptoms and respond well to antipsychotic drugs at the beginning. During the clinical course with periodic or repetitive relapses, they gradually shift to an antipsychotic drug-refractory, deteriorated state. In the latter subtype, dopaminergic hyperactivity mainly exists in the early stage but a long-term hyperdopaminergic state may induce glutamatergic hypofunction in the brain, resulting in the patients entering a chronic and deteriorated state.

The following points may therefore support the above inference. Firstly, psychoses induced by phencyclidine, an ion channel blocker of the NMDA receptor, are sometimes refractory to antipsychotic drugs[47,53] and cause schizophrenia-like symptoms, including negative ones. Secondly, glutamatergic ionotropic receptors such as KA, NMDA and strychnine-insensitive glycine-binding sites increased in our brain series obtained from patients with chronic schizophrenia and they showed significant negative correlations with glutamate concentrations.[44] Finally, the above-mentioned interactions between dopamine and glutamate in the brain will furnish valuable evidence.

Because biochemical post-mortem studies on brains of schizophrenic patients revealed abnormalities of several transmitter substances, for

example substance P and benzodiazepine receptors,[44] further intensive studies should lead to a better understanding of psychoses.

An endogenous antagonist at the NMDA receptor, *N*-acetyl-aspartyl-glutamate, appears to have enhanced activity in the frontal cortex and hippocampal formation in persons with these disorders. This means that drugs enhancing NMDA-receptor function reduce negative symptoms and cognitive deficits in persons with chronic psychosis who are receiving antipsychotics.[78] Table III summarises the types and properties of excitatory amino acid receptors.

Use of Antipsychotics in Psychiatry

Antipsychotics are among the most effective drugs used in psychiatry and reach the level of efficacy common for accepted medications in other fields of medicine. As shown by a number of double-blind studies lasting 4-8 weeks, antipsychotics are effective drugs in 50-80% of treated patients; in the maintenance therapy of schizophrenia, the relapse rate of patients treated with antipsychotics is several times lower than that of placebo-treated patients.[79] Efficacy in mania or in acute psychotic reactions is at least as great as in schizophrenia. In several other indications (e.g. delusional disorders, borderline psychoses, neurological conditions, behavioural disturbances), clinical study has been less comprehensive, often limited to particular antipsychotics or cases, but is also positive in terms of the remarkable improvement of patients. In psychotic exacerbations, in mania and acute schizophrenia, relatively high dosages of antipsychotics are indicated (e.g. in the elderly, haloperidol 10-20mg or chlorpromazine 25mg every 8 hours).[80] In disorders with minimal involvement of psychosis, treatment is started with a low dose that may be increased slowly according to therapeutic response. This is a rule, especially in the elderly. Abrupt discontinuation of antipsychotics may lead to withdrawal symptoms and should therefore be avoided.

Conventional antipsychotic drugs are D_2-receptor antagonists and inhibit dopaminergic neurotransmission in a dose-related manner. There is good agreement between the concept of dopaminergic equilibrium and therapeutic effectiveness.[81] Unlike purely sedating drugs, all of which may reduce psychomotor agitation, they decrease the intensity of all psychotic symptoms, although not necessarily to the same extent and with the same time course. Negative symptoms, related to withdrawal and flat affect, may persist to a much more striking degree than delusions, hallucinations and thought disorders. There is a dose-related incidence of EPS. At fixed, high doses of potent antipsychotics, the incidence and intensity of EPS are frequently judged to be excessively high.[81] In other studies, however, the same drugs are used at individually adapted doses below the antipsychotic threshold and yet produce the desired antipsychotic effect.[79,80] For most patients, adequate clinical improvement does not appear to depend on doses that result in disturbing adverse effects. Some of the more potent antipsychotics can be used intramuscularly for rapid neuroleptisation. The advantages of rapid control of psychosis must be weighed against the fact that in many patients thought disorders and other symptoms may require weeks of treatment to be resolved.

In daily practice, an antipsychotic is rarely selected at random, because the known differences in pharmacological spectrum and pharmacokinetics lead to differential prescription according to the severity of the condition and the characteristics of the patient (e.g. age). In fact, aging leads to remarkable changes in pharmacokinetics and pharmacodynamics, sensitivity to various potential adverse effects, and the requirements of rapid and complete recovery with the lowest possible dose. As regards the dosage, the choice is based on previous history, physical condition, age and clinical evolution. Additional measures, including psychotherapy, family education, social rehabilitation and social steps, may consolidate the results of pharmacotherapy. The most disturbing adverse effects can be avoided by using the most appropriate drugs and dosages.

Pharmacodynamic and pharmacokinetic considerations favour the specific, potent antipsychotics with good oral bioavailability. Clinically, the spectrum and intensity of symptoms, desirability of initial sedation, differences in potential adverse effects or in outpatient conditions, and other factors may vary sufficiently to consider several options from haloperidol-like to thioridazine-like antipsychotics and also new antipsychotics.[82] In fact, modern antipsychotics can be successfully used as first-line therapy, in both the young and the elderly.[82] In several clinical indications, the selection of particular drugs is imperative. For intense acute psychotic reactions, injectable preparations of potent antipsychotics with minimal cardiovascular or other autonomic effects are available, e.g. tiapride, olanzepine. The same compounds are preferable for other short-term or high-dose applications. If high-dose treatment of schizophrenia during the first 4-6 days is therapeutically ineffective or not tolerated, switching to a different antipsychotic for a second or third treatment period may lead to improvement.[83]

For psychosis in elderly patients and general medical indications, e.g. dementia, low doses of potent antipsychotics are considered the most appropriate and well tolerated. In monodelusional disorders and in predominantly negative schizophrenic syndromes, atypical antipsychotics are much more effective and well tolerated in the elderly. The injectable diphenylbutylpiperidine fluspirilene, in low-dose therapy, has marked activity in minor tranquilliser indications even if in such cases benzodiazepines appear to be more appropriate and safer. Apparent effectiveness (greater calmness, less aggressiveness) is the first sign of a reduction in psychomotor agitation, which is a preliminary step to a change in other core symptoms.[84]

True antipsychotic effects are obtained in the course of weeks of treatment, in which signs of hallucinations, delusions and thought disorders may regress. Frequently, the effect of appropriate doses of antipsychotics on negative and positive symptoms is sufficiently large to avoid long-term hospitalisation. If the expected remission does not start within 6 weeks and there are no disturbing adverse effects, higher doses can be used for a limited time, even though the proportion of responders decreases with increasing doses. Maintenance treatment at a dose lower than the acutely effective dose markedly reduces relapse rate. Every relapse further complicates the outcome for the patient.[84]

Moderate, individually adapted doses limit the incidence of disturbing EPS. Early recognition of treatment failures and avoidance of coadministration of anticholinergics with antipsychotics largely eliminate many other difficulties associated with antipsychotic treatment. Tolerance develops to the antipsychotic-induced sedative effects. Tolerance and cross-tolerance are also observed in behavioural and biochemical effects, particularly related to blockade of dopaminergic receptors in the basal ganglia.[35,81] These drugs are not addictive; however, a mild degree of physical dependence is manifested by muscular discomfort, and difficulty in sleeping may occur several days after abrupt discontinuation.[81] Adverse effects include, firstly, EPS, which are typical for antipsychotics. The second group of adverse effects involves non-EPS dose-dependent effects related to common activity components of the known antipsychotics. The symptoms associated with EPS are dose dependent and are observed with all antipsychotics at usual clinical doses, but with variable incidence and severity. The lowest incidence, about 4%, is observed with

clozapine, and the incidence increases several-fold with more specific, potent antipsychotics.[84] Two known factors have a major effect on the incidence of EPS. One is related to the pharmacological profile, since antimuscarinic and antiserotonin activity decrease the relative risk of EPS. The other factor is related to practical use. When using the less specific and weaker antipsychotics in the elderly, dosage increments are usually slower, and the upper limit is lower than in the young, leading to more gradual and less extreme D_2-receptor occupation. More conservative use of potent antipsychotics in sensitive individuals can prevent some of the EPS observed in clinical studies using fixed doses.[84]

Most patients with schizophrenia obtain a good clinical response with doses of antipsychotics not inducing distinct EPS. The antipsychotic threshold for EPS can be artificially raised by concomitant treatment with an anticholinergic. However, this second therapeutic agent has its own adverse effect profile and in fact conceals the effects of antipsychotic overdose. The dose of antipsychotic causing symptoms of overdose in the elderly varies depending on individual factors and drug-drug interactions, and of course it depends on the changes in pharmacokinetics and pharmacodynamics usually present during ageing. Therefore, a normal dosage in the young may be toxic in the elderly, leading, for example, to adverse effects, such as tardive dyskinesia, especially when combined with a drug that masks the neurological signs of the antipsychotics.

As can be expected from the chemical heterogeneity of antipsychotics, the metabolic and pharmacokinetic behaviour of these compounds is not uniform. Some antipsychotics appear to be better candidates for therapeutic monitoring than others. The ability to monitor pharmacokinetic parameters of a given antipsychotic has, in part, a technical basis. High pressure liquid chromatography generally provides the best separation of parent drug, isomer and metabolites; however, this approach may not always provide needed sensitivity. Radioimmunoassays are usually very sensitive, but specificity of the assay depends on the antiserum batch. The gas chromatographic/mass spectrometer approach is specific and sensitive, but the costs are high for such an instrument, and specially trained professionals are required for the assays and for maintaining the equipment. For practical drug monitoring, the radioreceptor assay may have advantages, because it measures, in the plasma sample, the total binding activity of the drug and active metabolite to D_2 receptors.[4]

In Vitro Receptor Binding Profile of Antipsychotics

The receptor binding affinity of the compounds for neurotransmitter receptor subtypes has been assessed by radioligands. Receptor subtypes are grouped according to neurotransmitter: dopamine (five subtypes), 5-HT (12 subtypes), adrenoceptors (four subtypes, none of the compounds binds to $_1$- or $_2$-adrenoceptors), histamine (one subtype), and muscarinic acetylcholine receptors (no subtype differentiation). Some compounds show high D_2-receptor affinity (i.e. haloperidol, promazine and clotiapine [Figure 1]); others show intermediate D_2 affinity (i.e. risperidone, 9-hydroxy-risperidone, sertindole, ziprasidone and zotepine [Figure 2 and Figure 3]). Others have low to moderate affinity[4] (i.e. olanzapine, clozapine, pipamperone and quetiapine [Figure 2 and Figure 3]). Olanzapine and clozapine show a similar binding affinity for D_1 and D_2 receptors (Figure 2), and ziprasidone has a 15-fold higher affinity for D_2 than for D_4 receptors. The contribution of D_4 receptor blockade to the therapeutic action of the compounds remains to be elucidated. The two butyrophenones, haloperidol and pipamperone, have quite different receptor-binding profiles. Haloperidol is the prototype of conventional antipsychotics, and shows high D_2-receptor binding affinity and has a moderate affinity for $_1$-adrenoceptors, and shows no or few interactions with other neurotransmitter receptors. On the contrary, pipamperone binds primarily to 5-HT_{2A} receptors, with a nearly equal affinity to D_4 receptors and a moderate affinity for 5-HT_{2C}, D_2, D_3, $_1$- and $_{2B}$-adrenoceptors. However, the compounds showing primary 5-HT_{2A}-receptor affinity include risperidone (Figure 2), pipamperone and sertindole (Figure 3).[4]

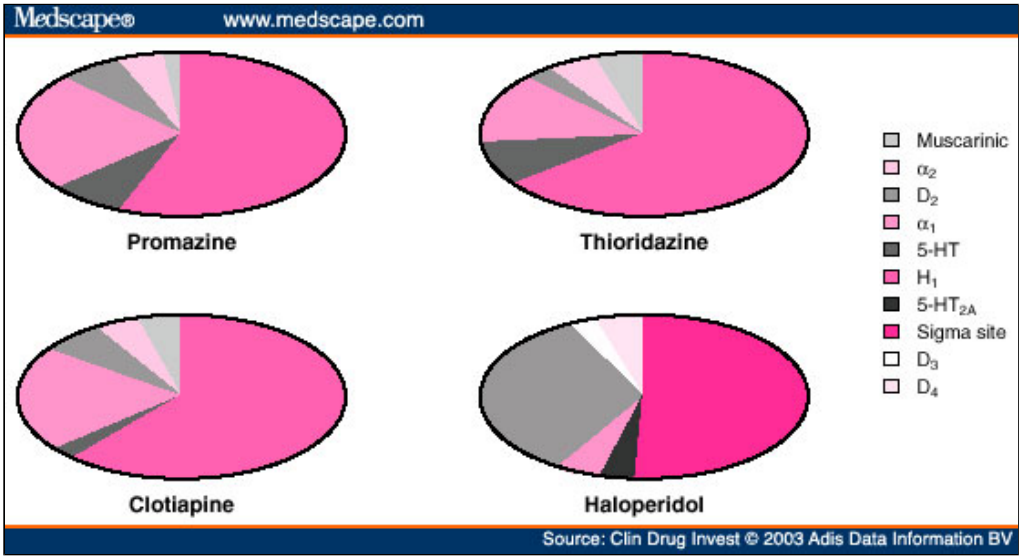

Figure 1. Receptor-binding profile of some antipsychotic agents. **D** = dopaminergic; **H** = histaminergic; **5-HT** = 5-hydroxytryptamine (serotonergic).

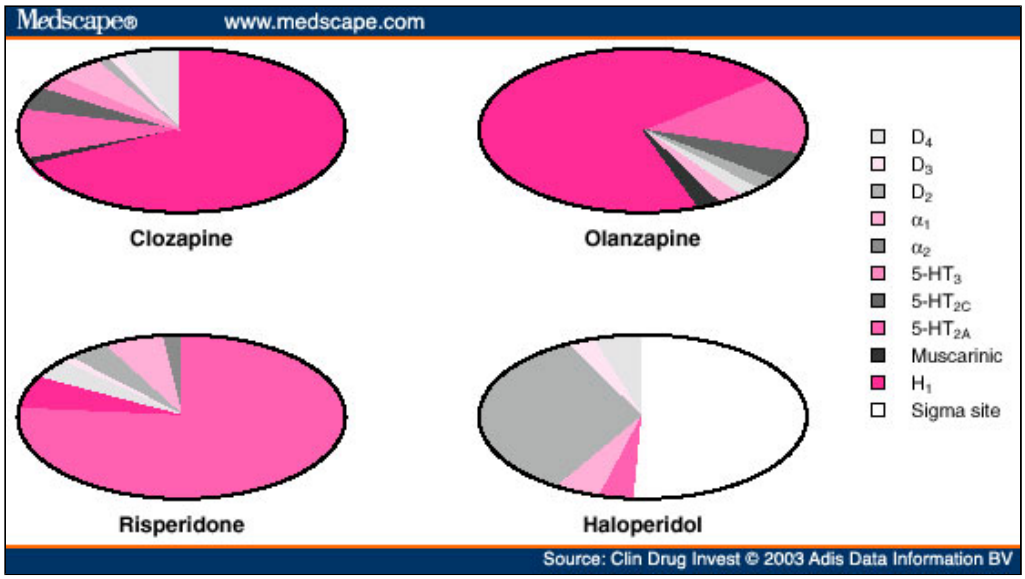

Figure 2. Receptor binding profile of the new versus conventional antipsychotic agents. **D** = dopaminergic; **H** = histaminergic; **5-HT** = 5-hydroxytryptamine (serotonergic)

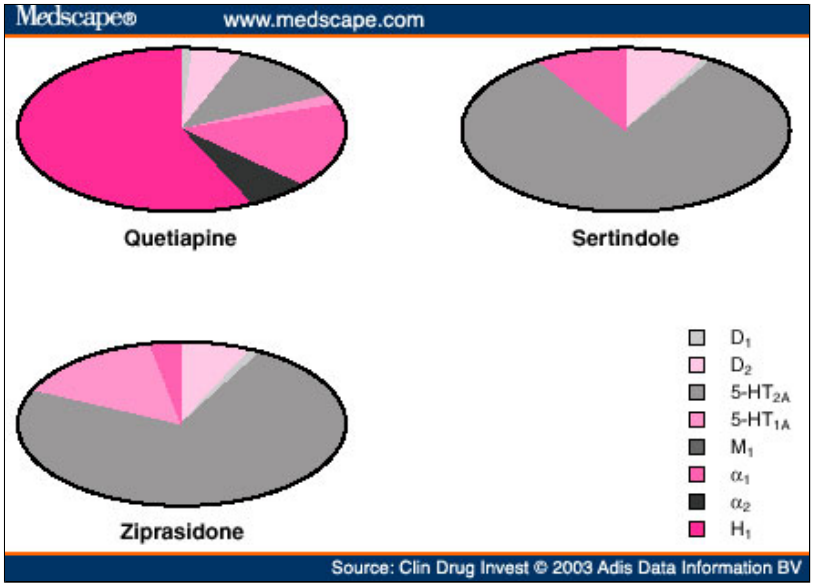

Figure 3. Receptor-binding profile of the new antipsychotics quetiapine, sertindole and ziprasidone. **D** = dopaminergic; **H** = histaminergic; **M** = muscarinic; **5-HT** = 5-hydroxytryptamine (serotonergic).

The tricyclic agents (clozapine, olanzapine, zotepine and quetiapine) have their highest affinity for H_1 receptors (Figure 2 and Figure 3);[4] this probably explains the highly sedative effects of these drugs and, in some cases, may contribute to weight increase. Moreover, quetiapine, clozapine, pipamperone, sertindole and zotepine show a very high potency at $_1$-adrenoceptors compared with D_2 receptors, whereas risperidone, 9-hydroxy-risperidone, ziprasidone and olanzapine have approximately equal affinity for D_2 and $_1$-adrenoceptors (Figure 2 and Figure 3). Haloperidol is more potent at D_2 than at $_1$-adrenoceptors. Central $_1$-adrenoceptor blockade may induce sedation, orthostatic hypotension and reflex tachycardia. Sertindole, zotepine, ziprasidone, clozapine and olanzapine show moderate affinity for 5-HT_{2C} receptors, the blockade of which results in their anxiolytic properties, may attenuate the rise in prolactin and may also contribute to considerable weight gain. As mentioned above, some antipsychotics may also bind to 5-HT_6 and 5-HT_7 receptors, but the roles of these receptors remain to be explained. The same can be said for 5-HT_1 receptors, which present some subtypes, but the mode of interaction with these receptors (agonism or antagonism) and their role in the therapeutic or adverse effect profile of these compounds is yet to be investigated. 5-HT_3-receptor antagonism by clozapine and olanzapine may contribute to their antipsychotic effects. It is worth noting that risperidone, 9-hydroxy-risperidone and clozapine interact with moderate affinity with $_2$-adrenoceptors; blockade of these receptors disinhibits adrenergic transmission and may contribute to enhanced cognition and antidepressant effects, while peripheral blockade can increase cardiac output.

Relatively potent muscarinic acetylcholine receptor binding is found for clozapine, olanzapine and quetiapine; anticholinergic activity accounts for various adverse effects such as delirium, confusion, cognitive deficits, blurred vision, dry mouth, urinary retention and constipation. It may reduce

EPS, but may promote the development of tardive dyskinesia.[4]

Antipsychotics in the Elderly

Antipsychotic treatment is common in the elderly and often indispensable. Results of an adequate multidimensional evaluation of a geriatric patient, including polypathology and polypharmacy on the one hand and comprehensive knowledge of drug-drug interactions and age-dependent pharmacokinetic and pharmacodynamic changes on the other, are essential for successful treatment.[85]

Age-Related Changes in Pharmacokinetics and Pharmacodynamics

Age-related changes in pharmacokinetics and pharmacodynamics may cause an increase in adverse drug reactions in elderly persons.

Pharmacokinetics. Ageing causes a number of changes in drug absorption, distribution, biotransformation and elimination.[86,87] Drug pharmacokinetics may change with age as a consequence of living habits in elderly individuals, such as diet, alcohol consumption, smoking, concomitant use of other drugs and genetic polymorphism of hepatic enzymes, diseases, etc.[88] (Figure 4).

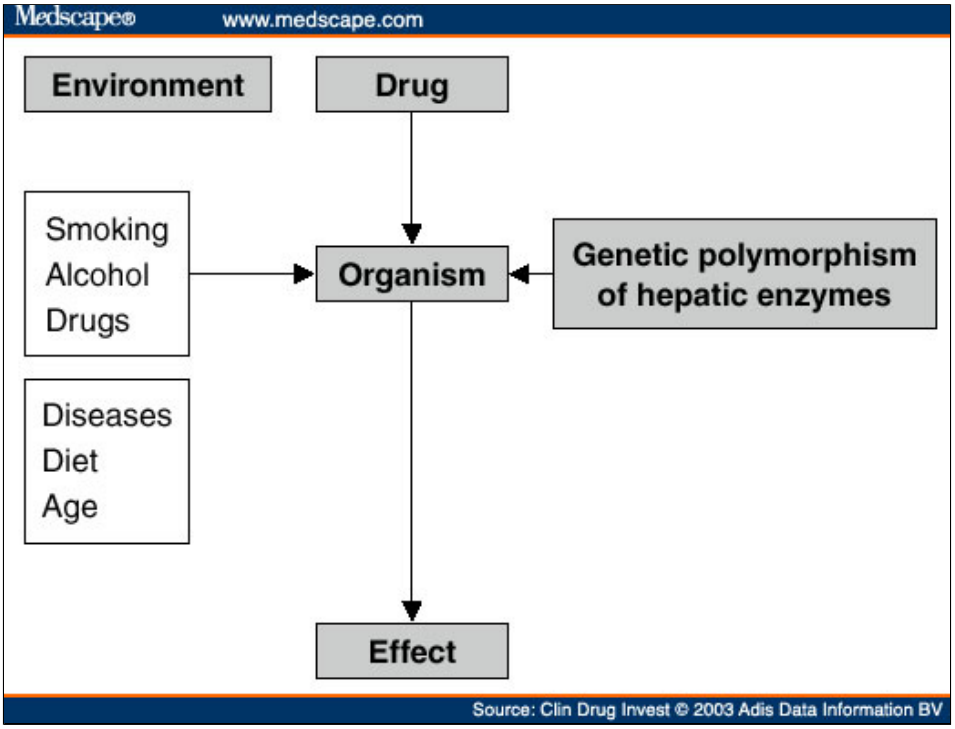

Figure 4. Factors influencing the effects of a drug.

The most important factors influencing drug absorption in the aged are:

- The increase in gastric pH, resulting from the reduction in acid output from the gastric parietal cells.[89] The increase in gastric pH increases the absorption of basic drugs and reduces the absorption of acid drugs;
- the reduction in gastrointestinal motility, with consequent delayed gastric emptying;[86]
- the reduction in splanchnic blood flow resulting from diminished cardiac output;[90]
- the decrease in absorption surface in the gastrointestinal tract.

The distribution of a drug is influenced by tissue blood flow, plasma protein binding and the physicochemical properties of the drug itself.[86] Moreover, it is influenced by lean and non-lean body mass, total body water and extracellular volume. Since adipose mass increases with aging, whereas total body water is reduced, the volume of distribution is less for water-soluble drugs and greater for lipid-soluble ones, such as diazepam, nitrazepam, amitriptyline, lidocaine (lignocaine), haloperidol, chlorpromazine and ^{3}H-spiperone.[91] Therefore, these lipid-soluble drugs tend to accumulate in adipose tissue, resulting in increases in their plasma half-lives and their duration of action, thus increasing the risk of iatrogenic effects in elderly persons.[81,89,92-94]

Plasma-binding proteins are albumin, $_{1}$-acid glycoprotein and lipoproteins. Aging causes reduced synthesis of these proteins; in persons older than 80 years, albumin synthesis is 20% less than in a young adult, while it is even less in elderly patients affected by liver and/or renal failure

(Table IV). These pathological conditions may alter plasma protein levels and cause accumulation of some substances competing with drugs in protein binding.[94] Albumin mainly binds to acid drugs, such as warfarin, salicylic acid, phenytoin, haloperidol and risperidone,[85,95] whereas $_1$-acid glycoprotein binds to basic drugs, such as lidocaine, propranolol, tricyclic antidepressants, pethidine (meperidine), chlorpromazine and thioridazine.[96,97] Plasma protein binding of chlorpromazine, propranolol and pethidine is virtually unaffected by age or may be slightly increased for chlorpromazine.[97]

Another crucial point in drug kinetics is metabolism. Liver clearance of a drug depends mainly on liver blood flow, which decreases with aging, and on liver enzyme activity. The latter depends on phase 1 and phase 2 reactions. In phase 1 reactions the involved enzymes are called mixed-function oxidases, composed of a number of haemoproteins, such as cytochrome P450 (CYP), cytochrome b5 and a flavoprotein, nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome-C-reductase. Phase 2 reactions involve acetylation and conjugation reactions with glycuronic acid. Phase 2 reactions are not influenced by age, whereas phase 1 reactions are strongly influenced by aging, sex and genetic factors. In fact, the existence of a genetic polymorphism in the oxidative metabolism of some drugs, such as antidepressants and -blockers, has been shown.[86,98-100] Therefore, genetic mutations inherited as recessive autosomal characters might cause reduced synthesis of various CYP isoenzymes (now named CYP2D6, CYP1A2, CYP2C9, CYP2C19 and CYP3A4) [Table V]. This means that for a given substance, i.e. the prototype debrisoquine, an experimental antihypertensive drug, there are fast metabolisers (90% of individuals) and slow metabolisers (10%; that is, those with genetic mutations).[101] Several years ago, Alexanderson et al.[98] administered the same dose of nortriptyline to monozygotic and dizygotic twins. The results were remarkable, as they showed that plasma nortriptyline concentrations were equal in monozygotic twins, but different in dizygotic twins. Furthermore, even in the monozygotic twins, the concentrations could be different if one was at the same time treated with other drugs. In fact, liver metabolism may also be influenced by smoking, liver disease, alcohol, nutritional status and, especially in the elderly, concomitant administration of various drugs. The last factor is important because drugs may increase or reduce microsomal enzymes that metabolise drugs. The former are called inducers, the latter inhibitors. Liver metabolism of a drug can also be reduced by another drug via competition for the same enzyme system.

Genetic Polymorphism of Hepatic Enzymes. CYP isoenzymes have a particular role in drug metabolism, both in adults and in the elderly. In humans, more than 30 CYP isoenzymes have been identified; CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 are important in the metabolism of a number of antipsychotics (Table V). A genetic polymorphism has been described for two of them (CYP2D6 and CYP2C19), and two phenotypes have been identified poor metabolisers and extensive metabolisers.[102-104] Therefore, all patients presenting a genetic deficiency of these enzymes may have a higher risk of adverse effects when they are treated with a drug that is a substrate of these isoforms.[105,106] On the other hand, the discovery of a gene amplification for CYP2D6 may explain the existence of ultrarapid metabolisers.[101] Isoenzymes of CYP1A2 and CYP3A4 have shown a high interindividual variability in their activity, which may be induced by some exogenous factors, such as smoking and drugs (i.e. barbiturates, carbamazepine, phenytoin) [Table V]. Moreover, CYP2D6 is the cytochrome whose polymorphism has been better studied. The activity of this isoenzyme is deficient or absent in 5% 8% of White people and 2% 5% of Black and Oriental people. This cytochrome is involved in the metabolism of some antipsychotics, i.e. thioridazine, perphenazine, fluphenazine, zuclopenthixol, haloperidol, risperidone, clozapine, olanzapine and sertindole (Table V) and also antidepressants, antiarrhythmics (e.g. propafenone) and -blockers. Other studies have shown that some selective serotonin reuptake inhibitors, such as fluoxetine and paroxetine, and some antipsychotics, such as thioridazine and perphenazine, can inhibit the activity of CYP2D6 *in vitro*.[107] The most powerful inhibitor seems to be paroxetine, followed by fluoxetine, norfluoxetine and sertraline.

CYP1A2 plays an important role in oxidative metabolism of caffeine, theophylline, some tricyclic antidepressants (TCAs) such as amitriptyline, imipramine and clomipramine, and some antipsychotics such as clozapine, olanzapine and haloperidol. It is inhibited by fluvoxamine and ciprofloxacin (Table V). CYP2C19 is responsible for demethylation of diazepam and tertiary amines of the TCAs. CYP3A4 is important for the metabolism of short half-life benzodiazepines, such as triazolam, some dihydropyridine calcium antagonists, immunosuppressants (cyclosporin), erythromycin and other macrolides, some TCAs, sertraline and citalopram, and it represents a secondary metabolism pathway for venlafaxine.[108,109] Other substrates are antiepileptics such as carbamazepine, felbamate and tiagabine and some antipsychotics such as haloperidol, clozapine, risperidone, quetiapine, ziprasidone and sertindole (Table V).

Drug Excretion. Ageing also causes reduced renal drug excretion. This occurs even in the absence of overt renal failure, because glomerular filtration in elderly persons is 30% 35% less than in young adults and tubular function and renal blood flow are also compromised.[110] Drugs that are excreted through glomerular filtration and are potentially toxic in the elderly include digoxin, lithium, aminoglycosides, procainamide, cimetidine and chlorpropamide. Moreover, in the elderly, a normal serum creatinine does not mean good glomerular filtration, or rather it can be misleading because it is slowed in individuals with decreased muscle mass. Therefore, determination of creatinine clearance is desirable, and a fast method is using a formula (see below), although direct determination based on 24-hour urine collection is preferable.[94,111,112]

Creatinine clearance = (140 - age in years) x bodyweight (kg)/72 x plasma creatinine (mg/dL).

Pharmacodynamics. Some drugs may have different pharmacological effects in the elderly than they do in the young. There are various reasons, including changes in the number of receptors and in binding affinity and the deficits in homeostatic mechanisms, that is, all the hormonal, biochemical and nervous compensatory reflexes limiting drug effect.[94,113] So, for example, an elderly individual may experience orthostatic hypotension following administration of an antihypertensive drug, because of reduced autonomic function.[90]

Geriatric patients frequently have medical conditions such as dementia, hypoalbuminaemia and chronic renal failure, which can alter pharmacological response. All these changes have to be taken into account, and they explain why, for example, elderly persons are more sensitive to benzodiazepine or antipsychotic effects, experiencing stronger sedation even with lower plasma concentrations of these drugs than those required for a sedative effect in younger persons. In other words, when considering therapy in elderly patients, we need to be careful to try to achieve an efficacious pharmacological response with the lowest dosage.

Characteristics of Individual Antipsychotics

As mentioned in section 4, conventional and atypical antipsychotics show significant differences both in receptor binding profile and in pharmacokinetic characteristics; we have focused in particular on some of them. A Medline search was made using the following keywords: conventional antipsychotics, atypical antipsychotics, elderly, pharmacokinetics, pharmacodynamics, side effects. The research was restricted to the last 5 years; further data on the drugs were obtained from Micromedex Healthcare Series (MICROMEDEX Inc., Englewood, CO, USA).[114] In addition, we included some studies that were referenced in reports from our pharmacovigilance centre.

Table VI presents the classification of conventional and atypical antipsychotics.

Conventional Antipsychotics

Haloperidol

Haloperidol is a high-potency antipsychotic structurally related to droperidol, and indicated for the symptomatic treatment of psychotic disorders, tics and severe behavioural problems both in adults and in the elderly. Haloperidol decanoate is a long-lasting intramuscular injection used for long-term treatment of schizophrenia or other psychotic disorders.[115,116]

Haloperidol can be administered orally, intramuscularly or intravenously; it is well absorbed from the gastrointestinal tract. First-pass metabolism in the liver reduces the bioavailability to approximately 60%, while the bioavailability of the lactate formulation is 75% when it is given intramuscularly. Peak plasma concentrations after oral administration are achieved within 2-6 hours and the maximum therapeutic activity within 30-45 minutes. After intramuscular injection of haloperidol decanoate, peak plasma concentrations are achieved after about 7 days. It is 93% plasma protein bound, especially to $_1$-acid glycoprotein, and is extensively metabolised in the liver through *N*-dealkylation to inactive metabolites and to an active metabolite, hydroxyhaloperidol. The latter undergoes extensive enterohepatic cycling. The elimination half-life of the oral dosage averages 24 hours. Half-lives of intramuscular haloperidol lactate and decanoate are 21 hours and 21 days, respectively. It is excreted mostly by the kidneys, and about 15% is eliminated through biliary excretion.

EPS frequently occur during treatment with haloperidol and seem to be a result of D_2-receptor blockade. It is not well known why they occur less frequently after intravenous than after intramuscular or oral administration. They are classified as dystonic reactions, akathisia and pseudoparkinsonism (i.e. reduced motor activity, resting tremors, hip rigidity, hypersalivation and postural abnormalities). Dystonic reactions usually occur 24-96 hours after the beginning of treatment and involve 30-64% of treated patients. Akathisia occurs in 25-26% of patients treated with high-potency antipsychotics and generally develops in several days to weeks; it may respond to dose reduction or to concomitant administration of a benzodiazepine (usually lorazepam) or a -blocker (e.g. propranolol, metoprolol). Pseudoparkinsonism usually appears 1-2 weeks after the beginning of treatment; its incidence is 15% 36% and it appears especially in the elderly and in women. Dystonia and pseudoparkinsonism are usually treated with an anticholinergic agent such as benzatropine or diphenhydramine. Neuroleptic malignant syndrome (NMS) may rarely occur in patients receiving haloperidol. Tardive dyskinesia, sometimes irreversible, may appear particularly in elderly women with medical conditions. Other adverse effects are somnolence (tolerance usually develops after prolonged therapy), hyperprolactinaemia (with gynaecomastia, galactorrhoea, impotence, infertility and ejaculation dysfunction), retinopathy, melanosis and haematological disturbances (anaemia, leucopenia and leucocytosis). Cardiovascular adverse effects include hypertension, ventricular tachycardia, QT prolongation and cardiac arrhythmias such as torsade de pointes (frequently with large dosages, e.g. >100 mg/day). QT interval corrected for heart rate (QT_c) is prolonged, especially in critically ill patients, when haloperidol is administered intravenously.[117]

Haloperidol is widely used in the treatment of schizophrenia, delusional disorders, dementia, agitation, aggression and chronic psychoses in elderly patients. Two studies have compared it with the newer antipsychotic risperidone in the treatment of behavioural disorders in demented patients.[118,119] Both studies demonstrated treatment failure and EPS more frequently with haloperidol than with risperidone. EPS are also more frequent in elderly demented than nondemented patients.[120] Recently, haloperidol has been shown to have lower efficacy than intramuscular olanzapine for treating agitation in schizophrenia.[121] The mean dosage in the elderly is 1.5-2mg/day; the maximum recommended dosage is 5-7 mg/day.[122]

Chlorpromazine

Chlorpromazine is an aliphatic phenothiazine used mainly as an antipsychotic. It is the prototype of the antipsychotic agents. It is rapidly absorbed after oral administration, but there is considerable individual patient variation in peak plasma concentrations, because the drug undergoes metabolism in the gastric mucosa and during the first pass through the liver. After oral ingestion, onset of sedation occurs within 30-60 minutes and lasts for 4-18 hours. Chlorpromazine is 92% 97% bound to plasma proteins, primarily to $_1$-acid glycoprotein; it crosses the placenta and distributes to breast milk. It is extensively metabolised to produce more than 100 metabolites, some of which, such as 7-hydroxy-chlorpromazine, have pharmacological activity. Mean plasma half-life is 27-37 hours, and the drug undergoes enterohepatic cycling. Excretion is primarily renal and elimination is via the biliary tract and faeces.

Clinical indications are represented by the treatment of psychotic disorders (schizophrenia, schizoaffective abnormalities) and severe behavioural abnormalities (also in adolescents).[122] EPS also occur frequently during treatment with phenothiazines because of D_2-receptor blockade, especially during high-dose use. Somnolence, dizziness, migraine, cerebral oedema and seizures may frequently appear. Anticholinergic effects include blurred vision, xerostomia, mydriasis, nausea, adynamic ileus, urinary retention, impotence and constipation. Leucopenia, including agranulocytosis, is the haematological disorder that has been reported most frequently during phenothiazine treatment. Allergic reactions, including obstructive jaundice, have been reported with chlorpromazine. It usually develops within 3-4 weeks of initiating drug treatment and is associated with skin reactions, jaundice, fever and eosinophilia. Prolonged therapy with phenothiazines can lead to skin hyperpigmentation, photosensitivity and pigmentary retinopathy. Hyperprolactinaemia and cardiovascular adverse effects are analogous to those reported for haloperidol.[91] Mean dosage in the elderly is 25-75 mg/day.[123]

Thioridazine

Thioridazine is a piperidine phenothiazine indicated for the treatment of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. It has also been used for the treatment of dementia, organic brain syndrome and, together with antidepressants, for the treatment of depression, although these are not approved indications. The mean oral dosage in adults is 50-100mg three times daily up to a maximum of 800 mg/day, while elderly patients usually require lower dosages (mean recommended dosage is 30-50 mg/day).[122].

Therapeutic blood levels range from 140 to 660 µg/L 3 hours after a single dose of 100mg. Peak serum levels are reached within 1 hour and levels may persist for 100-120 hours after withdrawal of the drug; the elimination half-life is 21-24 hours. Thioridazine undergoes extensive hepatic metabolism to active and inactive compounds, with minimal excretion of unchanged drug in the urine.

In the elderly, particular attention should be given to the use of concomitant medications that prolong the QT_c interval, since thioridazine has been shown to prolong the QT_c interval in a dose-related manner and may be associated with torsade de pointes-type arrhythmias and sudden death. Other adverse effects include agranulocytosis, thrombocytopenia, leucopenia, hypotension, confusion, tardive dyskinesia, EPS, NMS, nausea, vomiting, parotitis, sexual dysfunction, retinopathy, skin discoloration and phototoxicity. In particular, elderly patients should be treated with reduced doses of thioridazine and closely monitored for excessive parkinsonian adverse effects. Significantly higher plasma concentrations (1.5- to 2-fold higher) were reported in elderly patients (mean age 76 years) than in young adults.[123] Adverse effects (postural hypotension, dry mouth) were more frequent and severe in the elderly.[124] Concurrent use of anticholinergic agents (benzatropine, orphenadrine, procyclidine, trihexyphenidyl) to control EPS may reduce the absorption of thioridazine and antagonise its behavioural and antipsychotic effects, together with enhancing anticholinergic adverse effects. This occurs particularly in the elderly, in whom anticholinergic adverse effects are more severe (ileus, excessive sedation, dry mouth, hyperpyrexia). Therefore, its use in the elderly requires caution.

Promazine

Promazine is an aliphatic phenothiazine antipsychotic agent, with a low-potency antidopaminergic action, $_1$-adrenergic antagonism and anticholinergic properties. It is rapidly absorbed after oral administration; peak plasma concentrations occur at between 2 and 4 hours and its plasma half-life is about 6 hours. Promazine is highly bound to plasma proteins, especially albumin. It undergoes hepatic metabolism and is eliminated via the kidneys.[123]

Promazine is used in the treatment of schizophrenia, paranoid states, mania, toxic psychosis (caused by amphetamines, lysergide [LSD], cocaine), mental organic disorders with delirium, severe anxiety refractory to benzodiazepines, and depression associated with psychomotor agitation and delusions. In elderly demented patients it is usually administered when behavioural disturbances occur.[125] On the other hand, it may increase the sedative effects of benzodiazepines, hypnotics, anaesthetics and antihistaminic agents.[91] Its main adverse effects are sedation, somnolence, insomnia, anxiety, agitation, seizures, various anticholinergic effects (caution is required in association with anticholinergic drugs), EPS, dizziness, hypotension, sinus tachycardia, syncope, leucopenia, agranulocytosis, thrombocytopenia, hyperprolactinaemia, cholestatic jaundice and NMS. Mean dosage in the elderly is 15-60 mg/day.[122]

Fluphenazine

Fluphenazine is a piperazine phenothiazine antipsychotic agent indicated for the treatment of schizophrenia. Following intramuscular administration of fluphenazine dihydrochloride, peak serum levels are achieved at 1.5-2 hours. Intramuscular fluphenazine enanthate produces peak serum levels on days 2-3, whereas intramuscular fluphenazine decanoate produces peak levels on day 1. The half-life of oral fluphenazine is about 33 hours, and that of fluphenazine enanthate is about 3.5-4 days. The elimination half-life of fluphenazine decanoate is 6.8-9.6 days after a single injection and increases to at least 14 days after multiple injections.[123]

Fluphenazine can be used in geriatric patients, but at lower doses than in adults. Elderly patients should receive an initial oral dosage of 1-2.5 mg/day of fluphenazine, or 12.5-25mg of intramuscular fluphenazine decanoate every 4 weeks.[91]

Adverse reactions may include blood dyscrasias, such as leucopenia, agranulocytosis and thrombocytopenia. Hypertension and fluctuations in blood pressure have often been reported, and hypotension has occurred rarely, as have tachycardia and oedema.

The most common CNS adverse effects include pseudoparkinsonism, dyskinesia, opisthotonus, hyper-reflexia, dystonia and akathisia. These effects appear to be dose related and can be alleviated by dosage reduction and/or use of anticholinergic medication. Headache, cerebral oedema, drowsiness and lethargy have also occurred, as well as altered EEG tracings. The enanthate salt produces significant EPS more often than the decanoate salt, probably because of the longer duration of action of the latter.[126,127] Tardive dyskinesia, seizures and elevated prolactin levels are more prevalent in the elderly, especially in women. Furthermore, menstrual irregularities, impotence in men and increased libido in women have occurred. NMS and gastrointestinal symptoms such as loss of appetite, hypersalivation, dry mouth, constipation, paralytic ileus and weight gain have also occurred with fluphenazine.[91]

In the elderly, care must be taken with the coadministration of other drugs, particularly those drugs prolonging the QT_c interval, because of the well-known risks of increasing proarrhythmias.[91]

Perphenazine

Perphenazine is a piperazine phenothiazine antipsychotic agent used in the treatment of schizophrenia, psychoses, organic mental syndrome characterised by delusions, agitation and severe anxiety, and psychosis and behavioural disturbances in demented patients.[128] It blocks D_2 receptors and presents a high affinity for 5-HT_2 and histaminic receptors, whereas it has low adrenolytic and anticholinergic activity.[91,123] It is quickly absorbed, with bioavailability of about 20%. Peak plasma concentrations occur 1-4 hours after oral administration, plasma half-life is 8-21 hours, and the drug is excreted by the kidneys. The enanthate form is administered intramuscularly. Extensive metabolism into several metabolites occurs in the liver, by sulphoxidation, hydroxylation, dealkylation and glucuronidation. Perphenazine metabolism is mediated by CYP2D6.[91]

For treating schizophrenia and psychoses, recommended dosages in adults are 12-48 mg/day, whereas in elderly patients with psychotic manifestations recommended dosages are one-third to one-half of the usual adult dosage, whether given orally or intramuscularly.[91] Adverse effects are EPS, sedation, anticholinergic effects, seizures, agranulocytosis, endocrine effects, tardive dyskinesia and liver damage. Caution is especially required in the elderly because of postural hypotension as a result of antiadrenergic activity, and muscle weakness; an increased incidence of hip fracture has been reported in elderly patients.[91]

Zuclopenthixol

Zuclopenthixol is a thioxanthene antipsychotic with D_1 and D_2 antagonism, high affinity for 5-HT_2 receptors and low adrenolytic, muscarinic and histaminic activity. Peak plasma concentrations occur 2-4 hours after oral administration, with a plasma half-life of 20 hours. Metabolites have no pharmacological activity. Zuclopenthixol is also available as decanoate, esterified with a fatty acid and slowly released (long-lasting, about 3 weeks), and as acetate, which is highly lipophilic. The acetate is administered intramuscularly, slowly spreads in tissues and undergoes enzymatic degradation with formation of active zuclopenthixol.

Zuclopenthixol is used in schizophrenia when hallucinations, hostility, aggression and delusions dominate the clinical picture, in mania and in organic mental disorders (i.e. mental insufficiency, senile dementia). It is frequently used in the elderly, although caution is required, especially if cardiovascular disease, renal failure or history of seizures are present.[91,123] Mean recommended dosages in the elderly are 2-6 mg/day; dosage may be increased as needed up to 10-20 mg/day.[91,123] Adverse effects include dystonic reactions, akathisia, tremors, sedation, depression, confusion, hallucinations, increased transaminases and rarely tardive dyskinesia. Especially in the elderly, caution is required because of the frequent presence of cardiovascular effects such as hypotension, tachycardia, dizziness and orthostatic syncope, and autonomic effects such as xerostomia, urinary retention, constipation and accommodation disturbances.[91,123]

Levosulpiride

Levosulpiride is a benzamide and a dopamine agonist. It is used at low doses in dysthymia and at higher doses as an antipsychotic. It undergoes rapid absorption, with peak plasma concentrations occurring in 1-5 hours. Plasma half-life is biphasic, with a rapid phase of 2-5 hours and a slow phase of 15-18 hours. Steady state occurs in 48-72 hours. Levosulpiride undergoes hepatic metabolism, which leads to inactive compounds, and is excreted by the kidneys, mostly as an unmodified compound.[91,123]

The adverse effects of levosulpiride are particularly marked in the elderly and include sedation and hypotension, as well as precocious dyskinesia (stiff neck, oculogyric crises, trismus), EPS requiring antiparkinsonian treatment, tardive dyskinesia (observed in the case of prolonged treatment) and some endocrine effects, such as hyperprolactinaemia, galactorrhoea and gynaecomastia. It may also potentiate the effects of antihypertensive, hypnotic and analgesic drugs. Mean dosage in the elderly is 100-200 mg/day.[91,123]

Tiapride

Tiapride is a derivative of the substituted benzamide series of antipsychotics, characterised by a high affinity for D_2 receptors, whereas it has no affinity for adrenergic, cholinergic and histaminic receptors. It is rapidly absorbed after oral and intramuscular administration, with peak plasma concentrations after 60 and 30 minutes, respectively.[91,123] Tiapride has a plasma half-life of about 3-4 hours and undergoes renal excretion in 24 hours. It is particularly effective in behavioural disorders in the elderly at dosages of 100-300 mg/day, with less tendency to cause EPS compared with haloperidol.[91,128]

The main adverse effects are an increase in serum prolactin, somnolence, sleep disorders, dyskinesia, EPS, allergic dermatitis, muscle pains and, rarely, postural hypotension. Sedation and hypotension are the most common adverse effects in the elderly.[91]

Pimozide

Pimozide is a diphenylbutylpiperidine with high antidopaminergic activity resulting from the blocking of D_2 receptors, moderate affinity to 5-HT_2, low adrenolytic and anticholinergic activity, and no histaminic activity.

It is slowly absorbed, with peak plasma concentrations occurring 8 hours after oral administration. Pimozide undergoes hepatic metabolism, without active metabolites, and has a long plasma half-life (about 50-60 hours).[91,123]

In the elderly, the half-life may be longer; therefore, careful dosage adjustment and continuous monitoring of adverse effects are required. Adverse effects are mild EPS, and rarely sedation, somnolence, impotence and skin eruptions.[91] Pimozide may enhance the sedative action of anxiolytics and hypnotics, and the response to sulphonylureas and antiepileptics may be decreased. The activity of antihypertensive drugs may be potentiated. Caution must be exercised in patients, especially the elderly, treated with antiarrhythmics, -blockers, diuretics or antihistamines,

because of the risk of ventricular arrhythmias.

Pimozide is used in psychoses when aggression, psychomotor agitation or severe anxiety are not the most important symptoms. It has also been shown to be effective in the treatment of tardive dyskinesia induced by prolonged administration of phenothiazines.[129] Mean dosage in the elderly is 2-4 mg/day.[91,123]

Atypical Antipsychotics

Amisulpride

Amisulpride is an alkylsulphone derivative of the substituted benzamide series of antipsychotics, with high affinity for presynaptic D_2/D_3 dopamine receptors,[130] whereas it has no affinity for serotonergic, $_1$-adrenergic, histaminic or cholinergic receptors. Low doses of this drug may improve negative symptoms in schizophrenic patients and are also used in the treatment of patients with dysthymia, by enhancing dopaminergic transmission at the level of the mesolimbic system.[131] High dosages (>/=600 mg/day) have antidopaminergic activity and are therefore used for treating positive psychotic symptoms or acute delusional attacks.[131]

Amisulpride is rapidly absorbed and peak plasma concentrations in the elderly occur 1.5-2 hours after oral administration.[91] Food has modest effects on its absorption.[132] It is poorly protein-bound (11% 17%) and its plasma concentrations decrease in a biphasic manner, with a first C_{max} between 2-5 hours and a second beween 15-18 hours.[91,123] Amisulpride is weakly metabolised, with two inactive metabolites, undergoing *N*-dealkylation and oxidation; 70% of this drug is excreted by the kidneys.[91] The elimination half-life is 12-17 hours.[132]

Amisulpride has a low occurrence of EPS because of its preferential binding to dopamine receptors in extrastriatal regions rather than in the striatum.[133] Because amisulpride can cause sedation and hypotension, caution should be used in geriatric patients. Increases of half-life, maximum plasma concentration and area under the concentration-time curve were observed after a single oral dose of 50mg in these patients.[91] Furthermore, in the elderly, somnolence, sleep disorders, precocious and tardive dyskinesia, endocrinological effects (hyperprolactinaemia, galactorrhoea, gynaecomastia) and allergic dermatitis are often observed.[123]

Clotiapine

Clotiapine is an atypical antipsychotic agent with a tricyclic structure of the dibenzothiapine type; its general properties are similar to those of phenothiazines. It has a high affinity for D_2 and 5-HT_2 receptors; moreover, it has adrenolytic, anticholinergic and antihistaminic activity.[91]

Clotiapine is well absorbed after oral administration, is extensively metabolised and a major portion is excreted in the urine. Its elimination half-life is about 8 hours. It is especially used in psychoses and schizophrenia and its efficacy has been well known for several years.[134] Common adverse effects include fatigue, drowsiness, tremor, constipation, tardive dyskinesia, EPS and NMS. Other effects are postural hypotension, tachycardia, syncope, severe muscle stiffness, seizures and trouble with breathing. Its use in the elderly requires caution, and low dosages (10-30 mg/day) should be used,[91,123] especially when prostatic hypertrophy, glaucoma or paralytic ileus are present.[91]

Clozapine

Clozapine is a dibenzodiazepine derivative structurally related to loxapine; despite typical antipsychotic effects, it has greater specificity for the limbic system and a low incidence of EPS. Clozapine was the first atypical agent to be proven in the treatment of schizophrenia refractory to other medications, but it has the disadvantage of causing severe adverse effects such as agranulocytosis, which can be fatal.

It is rapidly absorbed after oral administration, and only 27% 50% of a dose reaches the systemic circulation because of significant first-pass metabolism.[135,136] Various individual factors can alter response, such as smoking, hepatic metabolism, gastric absorption, age and sex. Smoking cigarettes (tobacco) increases the clearance of clozapine and may result in a substantial reduction in plasma clozapine concentration.[137] Clozapine is rapidly and extensively distributed; it crosses the blood-brain barrier and 95% is bound to plasma proteins, primarily to $_1$-acid glycoprotein. Steady state is reached in about 7-10 days. Many weeks may be required for the onset of the antipsychotic effect, but maximum effects are obtained several months after the beginning of treatment. Metabolism occurs primarily via the CYP1A2 and CYP3A4 hepatic microsomal enzymes and leads to two metabolites, norclozapine and clozapine-*N*-oxide. The mean terminal half-life is 6-33 hours; about 50% of a dose is excreted in the urine and 30% in the faeces, but only small amounts consist of unchanged drug.[135]

Agranulocytosis, defined as an absolute neutrophil count <500/mm^3, is the most severe adverse effect, and treatment should not be initiated if the baseline white blood cell count is <3500/mm^3. Furthermore, clozapine lowers the seizure threshold and may precipitate grand mal seizures, particularly at dosages greater than 600 mg/day or after dosage increases greater than 100 mg/day. Clozapine is less likely to cause EPS than typical antipsychotic agents, but should be used with caution in patients with prostatic hypertrophy, paralytic ileus, closed-angle glaucoma or urinary retention, because it has strong anticholinergic activity that can exacerbate these conditions. Clozapine must be used with caution in patients with cardiac and/or pulmonary diseases; indeed, it may frequently induce tachycardia and orthostatic hypotension, and therefore it must be prescribed carefully in the elderly.[136] Furthermore, a number of studies have reported that clozapine may increase the plasma glucose level in patients with or without a prior history of diabetes mellitus.[138-140] The possible mechanisms of onset of diabetes are presented in Table VII. Weight gain and elevations in serum triglycerides were also widely observed in patients treated with clozapine.[141-143] On the other hand, according to several studies, diabetes mellitus may be more common in schizophrenic patients than among the general population.[144] There have been at least 20 case reports of diabetes induced or exacerbated by clozapine; diabetic ketoacidosis was the presenting symptom in ten cases.

[138,145] Another very common adverse effect is excessive sedation or somnolence. Abrupt discontinuation of clozapine is not recommended, unless required by the patient s medical condition (e.g. leucopenia).

Clozapine is used in schizophrenia refractory to other medications and in bipolar disorder. At very low doses, it has been shown to be very effective for the management of psychosis in elderly patients with Parkinson s disease,[146] and it is also effective in elderly schizophrenic and demented patients. Recommended dosages in the elderly range from 25 to 150 mg/day.[147]

Risperidone

Risperidone, a benzisoxazole derivative, is a first-line oral antipsychotic agent. At therapeutic dosages, the combined 5-HT_{2A} and D_2 antagonism of risperidone is thought to be responsible for its effectiveness on positive and negative symptoms of schizophrenia and its lack of EPS. These are its main advantages compared with other currently available antipsychotics.[136,148] In the limbic system, a dopamine excess is responsible for the positive symptoms of schizophrenia; in the mesocortical tract, dopamine blockade may be responsible for the negative symptoms of schizophrenia. In the nigrostriatal pathway, dopamine blockade is known to cause EPS. Therefore, risperidone may antagonise dopamine receptors in the limbic system only, thus treating positive symptoms. On the contrary, in the mesocortical tract risperidone exhibits selective 5-HT_2 receptor blockade, which causes an excess of dopamine and an increase in dopamine transmission, thus having an effect on negative symptoms.[148] Since risperidone does not affect dopamine in the nigrostriatal pathway, except at very high doses, EPS are usually avoided, although there is individual variability. Another dose-related adverse effect is dopamine receptor blockade in the tubero-infundibular tract, resulting in prolactin release, weight gain and menstrual irregularity. $_1$-Receptor blockade may cause hypotension and this has to be especially taken into account when an elderly person is treated.

Risperidone is administered orally without any regard to meals. Peak plasma concentrations are achieved within 1-2 hours and are dose proportional.[148,149] Risperidone is metabolised via the CYP2D6 hepatic microsomal isoenzyme (debrisoquine hydrolase) and also via dealkylation; its main metabolite, 9-hydroxy-risperidone, is active. Both risperidone and 9-hydroxy-risperidone are highly protein bound. All drugs inhibiting or inducing CYP2D6 may affect the plasma levels of both compounds, and therefore the incidence of adverse effects and the efficacy of risperidone (Table V). CYP3A4 and CYP3A5 microsomal isoenzymes have also been shown to metabolise risperidone to 9-hydroxy-risperidone; the former is the most abundant of the liver CYP isoenzymes and is polymorphically expressed, appearing in only about one-fourth of human livers.[150] Therefore, the contribution of CYP2D6 and CYP3A4 to the metabolism of risperidone may have significant value in predicting potential drug-drug interactions in the clinical use of risperidone, as can occur in elderly patients with polypathology. Polymorphism of metabolic enzymes, together with decreases in hepatic blood flow and renal clearance, may lead to increased blood levels of risperidone in the elderly.[151] Risperidone and 9-hydroxy-risperidone have half-lives of about 3 and 24 hours, respectively. Steady state for risperidone occurs after 1 day, whereas for 9-hydroxy-risperidone it occurs after 4.5 days. Excretion is mainly via the kidneys and a small amount is eliminated in the urine. Half-life is prolonged in patients with hepatic or renal disease.

In the elderly, an initial dosage of 0.5mg twice daily is recommended; if strictly necessary, increases of 0.5 mg/day or twice daily are well tolerated. However, as is also the case in adults, the effectiveness of dosages above 6 mg/day have not been demonstrated and such doses are associated with an increased risk for EPS.[91]

This atypical antipsychotic agent is commonly used in the treatment of psychotic disorders in the elderly.[152] It has also been found to be very effective in the treatment of some behavioural disorders such as agitation, aggression and wandering in patients with dementia. In fact, risperidone at dosages of 1-2 mg/day seemed to be effective in reducing noncognitive psychiatric and behavioural symptoms in demented patients.[33,119,125,153-157] Recently, it has been shown that crossover from haloperidol to risperidone is generally safe and effective and may produce favourable moods in agitated demented patients.[158] Madhusoodanan et al.[159] showed very good efficacy and safety of risperidone in the treatment of 103 elderly patients with schizophrenia or schizoaffective disorders. At present, few data are available on long-term results; Davidson et al.[160] carried out an open-label, long-term study evaluating the effects of risperidone in elderly psychotic patients. Results suggest that long-term treatment with risperidone is associated with a continuous improvement, a decrease in severity of pre-existing EPS and a low incidence of tardive dyskinesia. Several studies have also shown positive effects on cognition, especially in elderly patients;[161,162] this is probably because of the lack of antimuscarinic activity.

Adverse effects have to be carefully monitored, particularly in elderly patients. Arterial hypotension (and in elderly patients especially orthostatic hypotension) is a result of $_1$-receptor blockade. This adverse effect is more frequent at the beginning of treatment and is characterised by the onset of dizziness, sinus tachycardia or syncope. The incidence of EPS (akathisia, dystonic reactions, pseudoparkinsonism) is much lower with risperidone (roughly 2.1%) than with other antipsychotics such as haloperidol. This is probably because of the high serotonin antagonism exhibited by risperidone, counteracting its dopaminergic activity.[136] The low incidence of EPS is dose related, and dosages above 10 mg/day increase the risk of inducing these symptoms.[136] It is also possible that risperidone may mask the signs and symptoms of developing tardive dyskinesia. These symptoms may emerge on withdrawal of the drug. NMS occurs in a few patients receiving risperidone. Several predisposing factors, such as heat stress, physical exhaustion, dehydration and organic brain disease (frequently present in an elderly individual) can contribute to the development of NMS. Seizures were reported in 0.3% of patients.[136]

Both risperidone and its metabolite 9-hydroxy-risperidone are known to prolong the QT_c interval, so other drugs known to prolong this interval should be avoided or very carefully administered.[163] This can occur especially in the elderly, in whom polypathology and polytherapy are often present;[153] drugs usually involved are certain antiarrhythmics (such as quinidine, flecainide, amiodarone, sotalol and verapamil), other antipsychotics (haloperidol and phenothiazines), tricyclic antidepressants, antihistamines (terfenadine and astemizole), some antibiotics (grepafloxacin and erythromycin), cocaine, probucol and ketoconazole.

Somnolence was reported in 8% of treated patients.[33] Rare adverse effects are photosensitivity, constipation, abdominal pain, nausea, vomiting,

reduced or increased salivation, blurred vision, fatigue, impotence and ejaculation dysfunction.

Recently, the onset of diabetes was shown in two patients treated with risperidone; however, these patients had a family history of diabetes and obesity and the disease occurred 1 year after the beginning of treatment. This is partly in contrast with the time to onset of diabetes observed during treatment with other antipsychotics, such as clozapine and olanzapine (20 weeks). Furthermore, the increase in adipose tissue may have contributed to insulin resistance and to the onset of diabetes, and these patients were treated with several drugs.[164]

Olanzapine

Olanzapine is an atypical antipsychotic agent similar to clozapine in chemical structure and in mechanism of action. It is administered orally, and an intramuscular formulation of olanzapine is currently available in some countries for the treatment of acute psychotic symptoms and of acutely agitated demented patients.[165] The drug is well absorbed and peak serum concentrations are reached in approximately 6 hours. There is extensive first-pass metabolism, with about 40% of a dose being metabolised before reaching the systemic circulation. Steady-state concentrations are reached after approximately 1 week of continuous administration. Olanzapine is 93% bound to plasma proteins, primarily to albumin and $_1$-acid glycoprotein.[136] Olanzapine is primarily metabolised by glucuronidation and CYP oxidation, the involved microsomal enzymes being CYP1A2 and CYP2D6. Neither metabolite has any pharmacological activity. The elimination half-life averages 30 hours, and 57% and 30% of a dose is recovered in the urine and faeces, respectively.

The more common adverse effects are somnolence in 26% of patients, dizziness, agitation, constipation, akathisia, postural hypotension and weight gain. Tardive dyskinesia occurs in about 1% of patients treated with olanzapine and is sometimes irreversible. Akathisia and other EPS occur more frequently with dosages greater than 10 mg/day. The most common cardiovascular adverse effect is orthostatic hypotension, which occurs in about 5.5% of patients treated and may also be the cause of dizziness. Elevation of hepatic enzymes generally occurs in 9.2% of patients receiving olanzapine. Other rarely reported adverse effects are sexual dysfunction, rhabdomyolysis and hyperglycaemia. In particular, hyperglycaemia, diabetes mellitus and ketoacidosis are widely known to be induced by olanzapine.[139,140,166] In the reported cases, hyperglycaemia was present only during treatment, and treatment withdrawal resulted in regression of symptoms. However, the reintroduction of treatment (rechallenge) caused a new onset of diabetes. Family history was negative for this disease.[140] Latency time was also constant among the cases (about 16 weeks). The possible mechanisms of onset of diabetes are presented in Table VII. Both schizophrenia itself and the older antipsychotic medications have been reported to be associated with a similar risk for causing disruption in serum glucose control. Diabetes also has well-recognised associations with a number of medical disorders such as cardiovascular disease; therefore it is worthy of attention. Fifteen cases of diabetes following olanzapine treatment have been reported in the literature.[166]

A number of studies suggest that olanzapine is safe in treating adult patients of any age with schizophrenia, acute bipolar mania and behavioural and psychological symptoms of dementia.[167-170] Compared with risperidone, it has shown improvement in social functioning in elderly patients with dementia[171] and psychosis, but it has more adverse effects, such as cognitive deterioration, glucose metabolism disorders and decreased blood pressure.[170] Other studies have shown that 5-HT$_6$ antagonism by olanzapine causes acetylcholine release, thus improving cognitive functions.[172]

Recent studies suggest a role for olanzapine in the acute treatment of psychotic mood disorders.[173] An intramuscular formulation of olanzapine has been developed because there are no rapid-acting intramuscular atypical antipsychotic drugs currently available in the US for treating acute agitation in schizophrenic patients.[121] Premarketing studies included few elderly patients; therefore, further data are required in the elderly, especially in patients with comorbidity.

Madhusoodanan and co-workers[174] demonstrated the efficacy and safety of olanzapine (5-20 mg/day) in 11 hospitalised elderly patients aged between 60 and 85 years with schizophrenia or schizoaffective disorder. Solomos and Geiger[175] conducted a retrospective study in 58 elderly patients with psychotic symptoms refractory to conventional antipsychotics; 60.3% of them responded to treatment with olanzapine. Compared with young adults, elderly patients may have a 6-fold higher prevalence of tardive dyskinesia when treated with olanzapine.

As mentioned above, a number of studies have shown the efficacy of low dosages of olanzapine (5-10 mg/day) in the treatment of psychosis and/or aggression and psychomotor agitation in Alzheimer s disease.[167-169,176] Somnolence and weight gain were frequently observed; no increase in cognitive dysfunction, EPS or central anticholinergic effects was found at the dosages administered.

Wolters and co-workers[177] showed that, in 15 patients with Parkinson s disease and a drug-induced psychosis, psychotic symptoms decreased without evidence of a worsening of EPS. Similar results were reported by Aarsland et al.[178]

Few data have been published from controlled studies of risperidone compared with olanzapine in elderly psychotic patients. Madhusoodanan et al.[159] analysed data collected on 151 elderly hospitalised psychiatric patients, 114 treated with risperidone and 37 with olanzapine. Response to treatment, interruption of treatment and adverse effects were similar in the two groups. Furthermore, olanzapine does not contribute to QT_c prolongation in psychotic patients.[160] Recommended dosages in elderly patients are 5-20 mg/day.[147]

Quetiapine

Quetiapine is a dibenzothiazepine structurally similar to clozapine. It has good efficacy on positive and negative psychotic symptoms, without producing EPS.[179,180] Quetiapine is administered orally, is rapidly absorbed and peak plasma concentration is achieved in about 1.5 hours; about 83% is bound to plasma protein. It is largely metabolised in the liver, and less than 1% of a dose is excreted unchanged. The main metabolites are a sulphoxide inactive metabolite, produced by CYP3A4, and an acid metabolite produced by oxidation. Mean plasma half-life is about 6 hours and clearance is reduced by 40% in the elderly.

Therapeutic indications are treatment of psychotic and behavioural disorders. Quetiapine may cause orthostatic hypotension (because of $_1$-receptor blockade), associated with dizziness, tachycardia and, in rare cases, syncope. It should be used carefully in patients with heart disease, particularly those with heart failure, previous history of myocardial infarction or conduction abnormalities. Quetiapine rarely causes EPS, such as akathisia, tremors and hypokinesia. It more frequently causes weight gain, somnolence, constipation, xerostomia and dyspepsia. However, it was recently shown that long-term monotherapy with quetiapine is associated with a potentially normalising effect on weight, with a tendency towards weight gain in underweight patients and weight loss in severely obese patients.[181] The onset of seizures was demonstrated in 0.8% of patients treated with quetiapine. It is associated with dose-dependent reductions in total and free thyroxine and transient increases in hepatic enzymes (especially aspartate aminotransaminase).

Madhusoodanan and co-workers[182] showed the efficacy of quetiapine in seven elderly hospitalised patients aged 61-72 years with schizophrenia-related psychotic symptoms, schizoaffective disorder or bipolar disorder. Four patients responded to treatment; transient hypotension, dizziness and somnolence were the most frequently observed adverse effects. No EPS were found. The long-term efficacy and safety of quetiapine in elderly patients with psychosis has been studied by some authors.[183,184] No cardiovascular adverse effects were observed; QT_c interval changes on ECG are not frequent and patients who begin treatment with this drug do not require an ECG. Treatment-related EPS were no more frequent than those observed with placebo.[185] Recommended dosages in elderly patients are 50-300 mg/day.[147]

Ziprasidone

Ziprasidone is a new antipsychotic agent with a high ratio of 5-HT_2 receptor blockade to D_2 receptor blockade. It can be used intramuscularly in the treatment of acute psychosis, or orally, and is effective on both positive and negative symptoms and in affective symptoms. Ziprasidone is usually more effective in reducing the symptoms of psychosis and better tolerated than haloperidol, especially in movement disorders.[186] Given orally, it is rapidly absorbed; steady-state serum concentrations are achieved within 2-3 days.[187] The influence of age and sex on its pharmacokinetics is not clinically significant. Even mild to moderate renal and hepatic impairment does not cause significant alterations of its pharmacokinetics and therefore does not necessitate dose adjustment.[188,189] It may also have a more favourable cognitive profile than traditional agents in the elderly, because of its weak anticholinergic effects.[190] Unlike other newer agents, it does not appear to be associated with weight gain in most patients and shows a low risk of neurological and neuroendocrinological adverse effects.[191] It also causes no change in glucose utilisation and seems to bring about a reduction in cholesterol and triglyceride levels.[192] It may increase the QT_c interval.[193] Recommended dosages in elderly patients are 20-40 mg/day.[194]

Remoxipride

Remoxipride is an atypical antipsychotic. It is a pure enantiomer, without any action on 5-HT_{2A} receptors. After oral administration, the drug is rapidly and almost completely absorbed, with bioavailability above 90%.[195] It has no first-pass metabolism, its apparent volume of distribution is 0.7 L/kg, and it is about 80% bound to plasma proteins, mainly $_1$-acid glycoprotein. Remoxipride has a plasma half-life in the range of 4-7 hours; no significant changes in plasma half-life are found in the elderly. It is eliminated by both hepatic metabolism and renal excretion; more than 70% of the dose is recovered as urinary metabolites, while about 25% is excreted unchanged. Decreased renal function is usually associated with an increase in remoxipride plasma levels.[196] Steady-state levels are achieved within 2 days, and they increase linearly with dosages up to 600 mg/day. Drug-drug pharmacokinetic interactions with diazepam, alcohol (ethanol), biperiden and warfarin are not present.

The most common adverse effects are tiredness and EPS, especially in the elderly.[157] Remoxipride can be used in the treatment of psychosis and behavioural disturbances.[157] Recommended dosages in elderly patients are 50-100 mg/day.[197]

Zotepine

Zotepine is an antipsychotic drug acting on D_1, D_2 and 5-HT_2 receptors; it is also bound to $_1$- and H_1-receptors and is able to inhibit noradrenaline reuptake. It is administered orally, usually three times daily at the conventional dosages. It is well absorbed in the gastrointestinal tract and peak plasma concentrations are achieved 2-3 hours after administration. Zotepine undergoes extensive first-pass metabolism, producing inactive metabolites and the active metabolite norzotepine. Hepatic microsomal CYP1A2 and CYP3A4 are the main isoenzymes involved in zotepine metabolism. It is highly bound to plasma proteins (97%) and is excreted by the kidneys; its half-life is about 14 hours.

Zotepine should be used carefully in the elderly, since some severe adverse effects, such as tachycardia, hypotension, prolongation of QT_c interval, somnolence and sleep disorders, have been reported. Parkinsonian adverse effects were reported in about 5.3% of patients treated; in prone patients, seizures were observed, especially at high doses.[198] Weight gain, constipation, urinary retention, mydriasis and hepatotoxicity were sometimes described. Two cases of deep vein thrombosis were seen in patients receiving combined paroxetine and zotepine therapy.[199] Zotepine seems to be active especially against negative symptoms of schizophrenia and in the prevention of recurrence in patients with chronic schizophrenia.[200] Recommended dosages in elderly patients are 75-150 mg/day.[91]

Sertindole

Sertindole is a novel antipsychotic agent that was removed from the market in December 1998 because of reports of cardiac arrhythmias and sudden death.[201] It is implicated in the development of torsade de pointes, as a result of lengthened QT_c interval. Figure 3 shows its receptor-binding profile. It is well absorbed, with bioavailability of 75%, is 99% protein bound and is metabolised in the liver by CYP2D6 and CYP3A4 isoenzymes. Its half-life ranges from 55 to 90 hours.[91] Sertindole is effective in the treatment of psychoses; indeed, it is effective for both positive and negative symptoms of schizophrenia, with little or no motor impairment at therapeutic dosages. No dose adjustment is recommended in the

elderly, since pharmacokinetic studies showed no differences between young and elderly individuals.[202] The main adverse effects are nasal congestion, headache and insomnia; QT interval prolongation, postural hypotension and transient elevation of liver enzymes were sometimes observed.[91]

A recent study showed that sertindole has more antipsychotic activity than placebo, and is as well tolerated as placebo and better tolerated than haloperidol;[203] it was associated with fewer movement disorders than haloperidol, but was shown to cause more weight gain.[203] Sertindole is now being re-evaluated in a phase 4 study in patients with schizophrenia of all ages to assess whether it should be reintroduced. It will initially be given only to patients enrolled in the clinical study; patients treated with sertindole will be carefully selected and monitored to maximise the benefits of treatment and minimise any risks. Therefore, there is no information about its use in the elderly. Recently, a comparative study of mortality rates and cardiac arrhythmias in postmarketing surveillance studies of sertindole, risperidone and olanzapine was conducted. Although no statistically significant difference was shown in mortality rates between sertindole and comparator cohorts, the sertindole group was too small to rule out an association between the use of this drug and cardiovascular deaths.[204]

Aripiprazole

Aripiprazole is a new atypical antipsychotic agent (quinolinone derivative) that exhibits partial D_2-receptor agonist activity;[204] *in vitro* data indicate its D_2 agonist activity at presynaptic autoreceptors, with antagonist activity at postsynaptic D_2 receptors (regulating inhibition of cAMP synthesis).[204] It seems to be useful in the treatment of schizophrenia at dosages of 15-30 mg/day. Pharmacokinetic data are limited; peak plasma concentrations occur 3-5 hours after oral doses at steady state. Animal studies suggest hepatic metabolism; the elimination half-life is 48-68 hours during multiple dosing and is not dose dependent.[205] EPS and prolactin increases have been uncommon in available studies;[91,205] weight gain, nausea, vomiting and somnolence have been reported, but no significant QT prolongation was observed.[91] Aripiprazole will compete with other atypical antipsychotics that are characterised by relatively good efficacy and a low incidence of EPS (i.e. risperidone, olanzapine, quetiapine), and comparative studies with these agents are required. No data are available in the elderly.

Conclusions

The principal brain target of all antipsychotic drugs is the dopamine D_2 receptor; in fact, the older traditional antipsychotics, such as haloperidol, chlorpromazine, pimozide, fluphenazine and flupenthixol, bind more tightly than dopamine itself to the D_2 receptor, with dissociation constants that are lower than that of dopamine. Therefore, they induce extrapyramidal signs and symptoms and elevate serum prolactin. The newer atypical antipsychotics, such as clozapine, olanzapine, risperidone, quetiapine, remoxipride and ziprasidone, all bind more loosely than dopamine to the D_2 receptor and have dissociation constants higher than that of dopamine. As already shown by brain imaging findings, through positron emission tomography scans, atypical antipsychotics clinically help patients by transiently occupying D_2 receptors and then rapidly dissociating to allow normal dopamine neurotransmission; they also block 5-HT_{2A} receptors, thus balancing serotonin and dopamine.[170] This effect is remarkable, because it keeps prolactin levels normal, spares cognition and obviates EPS. Therefore, the use of newer antipsychotics is particularly advantageous in the elderly for adequate control of cognitive deficits and a decrease in EPS, especially if concomitant diseases and polypharmacy are present. On the other hand, the antipsychotic threshold of occupancy of the D_2 receptor for antipsychotic action remains at about 65% for both typical and atypical drugs, regardless of whether 5-HT_{2A} receptors are blocked. Recently, a number of studies have reported that some atypical antipsychotics, especially clozapine and olanzapine, may cause increased plasma glucose levels in patients with or without a prior history of diabetes; other agents, such as quetiapine, may interfere with plasma levels of triglycerides.[138,192] Therefore, careful monitoring of these metabolic adverse effects is required, particularly in patients with medical diseases or a family history of diabetes mellitus, or in elderly patients.

The use of antipsychotics in the elderly is an indispensable means available to all physicians for controlling the symptoms in psychoses, schizophrenia, schizoaffective disorders and behavioural disorders in demented patients. It is widely known that dosages have to be strictly individualised in the elderly; the changes in pharmacokinetics and pharmacodynamics must be taken into account to avoid a dangerous accumulation of the drug, with potential for harmful adverse effects.

Table VIII presents mean recommended dosages of some conventional and new antipsychotics in various diseases (schizophrenia, Parkinson s disease and dementia) for elderly patients.[91,123,147,206]

It is important to be alert for possible interactions between drugs, particularly with some types of drugs and in patients with different diseases and polytherapies. Elderly patients require an adequate titration of the dosage, with slow increases according to the clinical response, surveillance of adverse effects and a careful evaluation of coadministered drugs.

Tables

Table I. Molecular biology and pharmacology of the dopamine (D) receptors; the major characteristics are presented (modified from Jaber et al.[15])

	D_1-like		D_2-like		

Receptor	D_1	D_5	D_2		D_3	D_4
Chromosomal localisation	5q 35.1	4p 15.1-16.1	11q 22-23		3q 13.3	11p 15.5
Introns	No	No	Yes		Yes	Yes
Amino acids	446 (rat)	457 (rat)	Short	Long	446 (rat)	385 (rat)
	446 (human)	477 (human)	415 (rat)	444 (rat)	400 (human)	387 (human)
			414 (human)	443 (human)		
mRNA size (kb)	3.8	3.0	2.5		8.3	5.3
Agonists (high affinity)	Fenoldopam	Fenoldopam	Bromocriptine		Quinpirole	Apomorphine
	SKF-23390	SKF-38393	Dopamine		7-OH-DPAT	Quinpirole
	SKF-82526	Dopamine	Apomorphine		Apomorphine	Dopamine
					PD 128907	
Antagonists (high affinity)	SCH-23390	SCH-23390	Spiperone		Spiperone	Spiperone
	SCH-39166	SCH-39166	Raclopride		Raclopride	Clozapine
	(+) Butaclamol	cis-Flupenthixol	Sulpiride		Sulpiride	Sulpiride
	cis-Flupenthixol	(+) Butaclamol				Olanzapine
Signal transduction	Adenylyl cyclase (↑)	Adenylyl cyclase (↑)	Phospholipid hydrolysis (↑)		[^{3}H]thymidine uptake (↑)	Arachidonic acid release (↑)
	Phospholipid hydrolysis (↑)		Arachidonic acid release (↑)		Na^+/K^+ exchange (↑)	Adenylyl cyclase (↑)
			K^+ channels (↑)		Ca^{2+} channels (↑)	
			Ca^{2+} channels (↓)			
			Na^+/K^+ exchange (↑)			
			[^{3}H]thymidine uptake (↑)			
			Adenylyl cyclase (↓)			

↑ indicates increase.
↓ indicates decrease.

Table II. Features of serotonin 5-HT receptor subtypes (from Hoyer et al.,[38] Hoyer & Martin,[39] To et al.[40])

Receptor	Brain areas of highest density	Physiological response	Disease therapy	Agonist	Antagonist	2nd messenger response
5-HT_{1A}	Hippocampus, septum, amygdala, raphe nuclei. Widespread distribution: blood vessels	Hyperpolarisation, vasoconstriction	Postsynaptic agonist; autoreceptor antagonist for anxiety/depression	8-OH-DPAT	WAY-100635	Decrease cAMP; open K^+ channels
5-HT_{1B}	Globus pallidus, substantia nigra. Widespread distribution: cranial blood vessels	Inhibition of neuropeptide release	Antagonist for depression; agonist for migraine	Sumatriptan	GR-127935 (partial agonist)	Decrease cAMP
5-HT_{1C}	Trigeminal ganglia	Inhibition of	Agonist for	Sumatriptan	Ocaperidone	Decrease

		neuropeptide release	migraine		(nonselective)	cAMP
5-HT_{1D}	Caudate putamen, amygdala, frontal cortex, globus pallidus	Inhibition of neuropeptide release	Unknown	Unknown	Unknown	Decrease cAMP
5-HT_{2A}	Prefrontal cortex, claustrum, striatum cerebral cortex, tuberculum olfactorum, nucleus accumbens, pontine nucleus, ventral pallidum, striatum, latero-dorsal tegmental nucleus; vascular smooth muscle cells, platelets	Depolarisation, smooth muscle contraction	Antagonist for dysthymia, negative symptoms of schizophrenia; Impaired blood circulation	Dimethoxyphenyl-isopropyl-amines	Ritanserin, MDI-100907, ketanserin, risperidone, olanzapine, sertindole, clozapine, pipamperone, zotepine, ziprasidone	Rise in IP_3, arachidonic acid, intracellular calcium
5-HT_{2B}	Stomach fundus, endothelium of blood vessels, colon, small intestine; only recently detected in brain using antibodies	Fundus contraction		2-CH_3-5-HT	SB-200646A, SB-206553, SB-204741, LY-266097, BW-723686	Rise in IP_3
5-HT_{2C}	Choroid plexus. Very widespread distribution in forebrain-midbrain-hindbrain-spinal cord, not in periphery		Antagonist for anxiety, panic attacks; increases food intake	Dimethoxyphenyl-isopropyl-amines; chlorophenylpiperazine (mCPP)	Ritanserin, mesulergine, mianserin, olanzapine, clozapine, sertindole, zotepine, ziprasidone	Rise in IP_3, arachidonic acid, intracellular calcium
5-HT_3	Wide central and peripheral occurrence on neuronal cells; area postrema, nucleus tractus solitarius, substantia gelatinosa, trigeminal nerve, dorsal vagal complex	Depolarisation	Antagonist for chemo-/ radiotherapy-induced emesis	2-CH_3-5-HT, m-Cl-phenyl biguanide	BRL-46470, MDI-72222, Y-25130, GR-65630, tropisetron, ondansetron, granisetron	Pentameric cation channel permeable to Na^+, K^+, Ca^{2+}
5-HT_4	Basal ganglia, striatum, nucleus accumbens, intestinal myenteric plexus, heart	Increase in neurotransmitter release	Agonists for gastrokinetic stimulation with positive ionotropic effects	Cisapride, renzapride	RS-39604, SB-203186, SB-204070, GRI-13808, LY-297582	Increase cAMP
5-HT_{5A} (5B)	mRNA in cortex, hippocampus, habenula, olfactory bulbs, cerebellum. Immunocytochemistry: glial cells	Unknown	Unknown	Unknown	Unknown	Decrease cAMP
5-HT_6	Immunocytochemistry: tuberculum olfactorum, nucleus accumbens, striatum, frontal, enthorinal cortex, hippocampus, cerebellum	Unknown	Unknown	Lysergide (LSD-25)	Several antipsychotics (see Figure 2), antidepressants	Increase cAMP
5-HT_7	Hypothalamus, thalamus, hippocampus, brain stem, cortex; intestinal and vascular smooth muscle	Phase advancement of circadian rhythm; hypotension, smooth muscle relaxation		5-carboxamidotrypt-amine, 8-OH-DPAT	Several antipsychotics (see Figure 2)	Increase cAMP

cAMP = cyclic adenosine monophosphate; **IP_3** = inositol triphosphate.

Table III. Properties of excitatory amino acid receptors (modified from Toru et al. [65])

	NMDA			AMPA			
	receptor	modulatory site (glycine)	modulatory site (polyamine)	receptor site	modulatory site	Kainate	Metabotropic
Endogenous agonists	Glutamate Aspartate	Glycine	Spermine Spermidine	Glutamate	??	Glutamate	Glutamate
Other agonists	NMDA	D-serine		AMPA, quisqualate	Cyclothiazide, aniracetam, ampakines	Kainate, quisqualate	D-AP4, ACPD
Antagonists	AP-5, AP-7, selfotel (CGS-19755), CPP, D-CPPene (SDZ-EAA-494)	Kynurenic acid, chloro-kynurenic acid, HA-466	Ifenprodil	NNC-079202 (NBQX), CNQX	GYKI-52466, CFM-2		MCPG
Channel blockers	Dizocilpine (MK-801), phencyclidine, ketamine, dextromethorphan, Mg^{2+}						Not applicable
Effector mechanisms	Ligand-gated cation channel (slow kinetics, high Ca^{2+} permeability)			Ligand-gated cation channel (fast kinetics, low Ca^{2+} permeability)		Ligand-gated cation channel (fast kinetics, low Ca^{2+} permeability)	G-protein-coupled (IP_3 formation and release of Ca^{2+})
Location	Postsynaptic (also glial) Wide distribution			Postsynaptic		Pre- and postsynaptic	Pre- and postsynaptic
Function	Slow EPSP, synaptic plasticity (LTP, LTD), excitotoxicity			Fast EPSP, wide distribution		Fast EPSP ? presynaptic inhibition, limited distribution	Synaptic modulation, excitotoxicity

ACPD = 1-aminocyclopentane-1,3-dicarboxylic acid; **AMPA** = 2-amino-3-(3-hydroxy-5-methylisoxazole-4-)propionic acid; **AP-5** = 2-amino-5-phosphonopentanoic acid; **AP-7** = 2-amino-7-phosphonoheptanoic acid; **CFM**-2 = 7,8-dimethoxy-3,5-dihydro-4H-2,3-benzodiazepine-4-ones; **CNQX** = 6-cyano-7-nitroquinoxaline-2,3-dione; **CPP** = 3-(2- carboxypirazin-4-yl)-propyl-1-phosphonic acid; **D-AP4** = D-(-)-2-amino-4-phosphonobutyric acid; **EPSP** = excitatory postsynaptic potential; **GYKI-52466** = 1-(4-amino- phenyl)-4-methyl-7,8-methylendioxy-5H-2,3-benzodiazepine; **IP_3** = inositol triphosphate; **LTD** = long-term depression; **LTP** = long-term potentiation; **MCPG** = -methyl-4-carboxyphenylglycine; **NBQX** = 2,3-dihydro-6-nitro-7-sulfamoyl-benzoquinoxaline; **NMDA** = *N*-methyl-D-aspartate.

Table IV. Age-related pharmacokinetic changes

Variable	Young adults (20-30y)	Old adults (60-80y)
Body water (% bodyweight)	61	53
Lean mass (% bodyweight)	19	12
Body fat (% bodyweight):		

Women	26-33	38-45
Men	18-20	36-38
Serum albumin (g/dL)	4.7	3.8
Kidney weight (% of young adults)	100	80
Liver blood flow (% of young adults)	100	55-60

Table V. Substrates, inhibitors and inducers of the main isoforms of cytochrome P450 (CYP) involved in drug metabolism

Substrates		**Inhibitors**	**Inducers**
CYP1A2			
Antidepressants	Amitriptyline, clomipramine, imipramine, fluvoxamine, mirtazapine	Fluvoxamine	Rifampicin
Antipsychotics	Clozapine, olanzapine, haloperidol	Ciprofloxacin	Barbiturates
Methylxanthines	Theophylline, caffeine		Phenytoin
Other drugs	Paracetamol, *R*-warfarin, tacrine		Carbamazepine
			Cigarette smoking
CYP2C9			
NSAIDs	Diclofenac, ibuprofen, piroxicam, naproxen	Sulfaphenazole	Rifampicin
Antiepileptics	Phenobarbital, phenytoin	Amiodarone	Barbiturates
Other drugs	*S*-warfarin, tolbutamide, losartan potassium, torasemide	Fluconazole	Phenytoin
		Valproic acid	Carbamazepine
		Fluoxetine	
		Fluvoxamine	
CYP2C19			
Antidepressants	Amitriptyline, clomipramine, imipramine, citalopram, moclobemide	Omeprazole	Rifampicin
Other drugs	Phenytoin, diazepam, omeprazole, *R*-warfarin, proguanil, *S*-mephenytoin, propranolol	Ticlopidine	Barbiturates
		Fluvoxamine	Phenytoin
		Fluoxetine	Carbamazepine
		Felbamate	
CYP2D6			
Antidepressants	Amitriptyline, clomipramine, imipramine, fluvoxamine, nortriptyline, fluoxetine, paroxetine, fluvoxamine, citalopram, venlafaxine, mirtazapine, mianserin	Quinidine	No known agent
Antipsychotics	Thioridazine, perphenazine, fluphenazine, zuclopenthixol, haloperidol, risperidone, clozapine, olanzapine, sertindole	Propafenone, sertraline, norfluoxetine	
Opioids	Codeine, dextromethorphan, tramadol	Thioridazine	
-Blockers	Alprenolol, bufuralol, metoprolol, timolol, pindolol, propranolol	Perphenazine	
Antiarrhythmics	Encainide, flecainide, propafenone	Fluoxetine	
Other drugs	Debrisoquine, sparteine, phenformin	Paroxetine	
CYP3A4			
Antidepressants	Venlafaxine, clomipramine, citalopram, mirtazapine, sertraline	Ketoconazole	Rifampicin
Antipsychotics	Haloperidol, clozapine, risperidone, ziprasidone, sertindole, quetiapine	Itraconazole	Barbiturates

Benzodiazepines	Diazepam, bromazepam, triazolam	Fluconazole	Phenytoin
Antiepileptics	Carbamazepine, felbamate, tiagabine	Erythromycin	Carbamazepine
Calcium antagonists	Diltiazem, verapamil, nifedipine, and other dihydropyridines	Fluvoxamine	Hypericum
Other drugs	Terfenadine, astemizole, cyclosporin, erythromycin, clarithromycin, tamoxifen, amiodarone, quinidine	Nefazodone	Oxcarbazepine[a]
		Grapefruit juice	Topiramate[a]
			Felbamate

a Weaker enzymatic inducers.

Table VI. Classification of antipsychotics

Class	Drug
Sedative antipsychotics	
Aliphatic phenothiazines	Levomepromazine
	Chlorpromazine
	Promazine
Piperidinic phenothiazines	Thioridazine
Piperazinic phenothiazines	Fluphenazine
	Perphenazine
	Trifluoperazine
Dibenzoxazepines	Clotiapine
	Clozapine
Polyvalent antipsychotics	
Butyrophenones	Haloperidol
	Droperidol
	Bromperidol
	Trifluperidol
	Pipamperone
Benzamides	Sulpiride
	Levosulpiride
	Tiapride
	Remoxipride
Thioxanthenes	Zuclopenthixol
	Flupenthixol
Diphenylbutylpiperidines	Pimozide
	Clopimozide
Atypical antipsychotics	Amisulpride
	Clotiapine
	Clozapine
	Olanzapine
	Risperidone
	Quetiapine

	Sertindole
	Ziprasidone
	Zotepine
	Aripiprazole

Table VII. Possible mechanisms causing clozapine- and olanzapine-related diabetes mellitus

Histamine H_1-receptor antagonism
Serotonin 5-HT_{2C}-receptor antagonism
Excessive weight gain
Reduced responsivity of pancreatic cells
Pancreatic -cell damage, with reduced insulin secretion
Altered regulation of autonomic nervous system
Increased insulin resistance

Table VIII. Mean recommended dosages (mg/day) of some conventional and new antipsychotics in different diseases in elderly patients

Agent	Schizophrenia	Parkinson s disease	Dementia
Haloperidol	5-7	[a]	1.5-2
Promazine	60-200	10-15	15-60
Thioridazine	50-200	30-50	15-50
Clozapine	50-150	25-50	25-50
Risperidone	2-3	0.25-1	0.25-2
Olanzapine	10-20	5-7.5	5-7.5
Quetiapine	200-300	50-100	50-100

a Not recommended because of extrapyramidal symptoms

References

1. Keverne EB. GABA-ergic neurons and the neurobiology of schizophrenia and other psychoses. Brain Res Bull 1999; 48: 467-73
2. Gavrilova SI, Kalyn IB. Social and environmental factors and mental health in the elderly. Vestn Ross Akad Med Nauk 2002; 9: 15-20
3. Ostling S, Skoog I. Psychotic symptoms and paranoid ideation in a nondemented population-based sample of the very old. Arch Gen Psychiatr 2002; 59: 60-1
4. Leysen JE, Janssen PMF, Heylen L, et al. Receptor interactions of new antipsychotics: relation to pharmacodynamic and clinical effects. Int J Psychiatr Clin Pract 1998; 2: S3-S17
5. Delay J, Deniker P, Harl JM. Traitements d etats confusionnels par le chlorhydrate de diethylaminopropyl-N-chlorophenothiazine (4560 RP). Ann Med Psychol 1952; 110: 398-403
6. Carlsson A, Lindqvist M. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol Toxicol 1963; 20: 140-4
7. Toru M. Biological research on schizophrenia. Psychiatry Clin Neurosci 1998; 52 Suppl.: 170-2
8. van Rossum JM. The significance of dopamine receptor blockade for the mechanism of action of neuroleptic drugs. Arch Int Pharmacodyn Ther 1966; 160: 492-4
9. Randrup A, Munkvad I. Influence of amphetamines on animal behavior: stereotypy, functional impairment and possible animal-human correlations. Psychiatr Neurol Neurochir 1972; 75: 193-202
10. Egan MF. Weinberger DR. Neurobiology of schizophrenia. Curr Opin Neurobiol 1997; 7: 701-7
11. Grandy DK, Zhang Y, Bouvier C, et al. Multiple human D5 dopamine receptor genes: a functional receptor and two pseudogenes. Proc Natl

Acad Sci U S A 1991; 88: 9175-9
12. Jackson DM, Westlind-Danielson A. Dopamine receptors: molecular biology, biochemistry and behavioral aspects. Pharmacol Ther 1994; 64: 291-369
13. Gerfen CR, Engber TM, Mahan LC, et al. D1 and D2 dopamine receptor-regulated gene expression of nigrostriatal and striatopallidal neurons. Science 1990; 250: 1429-32
14. Gingrich JA, Caron MG. Recent advances in the molecular biology of dopamine receptors. Ann Rev Neurosci 1993; 16: 299-321
15. Jaber M, Robinson SW, Missale C, et al. Dopamine receptors and brain function. Neuropharmacology 1996; 35: 1503-19
16. Creese I, Schneider R, Snyder SH. [3H]-spiperone labels dopamine receptors in pituitary and brain. Eur J Pharmacol 1977; 46: 377-81
17. Demchyshyn LL, Sugamori KS, Lee FJS, et al. The dopamine D1D receptor: cloning and characterization of three pharmacologically distinct D1-like receptors from Gallus domesticus. J Biol Chem 1995; 270: 72-6
18. Tauscher J, Kufferle B, Asenbaum S, et al. Striatal dopamine-2 receptor occupancy as measured with [123I]iodobenzamide and SPECT predicted the occurrence of EPS in patients treated with atypical antipsychotics and haloperidol. Psychopharmacology 2002; 162: 42-9
19. Hersch SM, Ciliax BJ, Gutekunst CA, et al. Electron microscopic analysis of D1 and D2 dopamine receptor proteins in the dorsal striatum and their synaptic relationship with motor corticostriatal afferents. J Neurosci 1995; 15: 5222-37
20. Nyberg S, Nakashima Y, Nordstrom AL, et al. Positron emission tomography of in vivo binding characteristic of atypical antipsychotic drugs: review of D2 and 5-HT2 receptor occupancy studies and clinical response. Br J Psychiatry 1996; 168: 40-4
21. Farde L, Halldin C. D2 dopamine receptors in schizophrenia. In: Fog R, Garlach J, Hemmingsen R, editors. Alfred Benzon symposium 38: Schizophrenia, an integrated view. Copenhagen: Munksgaard, 1995: 190-9
22. Diaz J, Levesque D, Griffon N, et al. Phenotypical characterization of neurons expressing the dopamine D3 receptor in the rat brain. Neuroscience 1995; 65: 731-45
23. Bristow LJ, Kramer MS, Kulagowski J, et al. Schizophrenia and L-745870, a novel dopamine D4 receptor antagonist. Trends Pharmacol Sci 1997; 18: 186-8
24. Deberdt R. Pipamperone in the treatment of behavior disorders: a large scale multicentre evaluation. Acta Psyciatr Belg 1976; 76: 157-66
25. Ansoms C, De Backer-Dierick G, Vereecken JLTM. Sleep disorders in patients with severe mental depression: double-blind placebo-controlled evaluation of the value of pipamperone. Acta Psychiatr Scand 1977; 55: 116-22
26. Leysen JE, Gommeren W, Van Gompel P. Receptor binding properties in vitro and in vivo of ritanserin: a very potent and long acting serotonin-S2 antagonist. Mol Pharmacol 1985; 27: 600-11
27. Bersani G, Grispini A, Marini S, et al. 5-HT2 antagonist ritanserin in neuroleptic-induced parkinsonism: a double-blind comparison with orphenadrine and placebo. Clin Neuropharmacol 1990; 13: 500-6
28. Leysen JE, Janssen PM, Gommeren W, et al. In vitro and in vivo receptor binding and effects on monoamine turnover in rat brain regions of the novel antipsychotic risperidone and ocaperidone. Mol Pharmacol 1992; 41: 494-508
29. Megens AA, Awouters FH, Schotte A, et al. Survey on the pharmacodynamics of the new antipsychotic risperidone. Psychopharmacology 1994; 114: 9-23
30. Janssen PA, Niemegeers CJ, Awouters F, et al. Pharmacology of risperidone (R64766), a new antipsychotic with serotonin-S2 and dopamine-D2 antagonistic properties. J Pharmacol Exp Ther 1998; 244: 685-93
31. Davis JM, Janicak PG. Risperidone: a new, novel (and better?) antipsychotic? Psychiatr Ann 1996; 26: 9-23
32. Gallhofer B, Bayer U, Lis S, et al. Cognitive dysfunction in schizophrenia: comparison of treatment with atypical antipsychotic agents and conventional neuroleptic drugs. Eur Neuropsychopharmacol 1996; 6: S13-20
33. Katz R, Jeste DV, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbance associated with dementia: a randomized, double-blind trial. J Clin Psychiatr 1999; 60: 107-15
34. Leysen JE, Janssen PM, Schotte A, et al. Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and clinical effects: role of 5-HT2 receptors. Psychopharmacology 1993; 112: S40-54
35. Leysen JE, Gommeren W, Mertens J, et al. Comparison of in vitro binding properties of a series of dopamine antagonists and agonists for cloned human dopamine D2S and D2L receptors and for D2 receptors and for D2 receptors in rat striatal and mesolimbic tissues using [125I]2 -iodospiperone. Psychopharmacology 1993; 110: 27-36
36. Gellman RL, Aghajanian GK. Serotonin2 receptor-mediated excitation of interneurons in piriform cortex: antagonism by atypical antipsychotic drugs. Neuroscience 1994; 58: 515-25
37. Meltzer HY, Nash JF. Effects of antipsychotic drugs on serotonin receptors. Pharmacol Rev 1991; 43: 587-604
38. Hoyer D, Clarke DE, Fozard JR, et al. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacol Rev 1994; 46: 157-203
39. Hoyer D, Martin G. R. Classification and nomenclature of 5-HT receptors: a comment on current issues. Behav Brain Res 1996; 73: 263-8
40. To Z. P, Bonhaus DW, Eglen RM, et al. Characterization and distribution of putative 5-HT7 receptors in guinea pig brain. Br J Pharmacol 1995; 115: 107-16
41. Tamminga CA. Schizophrenia and glutamatergic transmission. Crit Rev Neurobiol 1998; 12: 21-36
42. Lidsky TI, Bannerjce SP. Contribution of glutamatergic dysfunction to schizophrenia. Drug News Perspect 1996; 9: 453-9
43. Kim JS, Kornhuber HH, Schmid-Burgk W, et al. Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. Neurosci Lett 1980; 20: 379-82
44. Toru M, Watanabe S, Shibuya H, et al. Neurotransmitters, receptors and neuropeptides in post-mortem brains of chronic schizophrenic patients. Acta Psychiatr Scand 1988; 78: 121-37
45. Sherman AD, Davidson AT, Baruah S, et al. Evidence of glutamatergic deficiency in schizophrenia. Neurosci Lett 1991; 121: 77-80
46. Sherman AD, Hegwood TS, Baruah S, et al. Deficient NMDA-mediated glutamate release from synaptosomes of schizophrenics. Biol Psychiatry 1991; 30: 1191-8
47. Melby Jr EC, Baker HJ. Phencyclidine for analgesia and anesthesia in simian primates. J Am Vet Med Assoc 1965; 147: 1068-72
48. Anis NA, Berry SC, Burton NR, et al. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br J Pharmacol 1983; 79: 565-75
49. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991; 148: 1301-8
50. Allen RM, Young SJ. Phencyclidine-induced psychosis. Am J Psychiatry 1978; 135: 1081-4
51. Simpson MD, Slater P, Royston MC, et al. Alterations in phencyclidine and sigma binding sites in schizophrenic brains: effects of disease process and neuroleptic medication. Scizophr Res 1991; 6: 41-8
52. Snyder SH. Phencyclidine. Nature 1980; 285: 355-6
53. Luisada PV. The phencyclidine psychosis: phenomenology and treatment. NIDA Res. Monogr 1978; 21: 241-53
54. Petersen R. C, Stillman R. C. Phencyclidine: an overview. NIDA Res Monogr 1978; 21: 1-17

55. Nishikawa T, Takashima M, Toru M. Increased [3H] kainic acid binding in the prefrontal cortex in schizophrenia. Neurosci Lett 1983; 40: 245-50
56. Healy DJ, Haroutunian V, Powchik P, et al. AMPA receptor binding and subunit mRNA expression in prefrontal cortex and striatum of elderly schizophrenics. Neuropsychopharmacology 1998; 19: 278-86
57. Rogers GA, Thorell JO, Johnstrom P, et al. Ampakines: labelling with 11C for PET distribution studies. J Labelled Comp Radiopharm 1997; 40: 645-7
58. Araj A, Kessler M, Rogers G, et al. Effects of a memory-enhancing drug on DL-[Unsupported Character]-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor currents and synaptic transmission in hippocampus [abstract]. J Pharmacol Exp Ther 1996; 278: 627-38
59. Staubli U, Perez Y, Xu FB, et al. Centrally active modulators of glutamate receptors facilitate the induction of long-term potentiation in vivo [abstract]. Proc Natl Acad Sci U S A 1994; 91: 11158-62
60. Staubli U, Rogers G, Lynch G. Facilitation of glutamate receptors enhances memory [abstract]. Proc Natl Acad Sci U S A 1994; 91: 777-81
61. Ingvar M, Ambros-Ingerson J, Davis M, et al. Enhancement by an ampakine of memory encoding in humans. Exp Neurol 1997; 146: 553-9
62. Larson J, Quach CN, LeDuc BQ, et al. Effects of an AMPA receptor modulator on metamphetamine-induced hyperactivity in rats. Brain Res 1996; 738: 353-6
63. Goff DC, Leahy L, Berman I, et al. A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia. J Clin Psychopharmacol 2001; 21: 484-7
64. Kornhuber J, Mack-Burkhardt F, Riederer P, et al. [3H]-801 binding sites in postmortem brain regions of schizophrenic patients. J Neural Transm 1989; 77: 231-6
65. Toru M, Kurumaji A, Ishimaru M. Excitatory amino acids: implications for psychiatric disorders research. Life Sci 1994; 55: 1683-99
66. Ishimaru M, Kurumaji A, Toru M. NMDA-associated glycine binding site increases in schizophrenic brains. Biol Psychiatry 1992; 32: 379-81
67. Mitchell PR, Doggett N S. Modulation of striatal [3H]-glutamic acid release by dopaminergic drugs. Life Sci 1980; 26: 2073-81
68. Maura G, Carbone R, Raiteri M. Aspartate-releasing nerve terminals in rat striatum possess D2 dopamine receptors mediating inhibition of release. J Pharmacol Exp Ther 1989; 251: 1142-6
69. Yamamoto BK, Davy S. Dopaminergic modulation of glutamate release in striatum as measured by microdialysis. J Neurochem 1992; 58: 1736-42
70. Chesselet MF. Presynaptic regulation of neurotransmitter release in the brain: facts and hypothesis. Neuroscience 1984; 12: 347-75
71. Giorguieff MF, Le Floc h ML, Glowinski J, et al. Involvement of cholinergic presynaptic receptors of nicotinic and muscarinic types in the control of the spontaneous release of dopamine from striatal dopaminergic terminals in the rat. J Pharmacol Exp Ther 1977; 200: 535-44
72. Roberts PJ, Anderson SD. Stimulatory effect of L-glutamate and related amino acids on [3H]-dopamine release from rat striatum: an in vitro model for glutamate actions. J Neurochem 1979; 32: 1539-45
73. Cheramy A, Romo R, Godeheu G, et al. In vitro presynaptic control of dopamine release in the cat caudate nucleus: II. facilitatory or inhibitory influence of L-glutamate. Neuroscience 1986; 19: 1081-90
74. Deutsch SI, Mastropaolo J, Schwartz BL, et al. A glutamatergic hypothesis of schizophrenia: rationale for pharmacotherapy with glycine. Clin Neuropharmacol 1989; 12: 1-13
75. Deutsch DG, Koul O, Kersten RS. Phencyclidine and analogues: effects on brain protein synthesis. J Neurochem 1984; 42: 407-11
76. Csernansky JG, Kaplan J, Hollister LE. Problems in classification of schizophrenics as neuroleptic responders and nonresponders. J Nerv Ment Dis 1985; 173: 325-31
77. Andreasen NC, Olsen S. Negative vs positive schizophrenia: definition and validation. Arch Gen Psychiatry 1982; 39: 789-94
78. Coyle JT. The glutamatergic dysfunction hypothesis for schizophrenia. Harv Rev Psychiatry 1996; 3: 241-53
79. Davis JM, Andriukaitis S. The natural course of schizophrenia and effective maintenance drug treatment. J Clin Psychopharmacol 1986; 6: 2S-10S
80. Bazire S. Psychotropic drug directory 2001/2002. Snow Hill, Dinton, UK: Mark Allen Publishing Ltd, 2001
81. Sanders-Bush E, Sulser F. Drugs used for the treatment of affective disorders. In: Munson PL, editor. Principles of pharmacology, basic concepts & clinical application. New York: Chapman & Hall, 1995: 309-24
82. Martin P, Gozlan H, Puech A. J 5-HT3 receptor antagonists reverse helpless behaviour in rats. Eur J Pharmacol 1992; 212: 73-8
83. Amery W, Marder SR. Safety and switching issues of novel antipsychotics. Int J Psychiatry Clin Pract 1998; 2: S43-9
84. Janssen PA, Awouters F. Antipsychotic drugs. In: Munson PL, editor. Principles of pharmacology, basic concepts & clinical application. New York: Chapman & Hall, 1995: 289-308
85. Gareri P, Falconi U, De Fazio P, et al. Conventional and new antidepressant drugs in the elderly. Prog Neurobiol 2000; 61: 353-96
86. Galeotta G, Paoletti V, Mammarella A, et al. La terapia farmacologica nel paziente anziano. Clin Ter 1990; 135: 181-92
87. Voltz HP, Moeller HJ Antidepressant drug therapy in the elderly: a critical review of the controlled clinical trials conducted since 1980. Pharmacopsychiatry 1994; 27: 93-100
88. Baumann P. Care of depression in the elderly: comparative pharmacokinetics of SSRIs. Int Clin Psychopharmacol 1998; 13: 35-43
89. Greenblatt DJ, Sellers EM, Shader RI. Drug disposition in old age. N Engl J Med 1982; 306: 1081-8
90. Safar M. Ageing and its effects on the cardiovascular system. Drugs 1990; 39: 1-8
91. Bruinink A, Lichtensteiger W. Effects of pH and ascorbic acid on 3H-spiperone and 3H-dihydroalprenolol binding in rat forebrain homogenates. J Recept Res 1984; 4: 127-39
92. Furlanut M, Benetello P. The pharmacokinetics of tricyclic antidepressant drugs in the elderly. Pharmacol Res 1990; 22: 15-25
93. Gareri P, Stilo G, Bevacqua I, et al. Antidepressant drugs in the elderly. Gen Pharmacol 1998; 30: 465-75
94. Montamat SC, Cusack BJ, Yestal RE. Management of drug therapy in the elderly. N Engl J Med 1989; 321: 303-9
95. Mannens G, Meuldermans W, Snoeck E, et al. Plasma protein binding of risperidone and its distribution in blood. Psychopharmacology (Berl) 1994; 114: 566-72
96. Rubin EH. Terapia con farmaci psicotropi: precauzioni particolari nell'anziano. Minuti 1987; 5: 11-21
97. Verbeeck RK, Cardinal JA, Wallace SM. Effect of age and sex on the plasma binding of acidic and basic drugs. Eur J Clin Pharmacol 1984; 27: 91-7
98. Alexanderson B, Price Evans DA, Sjoqvist F. Steady state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. BMJ 1969; 2: 764-8
99. Clark DWJ. Genetically determined variability in acetylation and oxidation: therapeutic implications. Drugs 1985; 29: 342-75
100. Kirchheiner J, Brosen K, Dahl ML, et al. CYP2D6 and CYP2D19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. Acta Psychiatr Scand 2001; 104: 173-92
101. Bertilsson L, Dahl ML, Sjoqvist F, et al. Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine [letter]. Lancet 1993; 341: 63

102. DeVane CL. Pharmacogenetics and metabolism of newer antidepressant agents. J Clin Psychiatry 1994; 55 (12 Suppl.): 38-45
103. Gonzalez FJ, Skoda RC, Kinenza S. Characterization of the common genetic defect in humans deficient in debrisoquine metabolism. Nature 1988; 331: 442-6
104. Gonzalez FJ, Korzekwa KR. Cytochromes P450 expression sites. Ann Rev Pharmacol Toxicol 1995; 35: 369-90
105. Baumann P. Pharmacokinetic pharmacodynamic relationship of the selective serotonin reuptake inhibitors. Clin Pharmacokinet 1996; 31: 444-69
106. Brosen K. Drug-metabolizing enzymes and therapeutic drug monitoring in psychiatry. Ther Drug Monit 1996; 18: 393-6
107. Crewe HK, Lennard MS, Tucker GT, et al. The effect of selective serotonin reuptake inhibitors on cytochrome P450 2D6 (CYP2D6) activity in human liver microsomes. Br J Clin Pharmacol 1992; 34: 262-5
108. Ereshefsky L. Drug-drug interactions involving antidepressants: focus on venlafaxine. J Clin Psychopharmacol 1996; 16: 37S-50S
109. Brunello N. Interazioni farmacocinetiche degli antidepressivi. In: Vella G, Siracusano A, editors. La depressione nell anziano, Il Pensiero Scientifico editore. NOOS, Rome 1998; 4: 16-28
110. Lamy PP. Geriatric drug therapy. Am Fam Phys 1986; 34: 118-24
111. Beers MH, Ouslander JG. Risk factors in geriatric drug prescribing. Drugs 1989; 37: 105-12
112. Friedman JR, Norman DC, Yoshikawa TT. Correlation of estimated renal function parameters versus 24-hour creatinine clearance in ambulatory elderly. JAGS 1989; 37: 145-9
113. Swift M. The family history in clinical psychiatric practice. Am J Psychiatry 1987; 144: 628-9
114. Micromedex Healthcare Series. Englewood (CO): MICROMEDEX Inc: 2001
115. Gilman JT, Tuchman RF. Autism and associated behavioral disorders: pharmacotherapeutic intervention. Ann Pharmacother 1995; 29: 47-56
116. Seneff MG, Mathews RA. Use of haloperidol infusions to control delirium in critically ill adults. Ann Pharmacother 1995; 29: 690-3
117. Tisdale JE, Rasty S, Padhi ID, et al. The effect of intravenous haloperidol on QTc interval dispersion in critically ill patients: comparison with QT interval prolongation for assessment of risk of torsades de pointes. J Clin Pharmacol 2001; 41: 1310-8
118. Frenchman IB, Prince T. Clinical experience with risperidone, haloperidol and thioridazine for dementia-associated behavioral disturbances. Int Psychogeriatr 1997; 9: 431-5
119. De Deyn PP, Rabheru K, Rasmussen A, et al. A randomised trial of risperidone, placebo and haloperidol for behavioural symptoms of dementia. Neurology 1999; 53: 946-55
120. Caligiuri MR, Jeste DV, Lacro JP. Antipsychotic-induced movement disorders in the elderly: epidemiology and treatment recommendations. Drugs Aging 2000; 17: 363-84
121. Breier A, Meehan K, Birkett M, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. Arch Gen Psychiatry 2002; 59: 441-8
122. Tesar GE, Stern TA. Rapid tranquilization of the agitated intensive care unit patient. J Intensive Care Med 1988; 3: 195-201
123. Torta R. Prontuario dei farmaci per il Sistema Nervoso Centrale. Turin: Solvay Pharma SPA, 2000
124. Cohen BM, Sommer BR. Metabolism of thioridazine in the elderly. J Clin Psychopharmacol 1988; 8: 336-9
125. Gareri P, Curcio M, Cotroneo A, et al. Efficacy of risperidone vs. promazine in the treatment of behavioral disorders in elderly demented patients [abstract]. International Conference The role of geriatric departments in general hospitals ; 2002 Apr 17-20; Rome. Geriatria XIV (Suppl) 1: 191
126. McLaren S, Cookson JC, Silverstone T. Positive and negative symptoms, depression and social disability in chronic schizophrenia: a comparative trial of dromperidol and fluphenazine decanoates. Int Clin Psychopharmacol 1992; 7: 67-72
127. Miller RS, Peterson GM, McLean S, et al. Monitoring plasma levels of fluphenazine during chronic therapy with fluphenazine decanoate. J Clin Pharm Ther 1995; 20: 55-62
128. Pollock BG, Mulsant BH, Rosen J, et al. Comparison of citalopram, perphenazine and placebo for the acute treatment of psychosis and behavioural disturbances in hospitalised, demented patients. Am J Psychiatr 2002; 159: 460-5
129. Claveria LE, Teychenne PF, Calne DB, et al. Tardive dyskinesia treated with pimozide. J Neurol Sci 1975; 24: 393-401
130. Wetzel H, Wiesner J, Hiemke C, et al. Acute antagonism of dopamine D2-like receptors by amisulpride: effects on hormone secretion in healthy volunteers. J Psychiatr Res 1994; 28: 461-73
131. Pelissolo A, Krebs MO, Olie JP. Traitement des symptomes deficitaires de la schizophrenie par l amisulpride: revue de la literature. L Encephale 1996; 22: 215-9
132. Product Information: Solian, amisulpride tablets. Maidenhead (UK): Lorex Synthelabo, 1999
133. Xiberas X, Martinot JL, Mallet L, et al. In vivo extrastriatal and striatal D2 dopamine receptor blockade by amisulpride in schizophrenia. J Clin Psychopharmacol 2001; 21: 207-14
134. Seminara G, Trassari V, Prestifilippo N, et al. Atypical tricyclic neuroleptics for treatment of schizophrenia: clothiapine and clozapine. Minerva Psichiatr 1993; 34: 95-9
135. Taylor D. Pharmacokinetic interactions involving clozapine. Br J Psychiatry 1997; 171: 109-12
136. Markowitz JS, Brown CS, Moore TR. Atypical antipsychotics: Part I. pharmacology, pharmacokinetics and efficacy. Ann Pharmacother 1999; 33: 73-85
137. Desai HD, Seabolt J, Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. CNS Drugs 2001; 15: 469-94
138. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998; 44: 778-83
139. Bonanno DG, Davydov L, Botts SR. Olanzapine-induced diabetes mellitus. Ann Pharmacother 2001; 35: 563-5
140. Mir S, Taylor D. Atypical antipsychotics and hyperglycaemia. Int Clin Psychopharmacol 2001; 16: 63-74
141. Gaulin BD, Markowitz JS, Caley CF, et al. Clozapine-associated elevation in serum triglycerides. Am J Psychiatry 1999; 156: 1270-2
142. Ghaeli P, Dufresen RL. Serum triglyceride levels in patients treated with clozapine. Am J Health Syst Pharm 1996; 53: 2079-81
143. Wirshing WC. The new antipsychotic compounds: is a clinical choice algorithm possible? West J Med 1998; 169: 43-4
144. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996; 37: 68-73
145. Smith H, Kenney-Herbert J, Knowles L. Clozapine-induced diabetic ketoacidosis. Aust N Z J Psychiatry 1999; 33: 120-1
146. Wolters EC, Berendse HW. Management of psychosis in Parkinson s disease. Curr Opin Neurol 2001; 14: 499-504
147. Jeste D. V, Eastham J H, Lohr J B, et al. Treatment of behavioral disorders and psychosis. In: Salzman C, editor. Clinical geriatric psychopharmacology. Baltimore (MD): Williams & Wilkins, 1998; 6: 106-49
148. He H, Richardson JS. A pharmacological, pharmacokinetic and clinical overview of risperidone, a new antipsychotic that blocks serotonin 5-HT2 and dopamine D2 receptors. Int Clin Psychopharmacol 1995; 10: 19-30
149. Byerly MJ, De Vane CL. Pharmacokinetics of clozapine and risperidone: a review of recent literature. J Clin Psychopharmacol 1996; 16:

177-87
150. Wrighton SA, Brian WR, Sari MA, et al. Studies on the expression and metabolic capabilities of human liver cytochrome P450IIIA5 (HLp3). Mol Pharmacol 1990; 38: 207-13
151. Pollock BG, Laghrissi-Thode F, Wagner WR, et al. Increased PF4 and -TG in depressed patients with ischemic heart disease [abstract]. Scientific abstract of the 34th Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico; ACNP, Nashville, TN, USA 1995, 101
152. Barak Y, Shamir E, Weizman R. Would a switch from typical antipsychotics to risperidone be beneficial for elderly schizophrenic patients?: a naturalistic, long-term, retrospective, comparative study. J Clin Psychopharmacol 2002; 22: 115-20
153. Gareri P, Cotroneo A, Marchisio U, et al. Risperidone in the treatment of behavioral disorders in elderly patients with dementia. Arch Gerontol Geriatr 2001; 33: 173-82
154. Herrmann N, Rivard MF, Flynn M, et al. Risperidone for the treatment of behavioral disturbances in dementia: a case series. J Neuropsychiatry Clin Neurosci 1998; 10: 220-3
155. Irizarry MC, Ghaemi SN, Lee-Cherry ER, et al. Risperidone treatment of behavioural disturbances in outpatients with dementia. J Neuropsychiatry Clin Neurosci 1999; 11: 336-42
156. Lavretsky H, Sultzer D. A structured trial of risperidone for the treatment of agitation in dementia. Am J Geriatr Psychiatry 1998; 6: 127-35
157. Robertsson B, Karlsson I, Eriksson L, et al. An atypical neuroleptic drug in the treatment of behavioural disturbances and psychotic symptoms in elderly people. Dementia 1996; 7: 142-6
158. Lane HY, Chang YC, Su MH, et al. Shifting from haloperidol to risperidone for behavioral disturbances in dementia: safety, response predictors and mood effects. J Clin Psychopharmacol 2002; 22: 4-10
159. Madhusoodanan S, Brecher M, Brenner R, et al. Risperidone in the treatment of elderly patients with psychotic disorders. Am J Psychiatry 1999; 7: 132-8
160. Davidson M, Harvey PD, Vervarcke J, et al. A long-term, multicenter, open-label study of risperidone in elderly patients with psychosis. Int J Geriatr Psychiatry 2000; 15: 506-14
161. Borison RL, Diamond B, Pathitaja A, et al. Pharmacokinetics of risperidone in chronic schizophrenic patients. Psychopharmacol Bull 1994; 30: 193-7
162. Jeste DV, Eastham JH, Lacro JP, et al. Management of late-life psychosis. J Clin Psychiatry 1996; 57: 39-45
163. Yerrabolu M, Prabhudesai S, Tawam M, et al. Effect of risperidone on QT interval and QT dispersion in the elderly. Heart Dis 2000; 2: 10-2
164. Wirshing DA, Pierre JM, Eyeler J. Risperidone-associated new-onset diabetes. Biol Psychiatry 2001; 15: 278-82
165. Meehan KM, Wang H, David SR, et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam and placebo: a double blind, randomized study in acutely agitated patients with dementia. Neuropsychopharmacology 2002; 26: 494-504
166. Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. Eur Neuropsychopharmacol 2001; 11: 25-32
167. Kennedy JS, Bymaster FP, Schuh L, et al. A current review of olanzapine s safety in the geriatric patient: from pre-clinical pharmacology to clinical data. Int J Geriatr Psychiatry 2001; 16: S33-61
168. Kennedy JS, Zagar A, Bymaster FP, et al. The central cholinergic system profile of olanzapine compared with placebo in Alzheimer s disease. Int J Geriatr Psychiatry 2001; 16: S24-32
169. Madhusoodanan S, Sinha S, Brenner R, et al. Use of olanzapine for elderly patients with psychotic disorders: a review. Ann Clin Psychiatry 2001; 13: 201-13
170. Seeman P. Atypical antipsychotics: mechanism of action. Can J Psychiatry 2002; 47: 27-38
171. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 2000; 57: 968-76
172. Meltzer HY. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 1999; 21: 106S-15S
173. Narendran R, Young CM, Valenti AM, et al. Olanzapine therapy in treatment-resistant psychotic mood disorders: a long-term follow-up study. J Clin Psychiatry 2001; 62: 509-16
174. Madhusoodanan S, Brenner R, Suresh P, et al. Efficacy and tolerability of olanzapine in elderly patients with psychotic disorders: a prospective study. Ann Clin Psychiatry 2000; 12: 11-8
175. Solomos K, Geiger O. Olanzapine use in the elderly: a retrospective analysis. Can J Psychiatry 2000; 45: 151-5
176. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 2001; 57: 968-76
177. Wolters EC, Jansen EN, Tuynman-Qua HG, et al. Olanzapine in treatment of dopaminomimetic psychosis in patients with Parkinson s disease. Neurology 1996; 47: 1085-7
178. Aarsland D, Larsen JP, Lim NG, et al. Olanzapine for psychosis in patients with Parkinson's disease with and without dementia. J Neuropsychiatry Clin Neurosci 1999; 11: 392-4
179. Pollak PT, Zbuk K. Quetiapine fumarate overdose: clinical and pharmacokinetic lessons from extreme conditions. Clin Pharmacol Ther 2000; 68: 92-7
180. McConville BJ, Arvanitis LA, Thyrum PT, et al. Pharmacokinetics, tolerability and clinical effectiveness of quetiapine fumarate: an open-label trial in adolescents with psychotic disorders. J Clin Psychiatry 2000; 61: 252-60
181. Brecher M, Rak IW, Melvin K, et al. The long-term effect of quetiapine (SeroquelTM) monotherapy on weight in patients with schizophrenia. Int J Psych Clin Pract 2000; 4: 287-91
182. Madhusoodanan S, Brenner R, Alcantra A. Clinical experience with quetiapine in elderly patients with psychotic disorders. J Geriatr Psychiatry Neurol 2000; 13: 28-32
183. McManus DQ, Arvanitis LA, Kowalcyk BB. Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders. Seroquel Trial 48 study Group. J Clin Psychiatry 1999; 60: 292-8
184. Tariot PN, Salzman C, Yeung PP, et al. Long-term use of quetiapine in elderly patients with psychotic disorders. Clin Ther 2000; 22: 1068-84
185. Green B. Focus on quetiapine. Curr Med Res Opin 1999; 15: 145-51
186. Brook S, Lucey JV, Gunn KP. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. Ziprasidone I.M. Study Group. J Clin Psychiatry 2000; 61: 933-41
187. Wilner KD, Tensfeldt TG, Baris B, et al. Single- and multiple-dose pharmacokinetics of ziprasidone in healthy young and elderly volunteers. Br J Clin Pharmacol 2000; 49, Suppl. 1: 15S-20S
188. Aweeka F, Jayesekara D, Horton M, et al. The pharmacokinetics of ziprasidone in subjects with normal and impaired renal function. Br J Clin Pharmacol 2000; 49 Suppl. 1: 27S-33S
189. Everson G, Lasseter KC, Anderson KE, et al. The pharmacokinetics of ziprasidone in subjects with normal and impaired renal function. Br J

Clin Pharmacol 2000; 49: 21S-6S
190. Byerly MJ, Weber MT, Brooks DL, et al. Antipsychotic medications and the elderly: effects on cognition and implications for use. Drugs Aging 2001; 18: 45-61
191. Keck Jr PE, McElroy SL, Arnold LM. Ziprasidone: a new atypical antipsychotic. Exert Opin Pharmacother 2001; 2: 1033-42
192. Goodnick PJ, Kato MM. Antipsychotic medication: effects on regulation of glucose and lipids. Expert Opin Pharmacother 2001; 2: 1571-82
193. Stimmel GL, Gutierrez MA, Lee V. Ziprasidone: an atypical antipsychotic drug for the treatment of schizophrenia. Clin Ther 2002; 24: 21-37
194. Wilner KD, Tensfeldt TG, Baris B, et al. Single- and multiple-dose pharmacokinetics of ziprasidone in healthy young and elderly volunteers. Br J Clin Pharmacol 2000; 49: 15S-20S
195. von Bahr C, Movin G, Yisak WA, et al. Clinical pharmacokinetics of remoxipride. Acta Psychiatr Scand Suppl 1990; 358: 41-4
196. Movin-Osswald G, Boelaert J, Hammarlund-Udenaes M, et al. The pharmacokinetics of remoxipride and metabolites in patients with various degrees of renal function. Br J Clin Pharmacol 1993; 35: 615-22
197. Swift CG, Lee DR, Maskrey VL, et al. Single dose pharmacodynamics of thioridazine and remoxipride in healthy younger and older volunteers. J Psychopharmacol 1999; 13: 159-65
198. Hori M, Suzuki T, Sasaki M, et al. Convulsive seizures in schizophrenic patients induced by zotepine administration. Jpn J Psychiatry Neurol 1992; 46: 161-7
199. Pantel J, Schroder J, Eysenbach K, et al. Two cases of deep vein thrombosis associated with a combined paroxetine and zotepine therapy. Pharmacopsychiatry 1997; 30: 109-11
200. Cooper SJ, Butler A, Tweed J, et al. Zotepine in the prevention of recurrence: a randomised, double-blind, placebo-controlled study for chronic schizophrenia. Psychopharmacol 2000; 150: 237-43
201. Goodnick PJ, Jerry J, Parra F. Psychotropic drugs and the ECG: focus on the QTc interval. Expert Opin Pharmacother 2002; 3: 479-98
202. Wong SL, Cao G, Mack RJ, et al. Pharmacokinetics of sertindole in healthy young and elderly male and female subjects. Clin Pharmacol Ther 1997; 62: 157-64
203. Lewis R, Bagnall AM, Leitner M. Sertindole for schizophrenia. Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 2. Oxford: Update Software, 2000
204. Wilton LV, Heeley EL, Pickering RM, et al. Comparative study of mortality rates and cardiac dysrhythmias in post-marketing surveillance studies of sertindole and two other atypical antipsychotic drugs, risperidone and olanzapine. J Psychopharmacol 2001; 15: 120-6
205. Inoue A, Nakata Y. Strategy for modulation of central dopamine transmission based on the partial agonist concept in schizophrenia therapy. Jpn. J Pharmacol 2001; 86: 376-80
206. Zanetti O, Binetti G. La terapia farmacologica. In: Trabucchi M, editor. Le demenze. 3rd ed. UTET, Arese (Mi) 2002: 517-38

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