Increased Antipsychotic Sensitivity in Elderly Patients: Evidence and Mechanisms

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Objective: The primary objective of this article is to review the literature regarding clinical effects, pharmacokinetics, and pharmacodynamics of antipsychotics in older people and to examine potential mechanisms underlying the age-related antipsychotic sensitivity.

Data Sources: Data for this review were identified by searches of PubMed (1950–2007) and references from relevant articles and books. Search terms included *antipsychotic, neuroleptic, elderly, aging, pharmacokinetics, pharmacodynamics*, and *dopamine*, and only articles written in English or Japanese were consulted.

Data Selection: Studies, reviews, and books pertaining to the clinical effects, pharmacokinetics, and pharmacodynamics with regard to the use of antipsychotics in older patients were selected.

Data Synthesis: The prevailing practices and clinical guidelines suggest that elderly patients can obtain therapeutic benefits at a lower dose and experience adverse effects from antipsychotics more often than younger patients, although there are still few trials that have directly compared elderly patients with the young. The literature suggests an age-related increase in brain access of drugs and demonstrates a decrease with age in the principal components in the dopaminergic system, including endogenous dopamine level and dopamine receptor density.

Conclusions: While clinicians conclusively hold that patients become more sensitive to antipsychotics as they become older, this proposition has only modest empirical support and warrants further investigation. Age-related functional decline in the dopaminergic system predicts lower antipsychotic doses for older patients. We propose a hierarchical series of testable hypotheses to address the relative contribution of age-related pharmacokinetic and pharmacodynamic changes to antipsychotic drug sensitivity.

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Antipsychotics play a central role in the treatment of schizophrenia, irrespective of patients' age. However, aging has been associated with an increased sensitivity to adverse effects from antipsychotics,[1,2] including an increased risk for falls and higher mortality.[3,4] It is therefore not surprising that clinical guidelines universally advocate the use of lower doses of antipsychotics in elderly patients.[5–9] For example, Expert Consensus Guidelines on the dosing of antipsychotics in elderly patients typically recommend half the adult dose for the treatment of primary psychotic disorders in late life.[6] The underlying biological mechanisms for the use of lower doses in this frail population are expected to be complex and need to be examined from various perspectives, including clinical and biological aspects. One reasonable strategy to explore this question would be an antipsychotic drug–oriented approach that focuses on the potential contribution of age-related changes in pharmacokinetics and pharmacodynamics of the drug. It is widely accepted that for a given dose, plasma drug levels are expected to be higher with advancing age. However, there are major limitations with this hypothesis, including inconsistent results regarding age-related increase in plasma antipsychotic levels. Little is known of contributory mechanisms beyond this theoretical pharmacokinetic explanation. Given that antipsychotic drugs exert their antipsychotic effects by binding to central D_2 receptors with varying degrees of antagonism,[10] age-related changes in brain access of the

drug, as well as changes in the dopaminergic system itself, would be expected to contribute to increased antipsychotic drug sensitivity in elderly patients. For example, it would be expected that the robust observation of an age-related decline in striatal D_2 receptor binding site at a rate of 5% to 13% per decade[11,12] would translate into lower dose requirements, though this has never been empirically tested. We therefore propose that a comprehensive understanding of age-related sensitivity to antipsychotics must take into account various levels of age-related pharmacokinetic and pharmacodynamic changes.

Therefore, we first review the relatively sparse clinical data on drug dosing and susceptibility to side effects from antipsychotic drugs in elderly patients. We then proceed to propose a theoretical framework incorporating peripheral pharmacokinetic, central pharmacokinetic, and pharmacodynamic mechanisms to better understand age-related sensitivity to antipsychotics, and present a synthesis of published data supporting this theoretical framework. On the basis of these data, we propose 3 nonexclusive and testable hypotheses to address the relative contribution of these age-related changes to antipsychotic sensitivity: (1) an increased plasma level for a given dose, (2) increased brain access and distribution for a given plasma level, and (3) increased pharmacodynamic effects for the same target receptor occupancy. The implications, testability, and limitations of these hypotheses are discussed.

SEARCH STRATEGIES AND SELECTION CRITERIA

Data for this review were identified by searches of PubMed (1950–2007) and references from relevant articles and books. Search terms included *antipsychotic*, *neuroleptic*, *elderly*, *aging*, *pharmacokinetics*, *pharmacodynamics*, and *dopamine*. Only articles written in English or Japanese were consulted. Studies, reviews, and books pertaining to the clinical effects, pharmacokinetics, and pharmacodynamics of antipsychotics in older patients were selected. Relevant authors' in press articles were also included. This search yielded articles and book chapters from 643 sources, which form the empirical basis of this review and proposed theoretical framework.

CHANGES IN CLINICAL RESPONSE WITH AGE

Do Physicians Use Lower Doses of Antipsychotics in Elderly Patients?

The available literature on antipsychotic dosing in elderly patients with schizophrenia consists mostly of cross-sectional studies of prescription practices and Expert Consensus Guidelines. To our knowledge, there are no published, formal, antipsychotic dose-finding studies that have been conducted in older patients with schizophrenia. However, 3 double-blind randomized control trials with flexible-dosing method were identified.[13–15] In the largest of these studies (N = 175), the median effective doses were 2 mg/day for risperidone and 10 mg/day for olanzapine.[15] In light of recent concerns about the safety and tolerability of antipsychotics in elderly patients,[4,16,17] it is quite surprising that antipsychotic dose requirements for older patients with schizophrenia have not been systematically addressed in clinical trials.

Expert Consensus Guidelines recommend the use of low antipsychotic doses in elderly patients with schizophrenia.[6] For example, while the package insert for risperidone recommends 4 to 8 mg per day for younger adults with schizophrenia (400–800 mg chlorpromazine equivalent chlorpromazine equivalent),[18] the guidelines recommend a dose range of 1.5 to 3.5 mg or 150 to 350 mg chlorpromazine equivalent.[6,19] Cross-sectional studies lend some support to these guidelines. In a naturalistic study of 64 ambulatory patients with schizophrenia older than 45 years treated with first-generation antipsychotics in San Diego, the mean dose was 443.0 mg chlorpromazine equivalent.[20] This inverse correlation between age and dose was also observed in other cross-sectional prescription surveys in Pittsburgh (N = 86)[21] and Tokyo (N = 1418).[22] In both of these studies, older outpatients received 50% to 75% of the mean daily dose prescribed to younger patients: 275 mg versus 378 mg chlorpromazine equivalent in those older than 60 years and those aged 21 to 40 years, respectively, in the Pittsburgh study and 323 mg versus 649 mg chlorpromazine equivalent in the fourth and seventh decades, respectively, in the Tokyo study. While limited by their cross-sectional design, these studies suggest that beyond the fifth decade of life, physicians are prescribing progressively lower doses of antipsychotics—a practice that may be a response to increasing drug sensitivity or adherence to practice guidelines.

Most large-scaled, double-blind, randomized controlled trials in elderly patients have been performed in patients with behavioral and psychological symptoms of dementia.[23–25] The published dose-finding studies used doses that are much lower than standard adult antipsychotic doses, even though a recent pivotal randomized placebo-controlled trial has questioned the efficacy of this therapeutic strategy.[25] With regard to risperidone and olanzapine, doses as low as 1 mg and 5 mg, respectively, have been used for behavioral and psychological symptoms of dementia.[23,24] While these low doses may be effective in some patients with behavioral and psychological symptoms of dementia, the relative contribution of age and the neurodegenerative processes involved in dementia on antipsychotic drug response cannot be conclusively ascertained.

Are Elderly Patients More Prone to Side Effects of Antipsychotics?

The high prevalence of neuroleptic-induced parkinsonism in elderly patients was first documented by

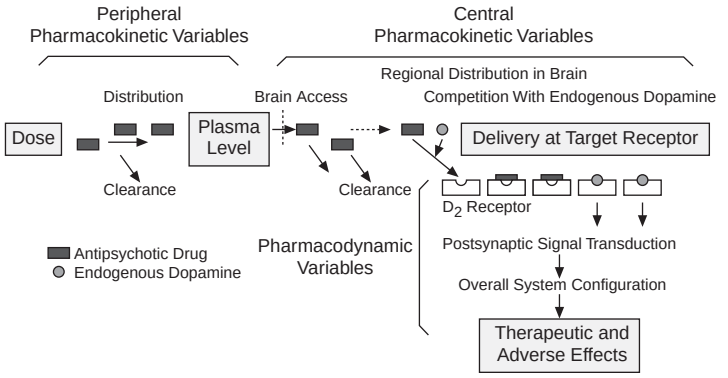
Ayd,[1] whereas akathisia occurs evenly across the life span[26] and dystonia is rarely observed among older patients.[27,28] Caligiuri et al.[2] confirmed this relationship between older age and neuroleptic-induced parkinsonism in 56 previously untreated elderly psychiatric patients (mean age = 70.5 years) within the first month of antipsychotic treatment, even after controlling for spontaneous parkinsonism. This age effect was also confirmed in a cross-sectional study of 100 psychiatric patients across the life span (mean age = 41.1 years, age range = 19–76 years), of whom 77% received a conventional antipsychotic.[29] The introduction of second-generation antipsychotics brought promise of lower burden of neurologic side effects from antipsychotic treatment. However, elderly patients still experience parkinsonism from these newer drugs more frequently than the young. In a re-analysis of 12 double-blind trials of risperidone in mixed age patients with schizophrenia (N = 2074), Lemmens et al.[30] found that longer duration of psychotic symptoms was associated with development of extrapyramidal symptoms, including parkinsonism as well as dystonia and dyskinesia—this was especially true for the older patients. This finding would suggest that the duration of illness and advancing age may each be contributory to a vulnerability to extrapyramidal symptoms.

With regard to tardive dyskinesia (TD), cumulative incidence varies widely from study to study, but most of the reports have shown that older patients develop this side effect more often and sooner when treated with first- or second-generation antipsychotics.[31–34] In an analysis that combined data from 11 studies and included 2769 patients treated with amisulpride, olanzapine, quetiapine, risperidone, or ziprasidone,[34] the weighted mean annual incidence of TD for second-generation antipsychotics was 0% in children, 0.8% in young adults, and 5.3% in those older than 53 years.

Although age may also have an effect on the incidence of other serious adverse effects of antipsychotics, such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or neuroleptic malignant syndrome, we are not aware of any published studies that have addressed this issue. However, since older people are at higher risk of developing SIADH from any cause and of having concomitant brain pathology, one would expect that antipsychotics are more likely to induce SIADH or neuroleptic malignant syndrome in older patients than in younger patients.[35]

In summary, the prevailing practices and clinical guidelines suggest that compared to younger patients, elderly patients may derive therapeutic benefits at lower doses and are at greater risk of experiencing motor adverse effects from antipsychotics.

Figure 1. Framework for Disposition of Antipsychotic Drugs

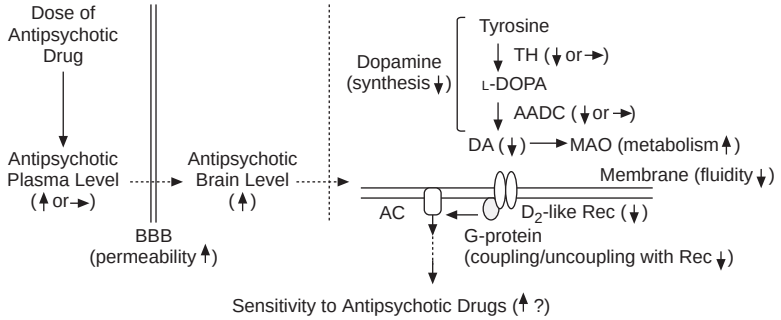


FRAMEWORK FOR UNDERSTANDING THE SENSITIVITY TO ANTIPSYCHOTICS

To better understand the potential contribution of age-related changes in pharmacokinetics and pharmacodynamics of antipsychotics, it is important to have a framework to conceptualize the different levels at which disposition and actions of antipsychotics may differ. Figure 1 illustrates a theoretical framework for understanding the biological mechanisms responsible for age-related sensitivity to antipsychotics.

Once a dose of an antipsychotic is ingested, it is differentially distributed in the body, including the bloodstream where it is measurable (henceforth, referred to as peripheral pharmacokinetics). The next step for a centrally acting drug is determined by its ability to reach and interact with the target receptors (e.g., dopamine D_2 receptors). This process involves at least 3 principal components: (1) ability to access the central nervous system (CNS) via the blood-brain barrier (BBB), (2) regional distribution within the CNS, and (3) competition for binding at dopamine D_2 receptor with endogenous dopamine (henceforth referred to as central pharmacokinetics). Finally, the presence of the drug effects changes in second messenger systems at the cellular level. In turn, this results in alterations and compensations at the system level, leading to the drug's therapeutic and adverse effects (henceforth referred to as pharmacodynamics). Since the net pharmacodynamic effects of an antipsychotic are the results of an interaction between the drug and the endogenous transmitters, changes in endogenous dopamine levels could also contribute to changes in antipsychotic sensitivity. These changes could be conceptualized either as a central pharmacokinetic phenomenon or a central pharmacody-

Figure 2. Potential Contributors to Age-Related Sensitivity to Antipsychotics[a]



[a]Arrows in parentheses indicate age-related changes.
Abbreviations: AADC = aromatic acid decarboxylase, AC = adenylate cyclase, BBB = blood-brain barrier, DA = dopamine, G-protein = guanine nucleotide binding protein, L-DOPA = 3, 4-dihydroxy-L-phenylalanine, Rec = receptor, MAO = monoamine oxidase, TH = tyrosine hydroxylase.

namic one—we describe the implications of such changes only in the central pharmacokinetics section of this review to avoid duplication.

PHARMACOKINETIC MECHANISMS

The Peripheral Pharmacokinetic Hypothesis and Its Limitations

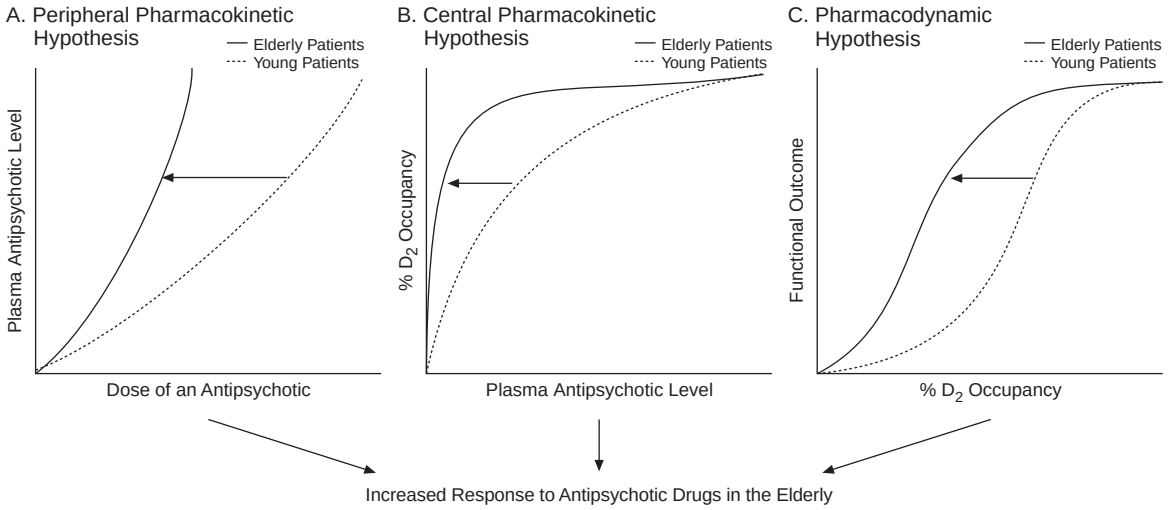
Peripheral pharmacokinetic changes associated with the aging process may contribute to increased sensitivity to antipsychotics. This hypothesis, referred to as the peripheral pharmacokinetic hypothesis, would predict that for a given dose, plasma levels in elderly patients will be higher and that this age-related increase would be expected to result in increased sensitivity to therapeutic and adverse effects (Figures 2 and 3).

However, there are major limitations with this hypothesis. First, despite popular belief, an age effect on plasma antipsychotic exposure has not been a consistent finding.[36–43] In a recent analysis of the data from the Clinical Antipsychotic Trials of Intervention Effectiveness, a nonlinear mixed-effects modeling was used to determine the population pharmacokinetics of olanzapine and evaluate potential contributors to drug exposure.[36] While sex, race, and smoking status were contributors, age did not have an effect on the exposure of olanzapine in patients with Alzheimer's disease (N = 117) or schizophrenia (N = 406). Other studies of olanzapine, risperidone, and ziprasidone have also failed to show a clinically significant influence of age in older patients or in healthy individuals.[37–39] Secondly, a relationship between plasma levels and therapeutic or adverse effects has not always been identified in past studies.[44,45] For instance, in a study that examined the ratio of concentration to dose in 165 patients treated with conventional antipsychotics, the ratio was higher in elderly patients but there was no relationship between plasma levels and extrapyramidal symptoms.[44] A recent comprehensive review concluded that current evidence on the relationship between plasma concentrations of second-generation antipsychotics and clinical outcomes or adverse effects is equivocal except for the proconvulsant effects of clozapine.[45] Finally, a dissociation of the kinetics of antipsychotic plasma levels and D_2 receptor occupancy has been reported in a positron emission tomography (PET) study examining single-dose kinetics of risperidone in healthy subjects.[46] In this study, mean plasma elimination half-life of single dose of risperidone was 10.3 hours, whereas it took 66.6 hours for a 50% reduction of peak striatal D_2 receptor occupancy. We therefore propose that peripheral pharmacokinetic changes with age, while possibly contributing to the overall sensitivity of elderly patients, cannot account for the full extent of the age-related sensitivity to antipsychotics.

Central Pharmacokinetic Changes With Age

Brain access. The BBB, a single layer of capillary endothelial cells joined together at tight junctions, regulates access of xenobiotics (including antipsychotics) to the CNS.[47] Loosening of these junctions would theoretically increase access of antipsychotics into the brain. However, the relationship between junction integrity and aging has not been investigated. Central concentration of many drugs, including antipsychotics, is also regulated by P-glycoprotein, which restricts the permeability of the BBB indirectly by pumping drugs back into the peripheral circulation. Although in vitro studies on age-related changes in P-glycoprotein activity are not consistent,[48–51] a recent report[52] examined the volume of distribution of (R)-[^{11}C]verapamil (a substrate of P-glycoprotein) in young and elderly human brains and found a higher verapamil BBB access in elderly compared to younger subjects with no significant differences in peripheral pharmacokinetics parameters between the 2 age groups. In addition, several PET studies showed an age-related increase in radioactivity per given radiation dose or plasma level in the cerebellum that is expected to be free of specific target receptors of an administered radiotracer.[53–55] These results are consistent with a previous report of higher brain/plasma concentration ratio of haloperidol in aged rats.[56] While quetiapine and risperidone have been reported to be good P-glycoprotein substrates in vitro,[57] we are not aware of any literature addressing age effects on P-glycoprotein in vivo with these drugs.

Figure 3. Three Hypotheses Regarding the Elderly's Increased Sensitivity to Antipsychotics[a]



[a]This figure explains 3 mutually nonexclusive hypotheses for the enhanced sensitivity to antipsychotics in the elderly: an increased plasma level for a given dose (peripheral pharmacokinetic hypothesis), increased delivery of antipsychotic to dopamine D_2 receptor for a given plasma level (central pharmacokinetic hypothesis), and increased functional outcome for a given occupancy (pharmacodynamic hypothesis).

Thus, higher drug-brain access may directly result from the loosening of the junction integrity of the BBB associated with aging or with an age-related decline in P-glycoprotein function.

Endogenous dopamine level. An age-related decline in endogenous dopamine in the brain has been a consistent finding in postmortem studies.[58,59] They suggest a decline in dopamine level of 5% to 15% per decade. Positron emission tomography imaging now allows for the study of the endogenous dopamine level in vivo (indirectly) by using paradigms involving competitive binding of endogenous dopamine and dopaminergic radiotracers to dopamine receptors in response to the administration of a psychostimulant. Using this paradigm, Volkow et al.[60] reported that dopamine release by methylphenidate, as measured using [^{11}C]raclopride binding, was inversely correlated with age, a finding that supports an age-related decline in synaptic dopamine release in response to a challenge.

There have been conflicting reports on the effect of aging on tyrosine hydroxylase activity. Initial postmortem studies showed an age-related decline in tyrosine hydroxylase activity in substantia nigra,[61,62] but subsequent postmortem studies using different techniques showed no change in caudate tyrosine hydroxylase activity beyond infancy.[63] Similar conflicting findings have been reported for age-related changes in aromatic acid decarboxylase (AADC) activity. One in vivo [^{18}F]DOPA PET study[64] reported a significant decrease (8.3% per decade) in the striatal uptake, but this finding was not replicated.[65] In an attempt to resolve the discrepancy among past reports, Kish et al.[66] employed quantitative blot immuno-labeling techniques in postmortem striata of 28 neurologically normal subjects. They found a significant age-dependent decrease in the concentration of AADC in the caudate (4.7% per decade) but not in the putamen. Ota et al.[67] recently demonstrated an age-related decline in the uptake constant for ^{11}C-labeled L-DOPA in the caudate (5.4% per decade) and the putamen (4.2% per decade) in the living human brain, which was more prominent than the decrease in the tissue fraction of gray matter. In summary, a majority of reports on age-related changes in the synthetic enzymes and precursor suggest that the synthesis of dopamine declines with age, and, consistent with this, the 1 PET study[64] examining the release of dopamine in response to a challenge also finds a decrease with age.

Dopamine transporter is responsible for terminating dopaminergic neurotransmission through dopamine reuptake, and the concentration of dopamine transporter is considered to reflect the homeostatic tone of the dopaminergic system.[68] Initial postmortem studies showed a linear decline in the number of [^{3}H]GBR-12935, a dopamine transporter radiotracer, binding sites with age (approximately 10% per decade).[69,70] Results from in vivo studies also show an age-related decrease, with a majority of these studies[71,72] demonstrating a linear age-related decline (approximately 5% per decade). In summary, the concentration and density of dopamine transporter have consistently been reported to decline with age.

Monoamine oxidase-B (MAO-B), the principle enzyme responsible for the catabolism of monoamine neurotransmitters,[73] also shows age-related changes. Initial postmortem studies found an age-related increase in MAO-B activity,[74,75] which was confirmed by an in vivo PET study demonstrating a linear increase with age (8% per decade).[76] This increased activity of MAO-B would

be expected to decrease the synaptic concentration of dopamine with age.

In summary, there are several age-dependent mechanisms acting to decrease brain dopamine levels in older persons, including decreased synthesis and increased clearance, although these effects may be counterbalanced by an age-related decline in dopamine transporter concentration. Thus, the net effect, as suggested in an in vivo PET study by Volkow et al.,[60] appears to decrease in dopamine release with age.

The Central Pharmacokinetic Hypothesis

The age-related antipsychotic sensitivity may be induced in part by changes in central pharmacokinetics—i.e., increased drug access and decreased dopamine—such that for a given plasma level a higher number of antipsychotic molecules reach target receptors and produce downstream changes (see Figures 2 and 3). According to this hypothesis—referred to as the central pharmacokinetic hypothesis—a given plasma level of antipsychotics would lead to a higher D_2 receptor occupancy in elderly compared to younger patients, as illustrated by a leftward shift of the drug concentration and D_2 occupancy with age in Figure 3. However, age-related changes in regional distribution and clearance of antipsychotics in the brain also need to be elucidated since they could affect synaptic level of antipsychotics.

PHARMACODYNAMIC MECHANISMS

Changes in Dopamine System With Age

Available evidence clearly indicates a gradual decline in the structural and functional status of the dopaminergic system with age. These changes would be expected to contribute to the age-related sensitivity of the system to dopamine antagonists.

Anatomical and histological changes. While the precise rate of decline remains unclear, there is consensus in the literature that the number of dopaminergic neurons in the substantia nigra in humans decreases with age.[62,77–79] Postmortem studies have reported that cell counts in the substantia nigra decline with age at the rate of approximately 10% per decade.[62] This age-related decrease in the absolute number of melanin-positive neurons has been confirmed by subsequent studies that used unbiased stereological cell-counting methods (6%–10% per decade).[77,78]

Dopamine D_2 receptor. A majority of in vitro studies showed an age-related decrease in dopaminergic binding sites in the basal ganglia.[80,81] A large postmortem study showed a decrease in dopamine D_2 receptors of 4.2% per decade in the caudate nucleus and 4.7% in the putamen.[80] This age-related decrease was observed also in another large postmortem study that demonstrated a decrease in dopamine D_2 receptors in the striatum of 2.2% per decade beyond 20 years of age.[81]

In vivo brain imaging studies have also consistently demonstrated an age-related decrease in striatal D_2 binding sites of 5% to 13% per decade,[11,12,82] with similar rates observed for other regions including the anterior cingulate cortex, frontal cortex, amygdala, and thalamus.[83] Comparable age-related changes in dopamine D_2 receptor density have been reported in patients with schizophrenia: the slope of age-related decrease in the D_2-like receptor density in the caudate nucleus was similar in 22 drug-naive schizophrenia patients (9% per decade) and 24 normal controls (8% per decade).[84] Thus, dopamine D_2 receptors have consistently been reported to decline with age in postmortem as well as in vivo studies.

Postsynaptic signal transduction. Dopamine receptors are coupled to guanine nucleotide binding proteins (G-proteins) that transduce the signal from receptors to effectors, such as adenylate cyclase, which, in turn, trigger downstream cellular response. Since G-proteins and adenylate cyclase are bound to, or embedded in, the cell membrane, age-related alterations in the structure of membrane could effect postsynaptic signal transduction. Thus, the well-established, age-related decrease in membrane fluidity[85] could restrict the function of G-proteins and theoretically result in a reduction of signal transduction. Indeed, an age-associated decreased coupling/uncoupling of receptors and G proteins has been demonstrated for other receptors.[86–88]

In summary, in addition to a decrease in endogenous dopamine level, both the absolute number of dopamine neurons and the density of dopamine D_2 receptors have been shown to decrease with age. While a decrease in the G-protein–mediated signal transduction is still not confirmed for dopamine receptors, these results are consistent with a gradual decline in the dopaminergic system with age.

The Pharmacodynamic Hypothesis

At the pharmacodynamic level, we propose that for a given level of occupancy, older patients may be more susceptible to clinical/adverse effects—hereby referred to as the pharmacodynamic hypothesis (Figures 2 and 3). A common misunderstanding is that an age-related decrease in the number of receptors should directly lead to an increase in percentage occupancy, as there are "fewer" receptors. In fact, the percentage occupancy of a receptor by an antipsychotic is independent of the absolute number of receptors but is determined mainly by a first-order process. Thus, a decline in receptor number would lead to a fewer total number of receptors occupied with no change in percentage occupied. Rather, it is the magnitude of the biological response that is dependent on the absolute number of receptors occupied by agonists. Therefore, as either the endogenous agonist or its receptor population decrease in number, the absolute number of receptors occupied by the endogenous agonist declines, resulting in a

lower downstream response. For example, inhibition of forskolin-stimulated cyclic adenosine monophosphate accumulation by dopamine was compared between hamster ovary cell line expressing high dopamine receptor density and those expressing low receptor density. In cells expressing high receptor densities, 50% inhibition was achieved by only 0.9% receptor occupancy, while 39% occupancy was needed for the same effect in those with low density.[89] Thus, a system with a lower number of receptors—as is the case in the brain of an older individual—would be expected to require a higher occupancy for the same downstream effect. In younger patients with schizophrenia, occupancy of more than 80% of striatal D_2 receptors with antipsychotics has been associated with extrapyramidal symptoms,[10] suggesting that a minimum of 20% of the receptor population must be free of antagonist for physiologic transmission to overcome extrapyramidal symptoms. In view of a decline in absolute receptor number with age, therefore, a greater percentage of receptors (20 + *x*%) must be free to provide an adequate level of physiologic transmission in elderly patients. Therefore, this would predict that while the younger patient would present with extrapyramidal symptoms when antipsychotics occupy more than 80% of dopamine D_2 receptors (100% – 20% = 80%), older persons with schizophrenia would show extrapyramidal symptoms at a lower occupancy (100% – 20% – *x*% = < 80%). This age-related decrease in the threshold would in turn lead to a lower dose requirement for older persons with schizophrenia. This threshold may be even lower in persons with behavioral and psychological symptoms of dementia: a decrease in dopamine D_2 receptors in patients with Alzheimer's disease compared to healthy elderly controls has been reported,[90] although there is no direct comparison in vivo in D_2 receptor density between schizophrenia and dementia in elderly patients.

Age-related decrease in signal transduction could also alter the sensitivity to antipsychotics in elderly patients. It is likely that homeostatic mechanisms compensate for early age-related changes in the dopaminergic system. However, the same homeostatic mechanisms may fail to maintain the desired balance in late life, though this needs to be tested in future studies. We propose that at some critical period in the aging process—possibly between the ages of 50 to 70 years—a threshold is crossed whereby the homeostatic mechanisms are overwhelmed and an altered overall system configuration results in different responses to external stimuli, including the blockade of neural transmission by antipsychotics.

QUALIFICATIONS AND LIMITATIONS

Our conclusions must be considered in light of the limitations in the literature we reviewed. Studies on age-related changes—particularly involving changes in central pharmacokinetic and pharmacodynamic changes—are sparse and await future replication. Further, the dopaminergic system may be influenced not only by the aging process itself but also by psychopathology of psychiatric illnesses, including schizophrenia and dementia, and long-term effects of antipsychotic drugs. Age effects described in this review may differ between persons with and without those illnesses. Our focus on the dopaminergic system is not intended to suggest that the resolution of psychotic symptoms with antipsychotics is solely related to effects in the dopaminergic system. Clearly this response is far more complex, and we certainly do not exclude the effects of other systems such as the serotonergic or cholinergic systems. In addition, other potential modifiers, such as estrogens, nutrition, and other dopamine receptor subtypes, should also be taken into consideration. Furthermore, this review does not address the metabolic, cerebrovascular, and cardiovascular adverse effects of antipsychotics, particularly second-generation antipsychotics, that have recently come to the forefront of scientific inquiry.[4,16,17]

CONCLUSION

We conclude that, while aging most likely is associated with increased sensitivity to antipsychotic drugs, the available literature is surprisingly inconclusive, and the age at onset of this sensitivity and the magnitude of its effect remain unclear. Furthermore, there are broad possibilities to account for this age-related sensitivity. This notwithstanding, age-related functional decline in the dopaminergic system would suggest the need for lower antipsychotic doses and a more careful dose titration in elderly patients. We conclude that while age-related peripheral and central pharmacokinetic changes may be contributory to age-related antipsychotic sensitivity, pharmacodynamic mechanisms may play the most significant role. All 3 hypotheses may be tested within the same study design by measuring both the plasma concentration of an antipsychotic and the dopamine D_2 receptor occupancy for a given dose of the drug and relating these findings to clinical outcomes in elderly and young patients. We are currently conducting a series of studies to address these hypotheses in older patients with schizophrenia, with the goal of understanding better the neurobiological basis for their increased sensitivity to antipsychotics. A better understanding of these factors will lead to a more sophisticated use of antipsychotic drugs in this frail population.

Drug names: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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