

REVIEW

Understanding of Antipsychotics in Elderly Patients with Dementia

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Elderly patients affected with dementia frequently accompany delusions, hallucinations and other psychotic symptoms. As such, these patients are commonly prescribed antipsychotic medications for the treatment of psychosis. However, in recent years, the use of antipsychotics has been widely debated for reasons concerning their efficacy and safety in these patients. Conventional antipsychotics have been widely used for behavioral psychological symptoms in dementia (BPSD) in the past. Atypical antipsychotics showed an efficacy superior to placebo in randomized studies in BPSD treatment, with a better tolerability profile versus conventional drugs. However, in 2002, the Food and Drug Administration alert the possible increase in cerebrovascular adverse events after using antipsychotics and consequent studies reported various adverse (including fatalities) events. Notwithstanding controversial data, antipsychotics are probably the best option for short-term treatment of severe BPSD. However, due to possible serious adverse events, long-term therapy is not recommended and clinician should decrease the dosage and discontinue treatment wherever a sufficient control of behavioral symptoms has been obtained. Before prescribing an antipsychotic drug, the possible risk factor should be structurally reviewed and monitored. The aim of this review is to assess systematically the efficacy and safety concern of antipsychotics in treating elderly patients with BPSD. And we also review how and what we should prescribe and monitor, if once antipsychotic medication is decided.

Key Words elderly, dementia, antipsychotics, behavioral psychological symptoms in dementia.

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INTRODUCTION

Behavioral and psychological symptoms are often apparent and major issues in elderly patients with dementia, and are potentially the cause of the caregiver's stress, thus leading these patients to nursing homes. Aging is a major risk factor for dementia, and using antipsychotics due to behavioral psychological symptoms in dementia (BPSD) present a challenge task in geriatric psychopharmacology, which is complicated not only by the effects of normal aging but by co-morbid medical ill-

ness. Elderly patients often present with subclinical syndromes or symptoms that are modified by co-morbid disease or partial treatment.

Antipsychotics were and are frequently used for the treatment of BPSD. However, in recent years, the use of antipsychotics (both conventional and atypical) has been widely debated for their efficacy in treating behavioral disturbances and the possible serious adverse events in elderly patients with dementia.¹⁻³ In the past, using conventional antipsychotics in the elderly patients with BPSD was strongly limited by their severe adverse events,^{4,5} whereas atypical antipsychotics were believed to have a far milder adverse effect profile than their older counterparts. However, several recent studies have raised questions about this belief.^{1,2} In 2002, trials with risperidone and olanzapine in elderly psychotic patients with dementia is-

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sued the first alerts about the possible increase in stroke events.¹ Since 2005, a lot of studies have been reported regarding this issue, even with opposing conclusions; the safety issues of antipsychotics still remain intense in medical society.

This article presents a clinical review and update the use of antipsychotic drugs focusing on the therapies in the elderly people with dementia. It will also deal with the characteristic binding profiles and the peculiar mechanism of action of these drugs, the side effects, and the potential risks of using antipsychotics in light of the recent safety concerns in elderly demented patients. Then, we eventually tried to draw updated clinical conclusions for the use of antipsychotics in elderly patients with dementia.

BASIC PSYCHOPHARMACOLOGY IN THE ELDERLY

Older age and age-related illness are associated with the pharmacokinetic and pharmacodynamic alternation (decreased renal and hepatic blood flow, decreased cardiac output, increase body fat, and decreased activity of a number of hepatic enzymes responsible for drug metabolism) which, in general, decrease the body's efficiency and ability to clear a drug. These pharmacokinetic and pharmacodynamic change may explain the increased sensitivity of elderly patients to the toxic effects of antipsychotics such as sedation, anticholinergic symptoms, extrapyramidal symptoms (EPS), and orthostatic hypotension. Understanding the impact of these aging changes is key to effective therapeutics, especially because the "therapeutic index" for antipsychotics is lower in older patients

than younger ones.

In general, pharmacodynamic response is a function of the neuronal receptor number and affinity, signal transduction, cellular response, and homeostatic regulation.⁶ Increased pharmacodynamic sensitivity to drugs with aging has been also postulated. Reduced density of muscarinic, μ opioid, and dopaminergic D2 receptors have been reported in elderly.⁷ The ability to up-regulate or down-regulate postsynaptic receptors also may decrease and the activities of a number of enzymes are reduced with aging.

The variability of these changes among individuals contributes significantly to the observed heterogeneity in pharmacologic response in the geriatric population. Further heterogeneity is occurred by genetic determinants of drug response because genes encoding drug metabolizing enzymes, drug transporters, and drug targets also show more variability in elderly patients. In general, this genetic susceptibility remains stable into old age. Thus, genetic heterogeneity with regard to pharmacologic response is amplified by aging effects. Though these changes are not yet clearly understood at this time, clinical and functional results are significant. The clinician should pay attention for both the pharmacokinetic and pharmacodynamic alterations and resulting decreased margin of safety in elderly patients with dementia.

MECHANISM OF ANTIPSYCHOTICS ACTION

Table 1 shows receptor binding affinity expressed as equilibrium constant K_i (e.g., low K_i means strong binding) of

Table 1. Receptor binding profiles and plasma half-life ($t_{1/2}$) of antipsychotic drugs

Drug class	Atypical antipsychotics							Conventional antipsychotics		
	AMI	ARI	ASE	CLO	OLA	RIS	QUE	ZIP	HAL	PER
D2	1.3	0.66	1.3	210	20	3.77	770	2.6	2.6	1.4
5-HT1A	>10000	5.5	2.5	160	610	190	300	1.9	1800	421
5-HT2A	2000	8.7	0.06	2.59	1.5	0.15	31	0.12	61	5
5-HT2C	>10000	22	0.03	4.8	4.1	32	3500	0.9	4700	132
α_1	7100	26	1.2	6.8	44	2.7	8.1	2.6	17	10
α_2	1600	74	1.2	158	280	8	80	154	600	500
H1	>10000	30	1.0	3.1	0.08	5.2	19	4.6	260	8
M1	N/A	6780	8128	1.4	2.5	>10000	120	300	>10000	1500
M2	N/A	3510	4.5	204	622	>10000	630	>3000	>10000	N/A
M3	N/A	4680	4.67	109	126	>10000	1320	>1300	>10000	1848
M4	N/A	1520	5.09	27	350	>10000	660	>1600	>10000	N/A
$t_{1/2}$ (hr)	12	50–72	23	12	30	3	6–7	7	3–6	8–12

Adapted and revised with permission from Correll CU. *Eur Psychiatry* 2010;25(Suppl 2):S12–S21. Data represented as the equilibrium constant (K_i ; nM), i.e., nanomolar amount of the antipsychotic needed to block 50% of the receptors *in vitro*.

AMI: amisulpride, ARI: aripiprazole, ASE: asenapine, CLO: clozapine, HAL: haloperidol, N/A: not applicable, OLA: olanzapine, PER: perphenazine, QUE: quetiapine, RIS: risperidone, ZIP: ziprasidone.

atypical antipsychotics (amisulpride, aripiprazole, asenapine, clozapine, olanzapine, paliperidone, risperidone, quetiapine) and conventional antipsychotics (sertindole, ziprasidone, haloperidol, perphenazine).

The cardinal pharmacodynamic feature of all antipsychotics is their ability to block the dopamine D2 receptor. The overall goal of treatment is to reduce the dopaminergic hyperactivity of pathways that, at least in part, mediate psychosis, mania, tics, and aggression. Simultaneously, the pathways that regulate motor movements, prolactin secretion and cognition need to be preserved. In addition, cortical areas with dopaminergic hypoactivity should ideally receive increased dopamine input (i.e., a potential benefit of partial dopamine agonists). The degree of receptor occupancy, intrinsic activity and dosage, at the target receptor to which the antipsychotic binds are all important determinants of therapeutic and adverse effects. With a full antagonist, approximately 60–75% dopamine receptor occupancy may be required for antipsychotic efficacy. With a partial agonist (e.g., aripiprazole), receptor occupancy is not equivalent to blockade and a higher degree of occupancy (at least 80–85%) may be needed to achieve the same level of therapeutic effects.⁸ Since each antipsychotics differ in their affinity for dopamine receptors, their effective dopamine D2 blockade is achieved at very different dose levels and adequate dopamine blockade is achieved either prior to, around, or only after the antipsychotic concentration is sufficient to block other receptor systems (Fig. 1). As a result, other (or side) effects associated with blockade of those other receptors occur either within the dose spectrum required for antipsychotic efficacy or not. In other words, whenever the K_i value is lower (signifying stronger affinity) for a receptor system than for the dopaminergic receptor, a side effect associated with the blockade of this receptor is likely to occur as part of antipsychotic treatment.

For example, the high-potency antipsychotic haloperidol

(and butyrophenones in general) has a tight D2 binding at doses where little blockade of other receptors occurs. Therefore, extrapyramidal side effects, hyperprolactinemia and secondary negative and cognitive symptoms are likely to as part of treatment. Atypical antipsychotics, on the other hand, have a stronger 5-HT_{2A} affinity than D2 affinity, which is thought to balance D2 blockade, reducing those adverse effects in frequency, at least, at low to moderate effective antidopaminergic doses. Conversely, chlorpromazine, clozapine, quetiapine or olanzapine have a stronger affinity for the histaminergic and cholinergic receptors than the dopaminergic receptor and are, thus, associated with fewer extrapyramidal effects, but are often other adverse effects (e.g., sedating).

Conventional antipsychotics show high D2-receptor affinity; in particular, D2-receptor blockade by haloperidol occurs in a dose-dependent fashion, this being responsible for the high risk in extrapyramidal adverse effects, especially in elderly patients. Haloperidol has also a moderate affinity for α_1 -adrenoceptors whereas it shows no or few interactions with other neurotransmitter receptors.⁴ Promazine, the prototype of phenothiazines, blocks in particular H₁ receptors, this being responsible for sedation. It is well tolerated in the elderly and relatively safe.⁴

The peculiar mechanism of atypical antipsychotics might be explained by the serotonin-dopamine interactions in the nigrostriatal, mesocortical, and tuberoinfundibular pathways. In the nigrostriatal pathway, the atypical antipsychotics binds to presynaptic 5-HT_{2A} receptor placed on dopamine neuron. The 5-HT_{2A} antagonism leads to dopamine release, so that there are usually no or less motor impairments compared with conventional antipsychotics.^{4,5} The same mechanism at the mesocortical pathway explains why fewer cognitive impairments occur in the atypical antipsychotics compared with conventional drugs. Furthermore, acetylcholine release by 5-HT₆ antagonism of olanzapine might improves cognitive functions

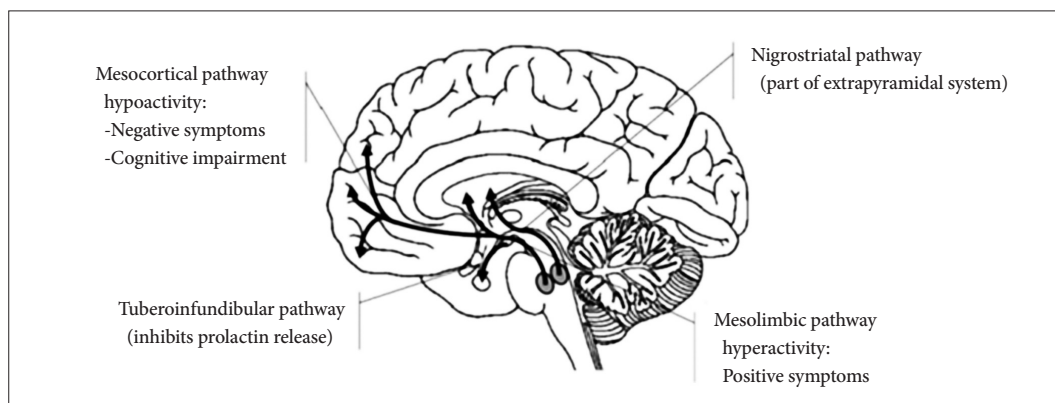


Fig. 1. The neuroanatomy of the dopaminergic pathways in the brain can explain the symptoms of psychosis and the therapeutic and side effects of antipsychotics.

too and is advantageous in the elderly, where brain levels of acetylcholine decrease.⁵ In tuberoinfundibular pathway, dopamine inhibits and serotonin stimulates prolactin release; therefore, 5-HT_{2A} serotonin antagonism counteracts the effects of D₂-receptor blockade.

In summary, atypical antipsychotics reduce dopaminergic hyperactivity at mesocortical pathway, thus leading to antipsychotic effects.^{4,6,7} On the other hand, atypical antipsychotic drugs might increase dopamine at frontocortical and nigrostriatal pathways and cause a less cognitive and motor impairments when compared with conventional antipsychotics. Moreover, atypical drugs occupy D₂ receptors transiently and then rapidly dissociate to allow normal dopamine neurotransmission (hit-and-run mechanism). These characteristics are the real pharmacological difference with conventional antipsychotic drugs in elderly people. All of them can be used in the elderly, even if they might have a number of adverse effects, which are still a controversial issue among doctors.

ATYPICAL ANTIPSYCHOTICS

As regards to atypical antipsychotics, the tricyclic agents (clozapine, olanzapine, and quetiapine) have their highest affinity for H₁ receptors and multiple other receptors.⁹ In fact, these agents are the so-called multi-acting receptor-targeted antipsychotics. Moreover, quetiapine and clozapine are antipsychotics that bind with a lower relative affinity to the dopaminergic receptor than endogenous dopamine. Thus, they are also said to be “loose” binding agents that can dissociate off the receptor quickly after binding and resulting in downstream effects.¹⁰ Clozapine is a dibenzodiazepine derivative with antidopaminergic and antiserotonergic activity, but it also binds to 5-HT₂, α₁, muscarinic, and histamine H₁ receptors.⁷ Moreover, it binds more to D₄, 5-HT₂, α₁, and H₁ receptors than to either D₂ or D₁ receptors. Furthermore, it has high affinity for serotonergic receptor subtypes 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{3C}, which may contribute to its antipsychotic properties and atypicality.¹¹ Olanzapine is more potent as a 5-HT antagonist and presents lower potency at D₁, D₂, and α₁ receptors.¹² Quetiapine is a lower potency compound with relatively similar antagonisms of 5-HT₂, D₂, α₂, and α₁ receptors. The H₁ receptor blockade is similar to clozapine, olanzapine, and quetiapine, and it is consistent with their sedative properties.⁴

On the contrary these cyclic agents, risperidone is a serotonin dopamine antagonist drug and it equally block D₂ and 5-HT₂ receptors. Furthermore, its D₂ receptors blocking potency is dose-dependent manner. This means that increasing dosages of risperidone proportionally block D₂ receptors.

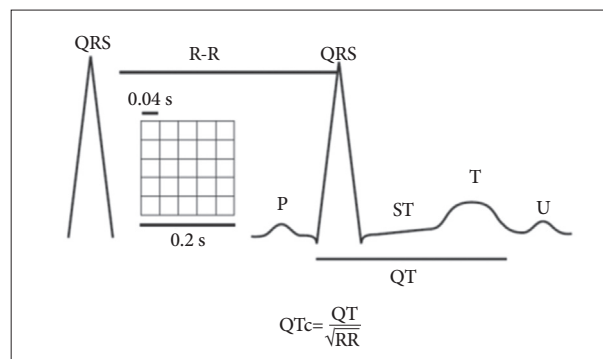


Fig. 2. The corrected QT interval (QTc) on the electrocardiogram (adapted from and revised with permission from Adler J “QTc Calculator”).

These pharmacological characteristics explains why risperidone may have a high risk of EPS in the elderly, especially at dosages superior to 2 mg/day.^{4,5}

Amisulpride is an alkylsulfone derivative of the substituted benzamide series of antipsychotics and this unique in that it binds strongly to dopaminergic receptors, without countering by serotonergic, cholinergic or histaminergic blockade, suggesting that it might selectively bind to dopaminergic receptors of mesocortical pathways or that activity at other dopamine receptors than D₂ receptors reduce the extrapyramidal side effect signal seen more with conventional antipsychotics. This presents a high affinity for presynaptic D₂/D₃ receptors, whereas it has no affinity for α₁-adrenergic, histamine, or cholinergic receptors.¹³ In particular, it has antagonist properties for D₃ and both pre- and post-synaptic D₂-like dopamine receptors in the rat striatum or nucleus accumbens *in vitro*.¹³ Doses between 400–1200 mg/day are used for the treatment of psychosis by inhibition of dopaminergic neurotransmission, whereas low doses in the range of 50–200 mg preferentially block inhibitory presynaptic autoreceptors. This results in improvement of dopamine activity, and for this reason low-dose amisulpride has also been used for treating dysthymia.

Aripiprazole is a new antipsychotic agent with partial agonistic effects on D₂ and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.^{6,7} Although aripiprazole has tighter binding to the dopamine D₂ than for the 5HT_{2A} receptor or to the histaminergic and anticholinergic receptor, its novel mechanism of partial dopamine agonism (i.e., not completely blocking all dopamine activity) leads to relatively minimal extrapyramidal effects and, even, to a lowering of prolactin levels. Ziprasidone has a high ratio of 5-HT₂ receptor blockade to D₂ receptor blockade; it is usually more effective in reducing psychotic symptoms and better tolerated than haloperidol, especially in movement disorders.^{6,7} Ziprasidone require careful use in acute stages since they are associated with a high-

er risk of arrhythmias.

Asenapine has a higher affinity for 5-HT_{2A} receptors than D₂ receptors. Asenapine also has a high affinity for several other serotonin receptors, including 5-HT_{2C}, 5-HT₇, 5-HT_{2B}, and 5-HT₆, in which it exerts antagonistic effects. In addition, asenapine has demonstrated a high affinity for dopamine D₃, D₄, and D₁ receptors, α ₁- and α ₂-adrenergic receptors, and H₁ receptors. It has moderate affinity for H₂ receptors.¹⁴ Though the newly approved drug asenapine might be a promising alternative for treating behavioral and psychotic disorders in dementia due to its peculiar mechanism of action, at present, it is indicated in bipolar disorder, and no evidence of its effectiveness has been proven in elderly patients with dementia.¹⁵

WHEN AND HOW TO USE ANTIPSYCHOTICS IN ELDERLY PATIENTS WITH DEMENTIA?

The conventional or atypical antipsychotics may be used

when some important symptoms are present (physical aggression, severe agitation, problematic psychoses, or homicidal behaviors).^{16,17} The other use for anxiety, depression, or as a pure sleep aid may not be justified. Furthermore, it cannot be justified either for nonspecific agitation or without any prior detailed workup.¹⁶ And if once a clinician decides to prescribe antipsychotics to control psychosis, standing rather than pro re nata (prn) doses should be used. In the case of elderly patients with dementia, antipsychotics must be prescribed at the lowest effective dosage and for the shortest period possible. If once these drugs are prescribed, the severity and frequency of symptoms, the global functioning and quality of life must be always monitored during treatment.

Frist, the choice of the antipsychotic drug is linked not only to the characteristics of the patient, to the severity of symptom, but to the particular condition being treated, comorbid medical conditions that might limit the use of certain drugs, prior response to treatment, and the potential for non-compliance (Table 2). Careful assessment of risks and benefits is required. Second, the therapeutic approach has to take into account the specific efficacy of each antipsychotic drug in the

Table 2. Specific recommended antipsychotics for specific patient groups

Specific conditions	Recommended antipsychotics
Hypotension	Avoid low-potency agents, clozapine, and risperidone Consider aripiprazole
Orthostasis	Avoid low-potency agents, clozapine, and quetiapine Consider aripiprazole
QTc prolongation	Avoid thioridazine and ziprasidone Consider olanzapine
Diabetes	Avoid clozapine and olanzapine Consider aripiprazole
Hyperlipidemia	Avoid clozapine and olanzapine Consider aripiprazole
Hepatic insufficiency	Reduce antipsychotic dose
Renal insufficiency	Antipsychotic dose adjustment generally not required
Glaucoma	Avoid thioridazine and clozapine Consider aripiprazole, risperidone, and quetiapine
Obesity	Avoid clozapine and olanzapine Consider aripiprazole and molindone
Prostatic hyperplasia	Avoid thioridazine, clozapine, and olanzapine Consider aripiprazole, risperidone, and quetiapine
Parkinsonism	Avoid haloperidol and risperidone Consider low-dose clozapine and quetiapine
Tardive dyskinesia	Avoid conventional antipsychotics Consider clozapine, olanzapine, quetiapine, and aripiprazole
Dry mouth	Avoid thioridazine and clozapine Consider aripiprazole, risperidone, and quetiapine

QTc: corrected QT interval.

Table 3. Factors to be assessed before prescribing an antipsychotic drug

Inquiry about medical conditions (presence of cardiovascular disease, renal/hepatic dysfunction, metabolic abnormalities, drug treatments and drug allergies, current health status)
Electrolyte imbalances (i.e., hypokalemia)
Familiar history for torsades des pointes
Concurrent use of drugs able to lengthen QTc interval on electrocardiogram
QTc: corrected QT interval.

different diseases occurring among the elderly patients.

Pretreatment evaluation

Antipsychotics should be used when BPSD are not effectively controlled by all the non-pharmacological measures. Therefore, before antipsychotic treatment, the possible trigger factors (fever, constipation, urinary retention, pain, hunger, neurosensitive deficits) should be explored and controlled. One also needs to exclude environmental (i.e., strong lights, noise, etc.) and iatrogenic factors (i.e., use of anticholinergics, benzodiazepines).

Prior to initiating treatment with an antipsychotic medication, the patient should be assessed for movement disorders, orthostatic blood pressure and pulse, and the following baseline laboratory studies should be checked: fasting blood sugar, lipid battery, white blood cells (WBC) count with differential, liver function battery, and electrocardiogram with corrected QT interval (QTc) read or calculated. Table 3 reports the factors to be assessed before prescribing an antipsychotic drug.

Dose and dose titration

There are generally two thresholds for stopping dose titration; either a satisfactory response is acquired, or distressing adverse effects occur. Depending on the pharmacodynamics and pharmacokinetic interactions between the antipsychotic and the individual patient's central nervous system and clinical status, doses higher or lower than those recommended in clinical trials may be required to achieve a therapeutic response. This may be more likely in patients not generally accepted into clinical trials, because of extreme elderly, medical co-morbidities, or taking multiple medications.¹⁸

For all elderly patients with dementia, antipsychotic dose is started at the lowest feasible dose, and some patients are sufficiently controlled by this minimum dose. Others will require upward dose titration, depending on factors such as age, renal function, hepatic function, and diagnosis. In general, dementia-related psychotic symptoms require lower doses of antipsychotics than those with schizophrenia.¹⁹⁻²¹

In younger patients with schizophrenia, antipsychotic are

generally titrated as rapidly as tolerated to target doses presumed to be therapeutic. In practice, initial titration usually proceeds at a rate of one to two dose increases per week. For frail elders or those who are medically compromised, titration should be even slower. For medications with a wide dosing range (e.g., low potency drugs like quetiapine), increases are made after the steady state target dose is attained in order to avoid overshooting the minimal therapeutic dose for the individual patient. During the initial stages of antipsychotic dose titration, it may be advisable to split doses (two to three times a day) or retarded formulation to minimize problems from side effects such as orthostatic hypotension and sedation. For clozapine, quetiapine, ziprasidone, and low-potency typical agents, continued divided dosing (usually two times a day) may be recommended. For olanzapine, risperidone, aripiprazole, and high-potency typical antipsychotics, single bedtime doses may be used.²²

Drug level

In schizophrenia, the therapeutic drug-level of clozapine, haloperidol, fluphenazine, thiothixene, and perphenazine were established, but whether these therapeutic drug levels are equally applicable to the elderly patients with dementia are uncertain. However, extreme values of serum level may be helpful to monitor the elderly patients with dementia: a zero level could confirm suspected noncompliance; conversely, a very high level could confirm suspected toxicity. Therefore, if clinically the non-compliance or toxicity are suspected, checking drug level may be helpful.

Managing treatment resistance

Initial management of apparent treatment resistance follows a logical sequence of confirming the diagnosis, ruling out comorbid substance abuse or other confounding conditions, ascertaining compliance, and adjusting the medication dose. Dose adjustments should be usually made on the basis of clinically observed therapeutic effects and adverse effects, but drug levels can be checked to determine extreme values (zero or far above therapeutic range). The patient experienced EPS or akathisia due to antipsychotics may benefit more from a dose decrease than a dose increase, since the adverse effect can be overwhelming the therapeutic benefit.

Until now, clinical guideline for treatment resistance in elderly patients with dementia is not yet established. In schizophrenia, if true treatment resistance is occurred, antipsychotics should first be switched to another atypical agent other than clozapine and maintained on an adequate dose of that agent for 6–12 weeks. If there is a partial response, the trial should be maintained up to 16 weeks. If there is still an inade-

quate response, a trial of clozapine should be considered. This trial should be continued, if possible, for a period of 6–12 months. Adjunctive therapies such as mood stabilizers could be used to augment a partial response.¹⁵

Switching antipsychotics

If patients do not respond to dose adjustment of antipsychotics and modulation of other aggravating factor, then the clinician should consider switching antipsychotics. However, switching antipsychotics can be a potentially destabilizing event. The risk for rebound and withdrawal phenomena is greatest when the pre- and post-switch antipsychotics are considerably different regarding binding affinity for specific receptors (i.e., pharmacodynamic rebound) or regarding their respective half life (i.e., pharmacokinetic rebound).²³ When one antipsychotics are switched to another, it is generally safer to taper and discontinue pre-switch antipsychotics before starting the second. When this is not clinically feasible because of severe psychotic symptoms, the post-switch drug can be added to the pre-switch drug, which can then be tapered and discontinued (cross-tapering). During the course of antipsychotic cross-tapering, careful attention should be paid to potential adverse effects such as cardiac conduction dysfunction, orthostatic hypotension and EPS. One-step switching, in which the first antipsychotic is stopped and the second started (often at a therapeutic or near-therapeutic dose), has not been demonstrated to be safe in elderly patients. It has been reported to be done safely in nonelderly patients with aripiprazole.²⁴ It cannot be done with clozapine.

In the course of cross-tapering to switch from an antipsychotic (e.g., conventional) to other antipsychotics (e.g., atypical), the patients can be clinically aggravated as the cross-taper proceeds. In this case, it is not easy to know whether the problem is the decreasing level of previous drug, the increasing level of switching drug, or rebound phenomena. It is in these patients more than in those switched for lack of efficacy where rebound phenomena are readily noticeable. Of note, however, the clinician should not prematurely conclude that the apparent reduced efficacy or symptomatic worsening is definitely due to the lack of efficacy of the newly initiated antipsychotic. Rather, intra-switch pharmacokinetic or pharmacodynamic rebound phenomena should be also considered. These can be managed by slowing down the switch schedule, which can maintain a sufficient dopamine blockade during the switch. Maintenance of sufficient blockade of dopamine or other relevant receptors can be achieved by either increasing the pre-switch antipsychotic back to a higher level and/or increasing the newly initiated antipsychotic to a more therapeutic dose. Alternatively, calming medications, such as ben-

zodiazepines, medications with antihistaminic effects, sleep aides, etc. can be given transiently to overcome potentially concerning or destabilising, but frequently transient rebound phenomena. The easiest way to minimize the chance for adverse events during a switch between antipsychotics that differ strongly pharmacokinetically or pharmacodynamically is to implement an overlapping or “plateau” cross titration or switch.

If clinically possible, it may be best to complete the cross-taper to give the second medication an adequate trial as monotherapy. This is consistent with current guidelines advocating antipsychotic monotherapy as the gold standard of treatment. Although the combination of a conventional and an atypical antipsychotic is not recommended in the treatment of elderly patients with dementia, it is sometimes used if the clinical response is not adequate in monotherapy.

Duration of treatment

The usual duration of antipsychotic medication treatment is various. The duration of treatment is practically indefinite in primary psychosis like schizophrenia and delusional disorders. Elders with schizophrenia are best maintained long-term with a stable, low dose of antipsychotic—preferably an atypical agent. For elderly patients with dementia, the usual duration of treatment is 3 months. After this time, periodic evaluation of the necessity of antipsychotics should be done and attempts to reduce the dose of the antipsychotic medication are recommended and most patients are controlled even in minimal dosage of antipsychotics. Unless adverse effects necessitate abrupt discontinuation, dose reduction should proceed slowly to minimize withdrawal symptoms.

Conventional antipsychotics given at the recommended geriatric (low) doses should be tapered over 2 weeks, at a minimum. Clozapine withdrawal should be carefully proceeded because of the anticholinergic and antiadrenergic activity as well as by the potential for rebound psychosis, such that the taper is best performed over a minimum of 4 weeks in elderly patients. An only slightly less protracted withdrawal period may apply to thioridazine because of its anticholinergic properties.

ANTIPSYCHOTICS USE IN SPECIFIC CONDITION OF ELDERLY PATIENTS

Rapid tranquilization

‘Rapid tranquillisation’ is a commonly practiced in patients with BPSD. The Royal College of Psychiatrists takes for its definition and its clinical guidance on managing violence: ‘All medication given in the short-term management of disturbed/

violent behavior should be considered as part of rapid tranquillisation.²⁵ The management of violence in patients with dementia should be a diagnosis-driven, and medication should be targeted not at the behavior itself, but at the underlying pathophysiology. According to this view, though, the pathophysiology of violent behavior is not completely understood in BPSD, antipsychotics, especially conventional antipsychotics (e.g., haloperidol injection) is justifiable in aggressive patients associated with BPSD. These usages can not only target the underlying pathophysiology, but also augment the previously prescribed antipsychotics. These treatments may be useful for patients with minimal effective dose, and presenting intermittent burst of psychotic episodes.

Delirium

Before symptomatic care of delirium, definitive treatment of the cause of delirium (e.g., correction of hyponatremia or treatment of urinary tract infection) should take precedence over symptomatic treatment. Antipsychotic medications can be used to treat psychosis (hallucinations, delusions, or thought disorganization) or severe and persistent agitation in the delirious patient when these symptoms cause suffering and pose a danger. Though, there is currently no consensus clinical guideline as to which antipsychotic agent is preferred; the most commonly used drugs are haloperidol, quetiapine, and risperidone.

Delirium is the only medical condition in geriatrics for which a conventional antipsychotic (haloperidol) continues to be used routinely. In the medically frail patients, haloperidol is useful because this has no significant hemodynamic effects at usual therapeutic doses, little or no respiratory depression, little effect on glucose regulation, and availability in intravenous form (so that low doses can be used with good effect and little adverse effect). A recent study reported an association of haloperidol use with lower hospital mortality in mechanically ventilated patients.²⁶ Haloperidol is also less expensive than comparator drugs. The disadvantage of haloperidol is that high doses can prolong the QTc interval. In addition, this drug can cause well-documented EPS, neuroleptic malignant syndrome and tardive dyskinesia when used long-term. These risks have been thought to be lower for the atypical agents.

The advantage of quetiapine is that it is highly sedating, and thus can calm down agitated patients with delirium, but this medication can result in overly sedating in the frail elderly patient. In addition, quetiapine can cause hypotension and glucose dysregulation, even with short-term use. Risperidone can be effective in reducing psychosis and agitation in delirium when dosed appropriately. Unfortunately, this medication is too often dosed and titrated as it is for the younger population,

resulting in akathisia in the delirious elder. Risperidone also can cause hypotension.

Regardless of which agent is used for the treatment of delirium, the duration of treatment should be limited; the medication should be used until symptoms abate and then should be tapered off over 3–5 days.

Dementia

BPSD may be the consequence of secondary to cognitive impairment or underlying primary pathological abnormalities, which change the clinical expression of dementia.²⁷ Agitation frequently occurs in dementia and antipsychotics can be effective, even if their use is off-label. A review performed in 2012 comparing the efficacy of off-label use of atypical antipsychotics in dementia suggested that olanzapine, aripiprazole, and risperidone have a moderate-to-high efficacy in agitation.¹⁵ Although the use of antipsychotics for dementia is off-label, antipsychotics is probably the best option for short-term treatment (6–12 weeks) of severe, persistent, and resistant aggression.²⁸ Serious possible adverse events are a major limitation to long-term therapy, thus recommending that dosage be decreased and treatment discontinued whenever behavioral symptoms have been sufficiently controlled. At present, olanzapine, quetiapine, and risperidone present the similar efficacy in acute stages of disease, without inducing the less neurological adverse effects, which frequently seen in haloperidol.

Conventional antipsychotics have been widely used for BPSD, even if some studies showed an efficacy comparable to placebo.^{3,4} Atypical antipsychotics (in particular risperidone and olanzapine) showed an efficacy superior to placebo in randomized studies in BPSD treatment, with a better tolerability profile versus conventional drugs.^{1,3,5,29,30} Such tolerability profile is due to their characteristic mechanism of action,^{4,6,7} as previously described. Eleven randomized, placebo-controlled trials were carried out using conventional antipsychotics for the treatment of BPSD; they mostly involved small sample sizes and were performed over periods of 4 and 12 weeks (only 1 up to 16 weeks' duration).^{28,31–33} A significant but modest advantage over placebo for behavioral symptoms has been reported (59% vs. 41%).²⁸ Some trials showed a significant improvement in aggression with haloperidol compared with placebo, but not in other symptoms of agitation. However, the use of typical antipsychotics is limited by the several severe adverse effects, such as parkinsonism, tardive dyskinesia, dystonia, and QTc interval prolongation. Furthermore, the use of several drugs in elderly patients, who are often affected by a number of comorbidities, raises the risk of drug interactions and consequent fatal adverse events.⁵ The QTc interval prolongation was most often reported following

the use of thioridazine and droperidol, both of which have been withdrawn.

Eighteen placebo-controlled studies have examined the efficacy of atypical antipsychotics in patients with Alzheimer's dementia (AD) over a 6- to 12-week treatment period. Among them, only 3 trials were carried out for 6 to 12 months.³⁴⁻³⁷ Meta-analyses have been conducted of risperidone and aripiprazole and showed the efficacy of these agents in the short-term management (6–12 weeks) of aggression.^{35,36} Both atypical drugs showed similar benefit. In other atypical antipsychotics (such as clozapine, sertindole, zotepine, amisulpride), no trials have investigated in AD yet.²⁸

Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) was a cornerstone clinical study performed in 421 elderly AD outpatients with psychosis or agitated/aggressive behavior from 45 centers.³⁸ The purpose of this study was to compare the effectiveness and adverse events of atypical antipsychotics and placebo in patients with AD and psychosis or agitated/aggressive behavior. The patients were randomly allocated into groups receiving olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks. The primary end point was the medication discontinuation time for any reason (phase 1). The secondary end points were improvement on the Clinical Global Impression of Change scale and the medication discontinuation time due to ineffectiveness or intolerance. This study revealed that olanzapine and risperidone were significantly more efficacious than quetiapine and placebo when the discontinuation time of treatment due to a lack of efficacy was analyzed (22.1 and 26.7 weeks with olanzapine and risperidone, respectively, vs. 9.1 and 9.0 weeks with quetiapine and placebo, respectively). The placebo group was superior to the 3 drugs on the analysis of treatment interruption due to intolerability.

This trial demonstrated that these drugs showed a high rate of adverse events and this can offset their efficacy, but some portion of patients can be benefited without adverse symptoms.³⁸ Furthermore, secondary analysis of CATIE-AD results showed that risperidone was effective in a variety of behavioral areas compared with placebo at the time of discontinuation, whereas patients medicating olanzapine improved in areas of hostility and suspiciousness, but they showed a worsening of depressive symptoms compared with placebo.³⁹

The results of the CATIE-AD have provoked the hot debate about the role of atypical antipsychotics in influencing cognitive performance in patients with AD. Some trials show that risperidone reduces the Mini-Mental State Examination scores in a statistically significant way compared with placebo, which is not the case with olanzapine and quetiapine. On the contrary, other trials indicate that quetiapine and olanzapine are

responsible for the greater cognitive decline. The samples of individual clinical trials are not enough to determine whether the cognitive decline varies with antipsychotic use; however, this decline has been evident for all the molecules compared to placebo.⁴⁰

A 2006 Cochrane Collaboration review of placebo controlled trials concluded that risperidone and olanzapine may improve aggression compared with placebo and risperidone that may improve psychosis relative to placebo.⁴¹

SAFETY OF ANTIPSYCHOTICS

It has long been recognized that conventional antipsychotics can increase the risk of EPS and tardive dyskinesia in elderly patients, so atypical antipsychotic has gradually replaced conventional antipsychotics in elderly patients. In 2002, however, the first warning for possible cerebrovascular events due to risperidone and olanzapine was reported.^{1,8} At that time, this alert was reported only for risperidone and olanzapine although a similar warning was later released for aripiprazole. The possible deaths related to the use of atypical antipsychotics were published three years after this first official warning.⁹ Finally, several studies also reported severe adverse events and death following conventional antipsychotics use. These studies have ignited a very hot debate in the medical community. Some authors argued these alerts on atypical antipsychotics usage as unnecessarily alarming and potentially detrimental for patients with dementia.⁴² Other researchers instead were concerned that there was no clear evidence to support a greater benefit with atypical relative to conventional antipsychotics.⁴³ Conventional antipsychotics, as well as atypical ones, may increase the risk of death in elderly people; therefore, they should not be used in their stead according to Food and Drug Administration (FDA).^{2,3,44,45} On the other hand, even the risk of stroke is not lessened by using conventional antipsychotics.⁴⁶ Although investigations and debates have continued regarding these issues, the FDA now requires boxed warnings for atypical antipsychotics regarding increased risk of mortality in elderly patients with dementia. In 2008, the FDA extended this warning to a conventional antipsychotics.^{10,11} A more in-depth look at all data is necessary, to better clarify which patients are more at risk for developing cerebrovascular adverse events and for comparing the risk profile with patients treated with placebo or other atypical or conventional antipsychotics.

Risk of overall death

A meta-analysis performed in 2005 including 17 placebo-controlled studies of 4 drugs (risperidone, olanzapine, quetiapine, and aripiprazole) enrolled a combined 5110 elderly pa-

tients with dementia.⁹ Studies revealed a 4.5% mortality rate among patients who had been treated with atypical antipsychotics and have demonstrated an approximately 1.6–1.7 fold increase compared to placebo treated patients in mortality in these studies. Cardiac (i.e., heart failure and sudden death) or infectious (pneumonia) events were the main causes of death.^{9,44}

However, other meta-analysis of randomized controlled trials³⁶ also found that haloperidol was associated with about 2-fold increased mortality versus placebo. A number of observational studies have been completed in the last few years^{2,3,41,44,47} and these studies also showed that the risk was even higher than that associated with the use of atypical drugs. A retrospective cohort study based on health insurance database on 22890 patients 65 years or older showed that conventional antipsychotics were associated with a significantly higher risk of mortality than were atypical antipsychotics at all intervals studied. The risk of death was higher within the first 40 days and with higher dosages of conventional antipsychotics.³ Similarly, Liperoti et al.⁴⁴ showed that, among 6524 new users of atypical antipsychotics and 3205 new users of conventional antipsychotics residents of nursing homes in 5 US states during the years 1998–2000, the rate of death was 22% higher for users of conventional versus atypical antipsychotics [hazard ratio, 1.26; 95% confidence interval (CI), 1.13–1.42]. A retrospective cohort study of 37241 elderly people residents in British Columbia showed a greater incidence in mortality associated with high dosages of typical antipsychotics and during the first 40 days of treatment.⁴⁸ A population-based cohort study of data on Medicaid, Medicare, the Minimum Data Set, the National Death Index, and a national assessment of nursing home quality was carried out to evaluate the risks of mortality associated with the use of antipsychotic drugs in elderly nursing home residents. The study was performed on 75524 elderly patients with behavioral disorders who were treated with haloperidol, aripiprazole, quetiapine, risperidone, olanzapine, and ziprasidone. The risk of mortality increased following higher doses of these drugs and was highest with haloperidol and least for quetiapine.⁴⁵

On the other side, a nested case-control study on 2385 elderly demented patients from the Dutch general practice database reported no statistically significant differences in the risk for all-cause mortality among users of conventional and atypical drugs.⁴⁷ Similarly, a retrospective cohort study of Medicaid patients in Tennessee of 44218 and 46089 baseline users of single typical and atypical drugs, respectively, and 186600 matched controls of antipsychotic drugs revealed higher rates of sudden cardiac death for users. Former users of antipsychotic drugs had no significantly increased risk. For both classes of drugs, the risk for current users increased signifi-

cantly with an increasing dose.² The risk is increased in elderly patients for the high number of drugs taken for comorbidities.

Cardiac effects

Cardiac adverse effects including sinus tachycardia, atrial and ventricular extrasystoles, QTc interval prolongation, T-wave inversion, ST-segment depression, and atrioventricular blocks have been reported for atypical and conventional antipsychotics.^{48,49} Among them, QTc prolongation associated with antipsychotics is most clinically worrisome for frail elderly patients.⁵⁰ As shown in Fig. 2, the QT interval spans the time from the start of ventricular depolarization (the Q wave of the QRS complex) to the end of ventricular repolarization (the T wave). The QT shortens as the heart rate increases and is corrected for heart rate (QTc) by one of several algorithms. The Bazett correction is most widely used formula and this is defined as $QTcB = \frac{QT}{\sqrt{RR}}$. Usually, QTc prolongation results from delayed repolarization, which may enable early after-depolarizations to occur and set the stage for extrasystoles and eventual torsades de pointes. QTc prolongation is defined as a QTc value >450 ms for men or >470 ms for women.⁵¹ The QTc intervals >500 ms are particularly worrisome, since they are associated with a significant risk of ventricular dysrhythmia, torsade de pointes and sudden death.^{52–54} Antipsychotic medications are known to affect the QTc in a dose and level-dependent manner.⁵¹ In one large epidemiologic study, patients taking antipsychotics in dose-equivalents of more than 100 mg thioridazine had a 2.4-fold risk of sudden death.⁵⁵ Pfizer/FDA reported that thioridazine had the greatest risk of prolonging QTc, following in descending order by ziprasidone, quetiapine, chlorpromazine, risperidone, olanzapine, aripiprazole, and haloperidol. Indeed, some epidemiologic studies have widely shown the direct relationship between conventional antipsychotics and the risk of sudden death;^{2,56} the risk is also increased with higher doses, both for conventional and atypical antipsychotic drugs² and with concurrent treatments in elderly people. Table 4 reports the degree of QT prolongation by antipsychotic drugs.^{53,57,58} Fig. 3 reports a practical algorithm expressing arrhythmogenic hazard risk according to QTc values.⁵⁹ Moreover, the studies on antipsychotic drugs have shown that atypical medications appear to be more “cardiosafe” than conventionals; only clozapine has been linked to serious cardiac adverse effects, such as myocarditis.⁵

Liperoti et al.⁶⁰ conducted a case-control study among nursing home residents in 6 US states using the Systematic Assessment of Geriatric drug use via Epidemiology database. Cases were residents hospitalized for ventricular arrhythmias or cardiac arrest between July 4, 1998, and December 30, 1999. The sample consisted of 649 cases and 2962 controls. The use

of conventional antipsychotics was associated with a nearly 2-fold increase in risk of hospitalization for ventricular arrhythmias or cardiac arrest [adjusted odds ratio (OR), 1.86; 95% CI, 1.27–2.74]. There was no increased risk associated with the use of atypical antipsychotics (OR, 0.87; 95% CI, 0.58–1.32). The risk of hospitalization for ventricular arrhythmias or cardiac arrest was 3.27 times higher among conventional users with cardiac disease (95% CI, 1.95–5.47).⁶⁰

Urgent treatment of prolonged QTc includes discontinuing all offending medications; suppressing early after-depolarizations by administration of intravenous magnesium, potassium, and lidocaine; and increasing the heart rate to shorten the QT interval by pacing or administration of isoproterenol. The patient may require sedation during the treatment period.

However, a recent article by Pariente et al.⁶¹ has shown that antipsychotic use is associated with a modest and time-limited increase in the risk of myocardial infarction among community-dwelling older patients treated with cholinesterase inhibitors. The risk is higher in the first 30 days of treatment (hazard ratio, 2.19; 95% CI, 1.11–4.32) and decreases over time.

Some of the atypical drugs were reported to cause congestive heart failure; however, this effect occurred infrequently following olanzapine (1/100 and 1/1000) and rarely following clozapine and quetiapine (<1/1000). Hypotension is a common adverse effect encountered with atypical drugs, especially following clozapine (9%), quetiapine (7%), and risperidone

and olanzapine (5%); ziprasidone and haloperidol rarely cause hypotension (1% of the cases reported).⁶² Therefore, this adverse effect has to be taken into account in elderly patients treated with antihypertensive drugs, for the possible pharmacodynamic interaction.

Cerebrovascular risk

Though, the FDA has issued a warning for stroke risk among elderly patients with BPSD who are medicated with risperidone, olanzapine, or aripiprazole, it is not yet clear whether other atypical or conventional antipsychotics should be included in this warning. A retrospective cohort study on 11400 people older than 65 years pooled results from 11 randomized controlled trials; it revealed increased incidences of cerebrovascular adverse events compared with placebo. Other studies reported a similar risk of stroke among users of both conventional and atypical antipsychotic drugs.^{63,64} Interestingly, differential risk was reported for subgroups of conventional antipsychotics, such as phenothiazines and butyrophenones compared with benzamides and atypical antipsychotics.⁴⁵ On the contrary, a UK-based electronic primary care records in the general practice research database reported that all antipsychotics are associated with an increased risk of stroke. The risk might be higher in patients receiving atypical antipsychotics than those receiving typical antipsychotics and in people with dementia compared with people without dementia.⁶⁵

Table 4. Degree of QT prolongation according to antipsychotics

Range	High	Mid	Low
Conventional antipsychotics	Thioridazine	Chlorpromazine	Haloperidol
Atypical antipsychotics	Ziprasidone	Quetiapine	Risperidone Clozapine Olanzapine Aripiprazole

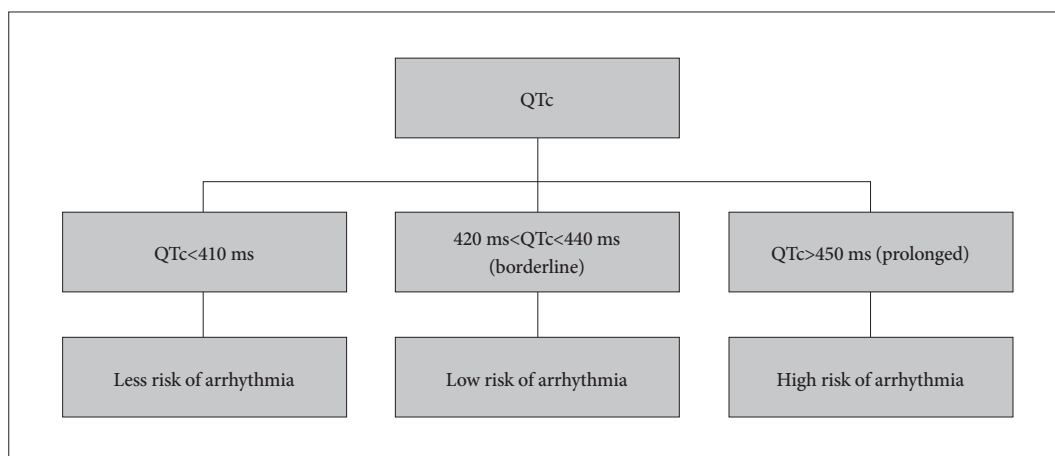


Fig. 3. Arrhythmia risk based on QTc values. QTc: corrected QT interval.

Potential mechanisms of stroke by atypical antipsychotics suggest cardiovascular effects (e.g., orthostatic hypotension, arrhythmias), thromboembolic effects, excessive sedation resulting in dehydration, and hemoconcentration and hyperprolactinemia.⁶⁶ In particular, α_1 -receptor blockade may cause orthostatic hypotension and tachycardia. Elderly people with a preexisting cerebrovascular disease might experience a transient ischemic attack or even a cerebrovascular adverse event as a consequence of hypotension, which on its turn worsens the deficit in cerebral perfusion.⁴⁸ Also, the rebound excess of catecholamines following orthostatic hypotension may cascade the consequent vasoconstriction and further aggravation of cerebral vascular deficit.

Other putative mechanisms are thromboembolism and hyperprolactinemia. Thromboembolism is probably related to immobility due to sedation for H1 receptor blockade; this enhances venous stasis, dehydration, and the consequent hemoconcentration. Hyperprolactinemia is frequently associated with the increase in endothelial dysfunction, platelet aggregation, and the decrease in insulin sensitivity.

Neuropsychiatric symptom

EPSs are by far more common in elderly demented patients because brain levels of dopamine are usually decreased in these patients. A substantial amount of literature supports the belief that EPS is occurred significantly lower in atypical antipsychotic agents than typical agents.⁶⁷ Because of the dose-dependent D2-receptor blockade, among atypical antipsychotics, risperidone is associated with the highest risk, whereas clozapine and quetiapine are associated with the lowest risk of EPSs.⁶⁸ Risperidone is poised between the typical and atypical agents in its extrapyramidal profile; at doses above 4 mg in elders, it may have effects as pronounced as those of the conventional agents, whereas at low doses (1 mg/day or less), it has little extrapyramidal effect, except perhaps akathisia. The EPS in elderly patients tend to differ clinically from that found in younger populations. The risk of akathisia and dystonia decreases with age, with a rate of 3% and 15% respectively found in those over 65 years of age.⁶⁹ On the other hand, drug-induced parkinsonism is more common among antipsychotic treated elders. This syndrome resembles idiopathic parkinsonism, with symptoms of bradykinesia, rigidity, impaired righting reflex, dysphagia, sialorrhea, autonomic instability, and even seborrhea. Symptoms do not usually occur immediately, but after 1–2 weeks of treatment.⁶⁹

When EPS is developed in antipsychotic-treated elderly, discontinuing or lowering the dose of medication or switching to an atypical agent should be tried. If the offending antipsychotic is discontinued, EPS are usually improved within several

weeks, but in some cases, signs and symptoms persist for a year or more. If parkinsonism is persisted, amantadine, dopamine reuptake blocker and D2 receptor agonist, can be used.

Tardive dyskinesia is an abnormal involuntary movements associated with antipsychotic medication treatment. This occurs more frequently among elderly patients, women, and patients with diabetes. All conventional and all atypical antipsychotics have been reported in association with tardive dyskinesia, but the risk introduced by atypical antipsychotics appears to be lower than the risk with conventional agents. As regards tardive dyskinesia, the use of atypical antipsychotics is associated with an incidence of 1% per year compared with 5% for conventional drugs.⁷⁰

Anticholinergic effects

Peripheral cholinergic receptor blockade result in tachycardia, dry mouth, blurred vision, exacerbation of glaucoma, constipation, and urinary retention, any of which could be troublesome in the elderly patient. Central muscarinic receptor blockade cause drowsiness, irritability, disorientation, impaired memory and other cognitive dysfunction, aggressiveness, and delirium. The patients with Alzheimer's disease, dementia with Lewy bodies characterized by cholinergic hypofunction are likely to be particularly affected. If these symptoms are misdiagnosed as a new-onset or exacerbating psychosis, the dose of antipsychotic may be increased, resulting in a vicious worsening cycle. Among conventional antipsychotics, chlorpromazine, thioridazine, and mesoridazine are the most anticholinergic, and among atypical antipsychotics, clozapine and olanzapine are the most anticholinergic. Although in younger patients the anticholinergic effects of olanzapine are considered negligible at usual therapeutic doses, this may not be the case in the elderly patients, particularly among those affected with dementia.⁷¹

Metabolic effects

Metabolic risk (weight gain, diabetes, obesity, dyslipidemia, metabolic syndrome) is another important adverse events of atypical antipsychotics.^{4,5} Weight gain is especially observed during the first 4 to 12 weeks of treatment following most of the atypical antipsychotic drug use.^{4,5,64,72–74} After this phase, weight gain continues, but at a slower rate or even stabilizes, whereas it continues over a long period following clozapine and olanzapine.⁷² Weight gain might be the result of increased food intake, due to the possible drug interactions with neuronal dopamine, serotonin, and histamine1 receptors.⁶⁸ Obesity might also be the result of 5-HT₂ receptor blockade by atypical antipsychotic drugs.

A number of studies have reported that both conventional

and atypical antipsychotic drugs may increase the plasma glucose level in patients with or without a prior history of diabetes mellitus.^{4,5,75-77} This especially occurs with regard to olanzapine and clozapine and in elderly patients for the previously mentioned reasons. Clozapine and olanzapine are associated with, respectively, a 1.4- and 1.3-fold higher risk of diabetes than conventional antipsychotics, whereas the relative risk appears to be slightly lower following quetiapine and risperidone.⁷⁵ The suggested mechanisms other than weight gain have been postulated in elderly patients:^{4,5} histamine H1-receptor antagonism, serotonin 5-HT_{2C}-receptor antagonism, reduced responsiveness of pancreatic cells, pancreatic cell damage and, as a consequence, reduced insulin secretion, and increased insulin resistance.

Some antipsychotics can also cause hypertriglyceridaemia.^{4,5,78-80} This is more evident following olanzapine and clozapine use in the elderly.⁸¹ In a retrospective chart reviewed comparative study, treatment with various antipsychotics resulted in high triglyceride serum levels in 56% of clozapine, 39% of olanzapine, and 21% of risperidone compared with none of haloperidol and 8% of fluphenazine-treated patients.⁸⁰ As shown by Koro et al.,⁸² there was a 3-fold higher risk of hyperlipidemia related to conventional antipsychotics compared with a control population without antipsychotic exposure.

Conversely, Rondanelli et al.⁸³ suggested that the treatment with low dose of atypical antipsychotics is not associated with weight gain or increased risk of diabetes mellitus or lipid metabolism abnormalities. The study involved only 36 patients affected with Alzheimer disease. A study on 95 patients affected with dementia receiving mostly olanzapine or risperidone showed no effect on any of the parameters of the metabolic syndrome based on the National Cholesterol Education Program Adult Treatment Panel III criteria.⁸⁴

The CATIE-AD showed a clear effect of all atypical antipsychotic drugs to increase weight gain and body mass index, with olanzapine having the greatest risk followed by risperidone. On the contrary, no effect was shown on glucose, total cholesterol, and triglyceride levels.³⁸

Hematologic effects

A decline in WBC counts can be seen with typical antipsychotics, particularly low-potency phenothiazines. Agranulocytosis (absolute neutrophil count <500/mm³), a potentially fatal condition, is associated with clozapine^{4,5} and much rarer with other phenothiazines (chlorpromazine, fluphenazine, perphenazine, thioridazine, and trifluoperazine). Some cases of olanzapine- and risperidone-induced neutropenia and agranulocytosis have also been reported.⁸⁵ In a study by Rettenbacher et al.⁸⁵ neutropenia (neutrophil count <2000/HL) was found

in the mixed group in 17.6% and in 11.8% of patients treated with clozapine during the first 6 months. There was no statistically significant difference between those groups with respect to the risk of developing neutropenia during the investigation period. However, there was no case of agranulocytosis, and neutropenia was transient in all patients. Eosinophilia occurred in some patients who developed neutropenia later on but had no significant predictive value. Another case of quetiapine-induced neutropenia was recently described.^{86,87} The risk of agranulocytosis with clozapine and other medications is highest in the first few months of treatment, but it can occur at any time and is not a dose dependent development. The overall risk is less than 1% but may be higher in the elderly patients.

Other effects

Pneumonia, deep venous thrombosis are recently found adverse effects. Age-related functional dependence and hematologic changes make these effects more apparent in elderly demented people. A population-based, nested case-control study by Trifirò et al.⁸⁸ was conducted on a cohort of people older than 65 years who used an antipsychotic drug, who were registered in the Dutch Integrated Primary Care Information database from 1996 to 2006. The study showed that the elderly patients with taking either atypical or typical antipsychotic drugs are associated with risk for community-acquired pneumonia in a dose dependent manner. The risk is high when treatment is started, and rapidly disappears when treatment is stopped. In particular, 25% of the case patients died in 30 days, and their disease was considered fatal. Current use of either atypical (OR, 2.61; 95% CI, 1.48–4.61) or conventional (OR, 1.76; CI, 1.22–2.53) antipsychotic drugs was associated with a dose-dependent increase in the risk for pneumonia compared with past use of antipsychotic drugs. The incidence rates of pneumonia were similar during past use of atypical and typical antipsychotic drugs, which supports the notion that the risk difference between the 2 classes was minimal. Only atypical antipsychotic drugs were associated with an increase in the risk for fatal pneumonia (OR, 5.97; CI, 1.49–23.98).

Pneumonia risk might be due to the anticholinergic action and antihistaminic H1-receptor blocking effect of antipsychotic drugs (more evident for some of these antipsychotic drugs). In fact, the anticholinergic effects may be responsible for dryness of mouth, impaired oropharyngeal bolus transport, dysphagia, and, as a consequence, aspiration pneumonia.⁸⁸ Furthermore, sedation as a result of H1-receptor blocking in the central nervous system is a well-known cause of swallowing problems, which could cause aspiration pneumonia. In fact, antipsychotic drugs with higher H1-receptor affinity, such as

phenothiazines, show increased risk for pneumonia compared with butyrophenones.

Also the use of conventional antipsychotic drugs may be a risk factor for aspiration pneumonia, because of such extrapyramidal effects as akinesia, and the adverse effect is by far more evident in elderly demented people who can experience dysphagia, especially in the late stages of dementia.

There is an association between the use of antipsychotic drugs and the risk of venous thromboembolism (VTE).^{89,90} In a large primary care population composed of 25532 eligible cases (15975 with deep vein thrombosis and 9557 with pulmonary embolism) and 89491 matched control subjects from a study population of 7267673, individuals who were prescribed antipsychotic drugs in the previous 24 months had a 32% greater risk of VTE than nonusers, despite adjustment for potential risk factors (OR, 1.32; 95% CI, 1.23–1.42).⁸³ The increased risk was more noted among new users and those prescribed atypical antipsychotic drugs.

Recent studies also showed an increased risk of pulmonary embolism with antipsychotic treatment, varying with type of antipsychotic drug and dependent on dose. Clozapine was associated with the highest risk.⁹¹ Atypical antipsychotic agents appear to increase the risk of VTE. However, these events are rare, and in clinical practice, the absolute risk should be weighed against the effectiveness of these medications in the elderly population. On the other hand, another study showed no evidence of an increased risk of VTE in elderly patients using antipsychotic drugs.⁹¹ The high risk for VTE is probably linked to the increase in platelet aggregation and to changes in fibrinolysis and coagulation.^{70,92} In particular, it is known that some conventional antipsychotics such as haloperidol, chlorpromazine, and fluphenazine increase platelet aggregation. Some atypicals such as risperidone, clozapine, and olanzapine can inhibit platelet 5-HT_{2A} receptors, thus modulating receptor density and affinity, even if they do not uniformly potentiate platelet adhesion and aggregation.⁹²

Atypical antipsychotics have a weak potential to cause hyperprolactinemia, except for risperidone and amisulpride. Plasma prolactin increase is usually dose related and is more common in women, but is independent of age.^{93,94} As previously mentioned, hyperprolactinemia is one of the suggested mechanisms for cerebrovascular effects induced by antipsychotics.

CONCLUSION

Treatment of behavioral disorders in dementia should initially consider non-pharmacological means. Should this kind of approach be unsuccessful, clinicians should consider start-

ing antipsychotics. Prescribing atypical antipsychotic drugs to elderly people is challenging due to the recent evidence of possible side effects; however, their rational use may improve the quality of life and functional status of elderly patients with BPSD.

In fact, elderly patients with dementia are at increased risk of adverse events due to antipsychotic drugs because of age-related changes in pharmacokinetics and pharmacodynamics and co-morbid medical conditions, polypharmacy, and potential drug interactions. FDA black box warnings have clearly demonstrated the potential risks of their use (e.g., cerebrovascular accidents, risk of sudden death). Furthermore, metabolic and other diverse adverse events can also be dangerous. Therefore, the use of antipsychotics in the elderly requires an individual assessment, case by case; particular caution is recommended.¹

Notwithstanding controversial data, antipsychotics are probably the best option for short-term treatment (6–12 weeks) of severe, persistent, and resistant aggression.²⁸ However, due to possible serious adverse events, long-term therapy is not recommended and clinician should decrease dosage and discontinue treatment wherever a sufficient control of behavioral symptoms has been obtained. Of course, should the therapeutic response be poor, switching to another antipsychotic drug is appropriate as well.

Regrettably, alternative drug treatments didn't prove any efficacy (i.e., trazodone; selective serotonin reuptake inhibitors such as citalopram; benzodiazepines; memantine; anticonvulsants such as valproate, carbamazepine, and topiramate). A study confirming all available data is strongly urged to better understand which patients may benefit and be at risk for adverse effects. We have to also take into account the possible drug-drug interactions involving antipsychotics, as well as the interactions with food and concomitant diseases. In fact, the interactions may potentially lead to the increase in antipsychotic plasma levels, thus possibly increasing adverse effects.

Antipsychotic drugs may increase the sedative effects of benzodiazepines, hypnotics, anesthetics, and antihistaminic agents. A number of diseases possibly accompanied by elderly patients with dementia might interfere with antipsychotics, for example, congestive heart failure, liver and kidney diseases, fever, anemia, change in antipsychotic pharmacokinetics, leading to the possible increase in their plasma levels and adverse effects.

Therefore, because elderly demented patients are often affected by concomitant diseases and are poorly treated, use of both conventional and atypical antipsychotics requires a careful case-by-case assessment.

Conflicts of Interest

The authors have no financial conflicts of interest.

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