CME

A Review of the Pharmacological Management of Cognition and Behaviour Problems in Older Adults with Advanced Dementia

The online component of this CME learning activity is offered under the auspices of the CE department of the University of Toronto. Participating physicians are entitled to one (1) MAINPRO-M1 credit by completing this program, found online at **www.geriatricsandaging.ca/cme_page.htm**

Medical management of Alzheimer's disease patients involves drugs that temporarily relieve or stabilize symptoms, or lessen the expected decline in cognition, function, and behaviour, but ultimately fail to halt progression of the disease. Commonly used agents in the management of early- to mid-stage dementias—albeit with modest outcomes—are the cholinesterase inhibitors (ChEIs). Antipsychotics have been used with mixed success to treat psychiatric symptoms that occur in 30–60% of patients with moderate-to-severe AD. In the terminal stages of dementia, palliation of symptoms and a focus on comfort care is important. Management of pain and relief from depression and anxiety are useful.

Key words: *dementia, Alzheimer's disease, cholinesterase inhibitors, behaviour, antipsychotics*

Ann Schmidt Luggen, PhD, GNP, *Professor, Department of Nursing and Health Professions, Northern Kentucky University, Highland Heights, KY; Gerontological Nurse Practitioner, Evercare, Cincinnati, OH, USA.*

Introduction

Dementia is a growing global health problem. Worldwide, 18 million people have dementia[1] and approximately 60–70% of adults aged 65 and over with dementia have Alzheimer's disease (AD).[3] Other common dementias include Lewy body dementia (DLB) and vascular dementia (VaD), and many patients have more than one form of dementia.

About four million people in the U.S., most of whom are 65 or older, have AD.[2] An estimated 420,000 Canadians over age 65 (or 8% of all seniors) have AD or a related dementia (NACA, 2005:2.1/2). Though the prevalence of AD doubles every five years after age 65 in the U.S., little is known about the pathophysiology and medical management of this disease. At best, we can treat AD patients with drugs that relieve some of the symptoms but fail to halt progression of the disease.[1]

Advanced Dementia

Symptoms of the advanced dementias are similar,[3] and in many cases it is difficult to distinguish between the different types. Patients have significant impairment of language skills with little meaningful speech; some of them become mute. It is common in the U.S. to place the older patient with advanced dementia in a long-term care facility, as she/he has difficulty with even the most basic activities of daily living (ADL). Many patients are unable to feed themselves and are incontinent of bladder and bowel. They become wheelchair bound and may become bed bound. Patients with advanced dementia have much comorbidity, such as malnutrition, pressure ulcers, and frequent urinary tract and pulmonary infections. Seizures may also be seen in late-stage dementia.[3]

Pharmacological Management of Dementia

Mild-to-Moderate Dementia

Commonly used agents in the treatment of primary symptoms of early- to mid-stage dementias—albeit with modest outcomes—are the cholinesterase inhibitors (ChEIs). At early stages of the disease, ChEIs act to improve or stabilize cognitive function and delay symptom progression by preventing the hydrolysis of acetylcholine (ACh) in the synaptic cleft. These agents do little to protect cholinergic neurons from cell death, though, and as the disease progresses and endogenous ACh levels decline, ChEIs become less effective. Second-generation ChEIs have been approved for the treatment of mild-to-moderate AD.

Cholinesterase inhibitors have shown some efficacy in forms of dementias other than AD. Galantamine, for example, has been shown to be effective in managing DLB.[4] Rivastigmine has been shown to improve cognition and behaviour in DLB,[5] as has donepezil in a small number of patients.[6]

The ChEIs are also effective in managing VaD. Donepezil has been reported to be efficacious in cases of cortical vascular and subcortical vascular dementia.[7] It has been reported to improve cognition, behaviours, and daily functioning, rather than stabilize or prevent decline as in AD. Galantamine has also been reported to be well tolerated and effective in maintaining cognitive function (Table 1).

Advanced Dementia

Many clinicians do not prescribe ChEIs for moderate-to-severe dementia because of the perception that they do not have efficacy in more severe AD.[8] Clinicians also often discontinue the use of ChEIs when their patients progress from the moderate to moderate-to-severe stages. However, several studies reported at an American Academy of Neurology (AAN) annual meeting reveal a newer perspective. One study from McGill Centre for Studies in Aging suggests that donepezil has clinically significant efficacy for patients with moderate-to-severe AD with Mini-Mental State Exam (MMSE) scores of 5–17.[9] Significant improvement, or less decline, in cognition occurred in a number of measures, including disability.

One controversial study found that at least one cholinesterase inhibitor (donepezil) was probably not cost effective and had minimal benefit to people with mild-to-moderate AD.[53] In the double-blind study, 565 community-based residents were randomized to donepezil 5 mg/day or placebo. Study endpoints were disease progression and placement in long-term care. There were no differences between the trial drug and placebo on the study endpoints.

Another report from the AAN meeting re-examined data from several large studies.[8] The studies of patients treated with rivastigmine or placebo found that rivastigmine efficacy was maintained in patients with mild, moderate, and moderate-to-severe AD.

Switching ChEIs is a strategy for improving control of symptoms in those patients who are intolerant of the initial drug or for whom the drug has been ineffective. A publication from Gauthier *et al.*[10] reports that, according to the data from a number of open-label studies, 50% of patients who lost efficacy with donepezil and were switched to rivastigmine responded to the second therapy. Further, tolerability problems with donepezil were not predictive of problems with rivastigmine. Common side effects of ChEIs include nausea, vomiting, diarrhea, loss of appetite, and, less often, sleep disturbances and extrapyramidal symptoms.

Memantine, the newest drug available for AD, was approved last year by the FDA and Health Canada for moderate-to-severe AD (patients with an MMSE of 14 or below). It is an NMDA receptor antagonist that acts as a partial receptor blocker for the excitatory amino acid glutamate.[11] Glutamate normally regulates the movement of calcium into cells, which is necessary for memory and learning. In AD, there are excessive amounts of glutamate because there are fewer brain cells available to take in the calcium. Memantine does not stop progression of AD but, compared with placebo, it improves function, cognition, and global scores in advanced dementia patients.[12]

Combination therapy of memantine and a ChEI has been evaluated in a study of 403 subjects.[13] A randomized, double-blind, placebo-controlled parallel group study of donepezil plus memantine has been evaluated for efficacy and tolerability in AD patients. Beneficial effects were observed when combining memantine with a stable dose of donepezil (5–10mg/day) in moderate-to-severe AD patients. Further, the combination was tolerated reasonably well; however, discontinuations were higher in the placebo group (12.4%) compared to memantine (7.4%) because of side effects. This combination therapy seems to be a good approach to management of moderate-to-severe AD. Long-term effects of combination therapy are unknown. However, this is the focus of an open-label extension of the study described above[13] and other trials.

Table 1: Main Side Effects of Dementia Drugs[14,50]

Drug	Side Effects
Donepezil	GI upset,* sleep disturbances
Galantamine	GI upset—minimize by taking on a full stomach
Rivastigmine	GI upset, weight loss, muscle weakness
Memantine**	Agitation (less than with placebo), dizziness, headache, constipation, confusion

*GI upset includes nausea, vomiting, diarrhea
**Not to be used concurrently with other NMDA antagonists, e.g., dextromethorphan, amantadine, ketamine

Dosing Guidelines in Dementia Management

In the case of the older patient first seen in the moderate stages of dementia, a ChEI may be initiated and some benefits may be noted. However, as the illness progresses and behavioural symptoms occur that are no longer managed by the ChEI alone, memantine may provide improvement in cognition, daily functioning, clinical global status, and behaviour.[21] Dosing recommendations and titration for moderate-to-severe dementia management are listed in Table 2.

Alternative Medications

A number of other medications, herbals, and nutraceuticals have been tried and tested in AD research.[14] Among these are estrogens, Ginkgo biloba, nonsteroidal anti-inflammatory drugs (NSAIDs), and antioxidants. None are thought to be useful in advanced dementia and are therefore not recommended here.

One nutraceutical, however—Huperzine A, a naturally occurring ChEI with antioxidant and neuroprotective properties—is currently being studied in an RCT by the National Institute for Aging.[15] The study included subjects with mild to severe dementia who are still able to swallow medication.

An extract from the plant Salvia officinalis has been tested in treatment of moderate AD.[16] The herb has been used for centuries to modulate mood and cognitive performance. Compared to placebo, Salvia had significantly better outcomes on cognitive function in this trial of 42 subjects.

There are a number of drugs that are commonly prescribed that have anticholinergic effects and should be avoided with AD therapy (Table 3).

Table 2: Dosing and Titration Recommendations for Management of Moderate-to-Severe Dementia

Drug	Starting Dose	Titration Interval	Usual Dosage Range
Donepezil*	5mg q.h.s.	4–6 weeks; 5mg increase per titration (q 4–6 weeks) hs (with/without food)	10mg q.h.s.
Galantamine	4mg b.i.d.	4–6 weeks; 4mg b.i.d. per titration with a.m. and evening meals	12mg b.i.d.
Rivastigmine	1.5mg b.i.d.	2–4 weeks; 1.5mg per titration with a.m. and evening meals	6mg b.i.d. max dose 9.4mg, usual dose
Memantine	5mg/day	min.1-week intervals; 5mg per titration; give b.i.d.. Then, next titration, give 5mg and 10mg as separate doses; then 10mg b.i.d.	5–20 mg/day

* when switching within a class of drugs here, no washout is necessary

Sources: Hsiung GR, Feldman H, 2004; www.aricept.com; www.exelon.com; www.reminyl.com; Alzheimer's disease medications fact sheet. ADEAR (Alzheimer's Disease Education and Referral Center, NIA. www.alzheimers.org/pubs/medications.htm. Retrieved 12/27/04.

Treating Behavioural Symptoms in Dementias

Dementia, especially in the moderate-to-severe stages, is often the cause of long-term care placement. Behaviours that are unmanageable by the family are more easily managed in the protective setting of the long-term care facility. Behavioural disturbances are seen in as many as 40–95% of long-term care facility residents.[22]

Psychotic symptoms occur in 30–60% of those with AD.[23] Not only is there increased cognitive impairment in these patients but the decline in cognitive ability is more rapid. Two subtypes of patients have been identified: one with hallucinations and misidentifications, the other with persecutory (paranoid) delusions. Patients with the former subtype are significantly more impaired than the latter or those with AD without psychosis.

Psychosis is similar in each type of dementia in its late stages. However, the profile of delusions and hallucinations is different from that seen in schizophrenia.[24]

Agitation is a symptom that clinicians use to provide a rationale for treatment with medications. It is a term that can mean many things and is probably best described in more specific terms when considering pharmacologic management. It is easier to evaluate the effect of a drug given for agitation when you have specific symptoms (often labelled as agitation) that you wish to suppress and can monitor (Table 4). These symptoms have all been observed in 60–98% of dementia patients.[25]

Typical Antipsychotics

Antipsychotics, in general, are used in 50–75% of all long-term care residents.[22] While a growing number of antipsychotics are prescribed, there are nevertheless many unanswered questions about the appropriateness, safety, and efficacy of these agents in older patients. Currently, there is a paucity of good quality research on antipsychotic drug use in older people. Towards addressing these concerns, an expert panel recently consolidated recommendations for the use of antipsychotic agents in patients 65 years of age and older.[26] According to the physicians surveyed in the study, these agents are commonly used to manage the behavioural and psychological symptoms of dementia, but newer atypical antipsychotic therapies are generally believed to have better efficacy and adverse event profiles than typical antipsychotic drugs.

Sink *et al.*[25] conducted a systematic review of randomized controlled trials (RCTs) completed between 1996 and 2004 involving typical antipsychotics and found no clear evidence that these drugs are useful for treating psychotic symptoms in patients with dementia. Moreover, there was no difference in efficacy observed among specific agents. Adverse effects (extrapyramidal symptoms and somnolence) were common.

For dementia with coexisting parkinsonism, the typical antipsychotics have been demonstrated to worsen parkinsonian symptoms.[27] They are also associated with severe extrapyramidal reactions in some types of dementia.

Table 3: Medications with Anticholinergic Effects to Be Avoided in Dementia Management

Warfarin	Ranitidine	Furosemide
Digoxin	Codeine	Dipyridamole
Theophylline	Cimetadine	Isosorbide
Captopril	Dyazide (triamterene & hctz)	

Source: Tune L, 2001.[51]

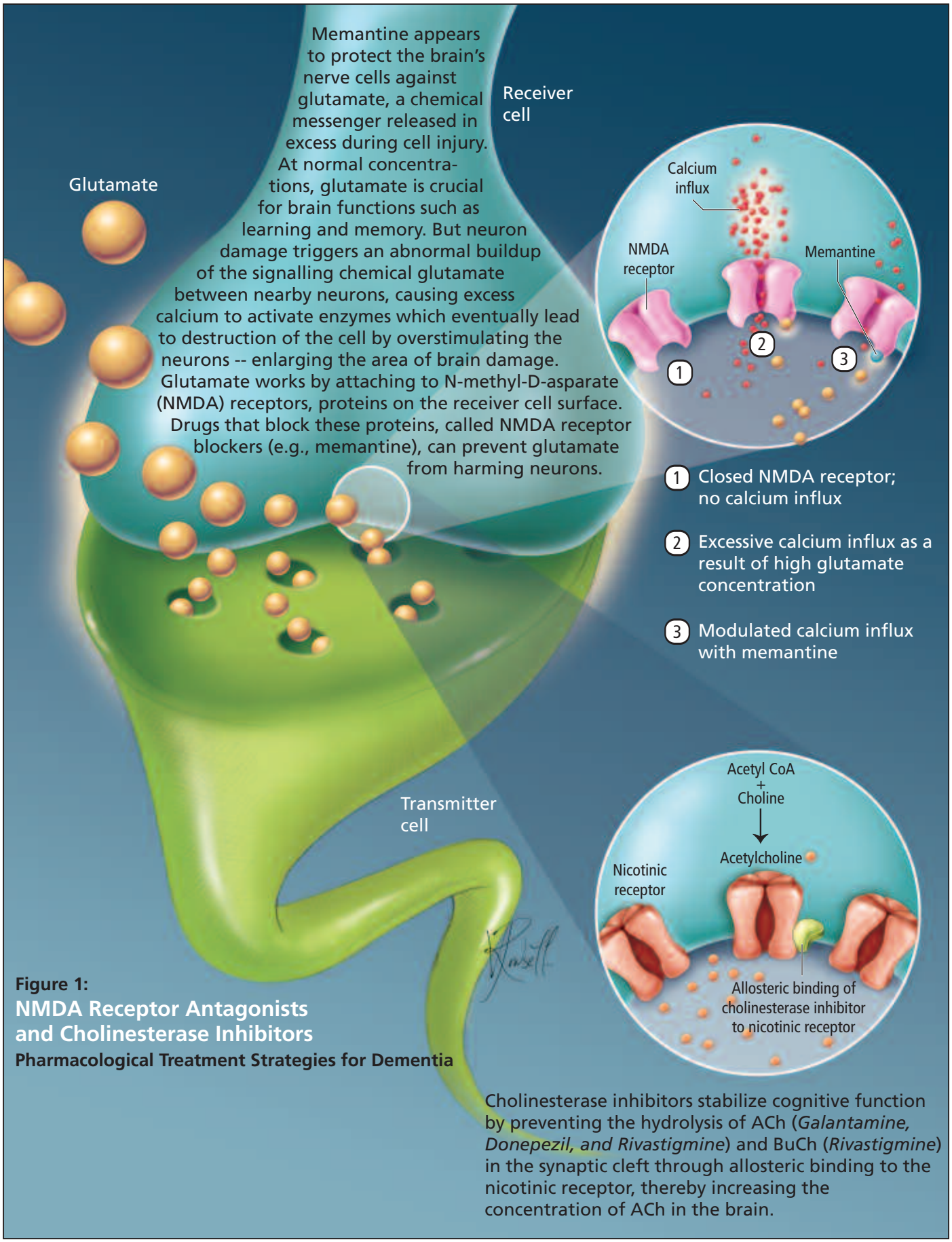

Figure 1:
NMDA Receptor Antagonists and Cholinesterase Inhibitors
Pharmacological Treatment Strategies for Dementia

Table 4: Symptoms Commonly Described as Agitation

Physical	Verbal
Biting	Screaming
Hand-wringing	Obscenities
Kicking	Threats
Spitting	Accusations
Hitting	Complaining
Grabbing	Name-calling
Scratching	Attention-seeking
Pacing	

Source: Jackson-Siegal J, 2004.[52]

Atypical Antipsychotics

Atypical antipsychotics have not been approved by the FDA for use in psychosis in dementia. Further, they have not been demonstrated to be superior to other antipsychotics in the treatment of older patients with dementia;[28] however, there is less risk of extrapyramidal symptoms and anticholinergic toxicity (except with clozapine) with the atypical antipsychotics.

Sink *et al.* reviewed evidence for atypical antipsychotics and found a modest but statistically significant beneficial effect of risperidone (1mg/day) and olanzapine (5–10mg/day), and minimal adverse effects at lower doses.[25] There is a dearth of trial data on the atypicals olanzapine and clozapine. Furthermore, the review found no RCTs comparing efficacy of typical and atypical antipsychotics. Potential adverse effects with the atypical antipsychotics (Table 5) need to be discussed with patients and caregivers prior to starting a drug.

Head-to-head trials to compare the efficacy of atypicals have not been conducted.[28] The practitioner should determine the side effect profiles of the considered drugs and match them to the patient's symptoms and comorbidities. An expert consensus guideline was published in 2004 for antipsychotic agents in older adults.[26] The panel's first-line choice for agitated dementia with delusions was risperidone 0.5–2.0mg/day. Second choice was quetiapine 50–150mg/day and olanzapine 5.0–7.6mg/day (Table 6). When there is a history of side effects with antipsychotic therapy such as EPS, quetiapine is the preferred atypical. Quetiapine is presently being tested in an NIA study for dementia in Parkinson's disease. To date, the efficacy and tolerability of atypical antipsychotics have not been tested in older patients with primary dementia with coexisting parkinsonism.[27]

Divalproex has been studied for treatment of agitation associated with dementia.[29] In this study there were only mild side effects, and there was a moderate improvement in agitation compared to placebo. Valproate is presently being studied in an NIA clinical trial to determine if valproate therapy can delay the emergence of agitation and/or psychosis in individuals with probable AD who have not experienced agitation and psychosis as part of their dementia.[30] The study will also assess the tolerability and safety of low-dose, long-term valproate therapy. Valproate is of potential usefulness because of its possible symptomatic efficacy for agitation, its known safety profile, and its probable neuroprotective potential in AD.

Gabapentin has been evaluated for treatment of agitation in dementia. One retrospective study revealed significant symptom improvement in 17 of 22 subjects, some improvement in four subjects, and no improvement in one.[31] Two patients discontinued the drug due to sedation. There were no other side effects noted.

In acute psychotic agitation, oral medications are difficult to deliver. Intramuscular ziprasidone, an atypical antipsychotic, is an atypical available in intramuscular (IM) formulation.[32] This medication has demonstrated control of acute agitation within minutes and improvement is maintained for nearly four hours. There is a low incidence of EPS and low sedation. Olanzapine is also available in IM formulation and a review found it to be comparable to haloperidol or lorazepam monotherapy in managing acute agitation of dementia.[33] Olanzapine has fewer side effects than IM haloperidol.

The psychiatric symptoms associated with Parkinson's disease (PD) include depression, anxiety, cognitive impairment, apathy, hallucinations, delusions, manic symptoms, and delirium.[34] In addition to regulating the PD medications

Table 5: Adverse Effects of Atypical Antipsychotics

Drug	Adverse Effect
Risperidone	– Cerebrovascular events: 3.8% vs. 1.5% in placebo* – TIAs, stroke – Ischemia
Olanzapine	– Cerebrovascular events: 1.3% vs. 0.4% in placebo** – Mortality rate increase: 3.5% vs. 1.5% in placebo
Quietapine	Somnolence ***
Aripiprazole	Somnolence ****

*2003 Safety Alert—Risperdal (risperidone)
**2004 Safety Alert—Zyprexa (olanzapine)
***Tariot P, Schneider L, Katz I et al. Quietapine in nursing home residents with Alzheimer's dementia and psychosis. Am J Geriatr Psychiatry 2002;10(1 Suppl):S93.
****DeDeyn P. Aripiprazole treatment for psychosis in patients with Alzheimer's disease. Poster: Am Assoc Geriatr Psychiatry Annual Meeting, Honolulu, HI, Mar 2003.

Table 6: Dosing and Titration Recommendations for Atypical Antipsychotics

Drug	Starting Dose	Titration Time (Usual Range)
Risperidone	0.5mg/day	1–2mg/day
Olanzapine	2.5mg/day	5–10mg/day
Quetiapine	25mg/day	50–250mg/day
Aripiprazole	2.5–5 mg/day	5–10mg/day
Ziprasidone	n/a	n/a

Source: Jackson-Siegal J, 2004.[52]

atypical antipsychotics often worsen the extrapyramidal symptoms (EPS), with the exception of quetiapine and clozapine. One open label study with risperidone in individuals with PD observed few EPS.[35] Depression, which is common in early and advanced PD, is managed with the SSRIs (selective serotonin reuptake inhibitors).

Treatment of Sexual Disinhibition in Dementia

Gabapentin, an antiepileptic agent, has been tested in the management of behavioural problems in older patients with dementia, including agitation and aggression.[36] The authors have effectively managed three cases of patients with gabapentin who had been exhibiting sexual disinhibition in a long-term care.

Other Therapies for Agitation in Dementia

Transdermal nicotine has been used in select cases in an inpatient geropsychiatry unit.[37] Four patients were treated and a beneficial response was noted.

There has been a surge in interest in recent years regarding the use of nutraceuticals and herbals to manage many different medical problems. Vitamin E is one of those nutraceuticals. One report of a review of 19 studies looking at vitamin E and vitamins vs. placebo found that people who were taking >400 international units of vitamin E every day died at a higher rate than those who did not take the supplements.[38] The NIH is currently studying the use of vitamin E for dementia.

Side Effects of Antipsychotic Drug Therapy

The side effects of conventional antipsychotics are well known. They seem to be worse in older patients. Saltz *et al.* reviewed side effects and found that, after one year of exposure to antipsychotics, the incidence of tardive dyskinesia in younger patients was about 5%, whereas in older adults it was 25%.[22] After three years of treatment, the incidence was 15% in younger patients and 43% in older adults—a striking contrast.

The side effects of antipsychotics include four major categories of movement/motor side effects: drug-induced parkinsonism, akathisia, dystonia, and tardive dyskinesia (Table 7).[22] These side effects can compromise quality of life. The akathisia is manifested by restlessness. The dystonia demonstrates sustained muscle contractions. The most easily recognized is tardive dyskinesia (TD), which involves involuntary body movements such as lip smacking (hyperkinesias).

Management of the symptoms usually means lowering the dose of the causative medication. Changing to an atypical antipsychotic or even discontinuing the drug is another alternative. For managing the akathisia and dystonia, Saltz recommends adding an anticholinergic agent in addition to lowering the dose.[22]

Rarely, the older patient may have an acute reaction to the antipsychotic even early in the therapy. Benztropine is used to treat drug-induced parkinsonism, but should be used sparingly as its anticholinergic side effects contribute to other problems.[22]

Akathisia disappears when the drug is discontinued or the dose is lowered.[22] Other treatments for this side effect include benzodiazepines, low-dose propanolol, and clonidine. All of these will have their own assortment of side effects and should be slowly discontinued over 5–10 days.

Dystonia responds well to anticholinergics such as benztropine or diphenhydramine.[22] IM administration is necessary in an acute episode of sustained muscle contraction, especially in an oculogyric crisis involving the eye muscles.

Tardive dyskinesia may not abate with discontinuation of the drug.[22] Older patients with a history of alcohol abuse, diabetes, or ECT are at greater risk. Management will include lowering or discontinuing the drug, or switching the drug to an atypical antipsychotic. Older adults at greater risk for TD should not be started on a conventional antipsychotic. Most cases of TD in older patients are mild and not greatly disabling. However, evaluation of the need for the antipsychotic should be reviewed on a regular basis, usually every four to six months.

Issues with Atypical Antipsychotics

A possible diabetic effect was identified in antipsychotics many years ago.[39] Disturbed glucose metabolism may be even more of an issue now with the atypical antipsychotics. A retrospective analysis of individuals taking olanzapine or one of the typical antipsychotics revealed a higher random plasma glucose level in the atypical group compared to the

Table 7: Parkinsonian Side Effects of Antipsychotic Drugs

Drooling	Micrographia
Seborrhea	Bradykinesia
Increased muscle tone	Tremors
Loss of spontaneity	Postural instability

Source: Saltz *et al.* 2004.[22]

conventional group (12.5% vs. 5.2% for glucose >160mg/dl, 5.4% vs. 1.7% for glucose >200mg/dl).

Drugs in this class seem to be associated with significant risk of weight gain and disorders of glucose and lipid metabolism.[40] There is risk of exacerbation of existing Type 1 or Type 2 diabetes, as well as new onset Type 2 diabetes and DKA with antipsychotic use.[28] Agents associated with greater risk of weight gain, diabetes, and dyslipidemia are clozapine and olanzapine, while drugs with a reduced risk are aripiprazole and ziprasidone. The American Diabetes Association recommends that fasting plasma glucose, lipid levels, and blood pressure be assessed within three months of initiation of antipsychotic drug therapy.[41] Plasma glucose levels should then be assessed annually. If the patient develops hyperglycemia, a diabetes management protocol should begin with consideration to switching the antipsychotic to one less likely to have this effect.

Clozapine was the first atypical antipsychotic developed and unique to other agents in its class. It is more effective than placebo and conventional antipsychotics,[42] its incidence of extrapyramidal symptoms are as low as placebo, and those who fail conventional antipsychotics often respond to clozapine. However, its side effect profile (a risk of agranulocytosis) limits its usefulness. It can still have a place in the management of neurological disorders; specifically, psychosis in dementia and parkinsonism with very close management.

Stopping Medications in Advanced Disease

That dementia is a terminal illness is not always recognized. The length of time from diagnosis to death ranges from 4–6 years but may extend to as long as 9–10 years.[43] In advanced dementia, feeding difficulties often occur and the patient is often fitted with a feeding tube. There is no evidence that this improves quality of life or even prolongs life when compared to similar patients who are not tube fed.[44] Further, tube feeding may worsen the outcome. Patients may pull them out or the tube may become clogged. Diarrhea is also a common problem.

Frequently, infection or other illness can cause more pronounced losses in cognition and in functional abilities. There is an abrupt increase in the life to death trajectory.

In the terminal stage, palliation of symptoms and a focus on comfort care is important. Management of pain and relief from depression and anxiety are useful. Many clinicians do not recognize signs of pain. Demented patients are as likely to suffer pain as other older patients with chronic disease. Pain is often a cause of behavioural changes and recognizing the signs of pain is imperative. Prevention of bedsores and constipation is essential. Medications for dementia are no longer useful at this stage. Whether antipsychotics are useful at this time is unclear. There have been no studies that have included this measure of comfort.[45]

The Future

Research continues into the cause of AD and other dementias. It is debatable whether the cause is one event or multiple pathologies, though one report suggests that AD may be an autoimmune disease.[46] A key finding has been the anomalous presence of immunoglobulin (Ig) detection in the brain parenchyma of AD patients. Specific neurons that showed degenerative apoptotic features contained the vascular-derived antibodies. This research suggests that the presence of antineuronal antibodies, a finding that has been previously dismissed, may have a pathological consequence when there is an impaired blood-brain barrier (BBB) which occurs in age-related vascular diseases. The impaired BBB would then allow the autoantibodies access to specific targets in the brain, causing cell death. This theory opens new avenues for pharmacological research. One such study is a National Institute of Mental Health (NIMH) clinical trial, which is presently recruiting patients.[47] It is evaluating the effects of the drug cyclophosphamine on inflammation and immune responses in patients with AD.

Other dementia clinical trials at the NIMH presently recruiting subjects include the use of high intensity light therapy in AD; fish oil and alpha-lipoic acid; AD treatment with CX516 (Ampalex); PREADVISE trial for prevention of AD with vitamin E and selenium; the use of short-term statins and NSAIDs; effects of anti-inflammatory drugs; cholesterol-lowering; valproate in dementia (VALID); and huperzine A treatment in AD. In all, there are 48 such studies presently in the recruitment phase.[47]

One study that was completed in October 2004, but is not yet published, is the CATIE project (clinical antipsychotic trials of intervention effectiveness). It is a study of antipsychotics (risperidone, olanzapine, quetiapine) and citalopram for managing hallucinations, delusions, or agitation in individuals with AD.[48]

Another area of AD research is in ACE inhibitors. A prospective trial has been conducted in Japan in moderate AD patients, excluding non-AD dementias.[49] The study showed benefit even in patients with limited ADLs. There are problems with methodology in this study but other studies will be conducted.

At the present time, however, the slowing of cognitive impairment and moderation of behavioural disturbances represent the best outcomes of the pharmacologic therapy for dementia. ◆

No competing financial interests declared.

References

1. WHO. World health report 2001: audio clips on mental health. World Health Organization, 2001;www.who.int/multimedia/whr2001/audio.
2. National Academy on an Aging Society. Alzheimer's disease and dementia—challenges for the 21st century: chronic and disabling conditions. Public Policy and Aging Report 2000;11:1–6.
2.5 National Advisory Council on Aging. The NACA Position on Alzheimer disease and related dementias. No. 23. www.naca-ccnta.ca/position/23_alzheimer/alzheimer2_e.htm. Retrieved 3/18/2005.
3. Sink KM, Yaffe K. Cognitive impairment & dementia. In: Landefeld C, Palmer R, Johnson MA, et al., editors. Current Geriatric Diagnosis and Treatment. New York: McGraw-Hill, 2004:60–73.

4. Edwards K, Hershey L, Bednarczyk E, et al. Results of a 24-week, open-label, flexible-dose trial to assess the safety and efficacy of galantamine in patients with dementia with Lewy bodies. Neurology 2003;60:A193–4.
5. McKeith I, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies: a report of the CDLB international workshop. Neurology 1996;47:1113–24.
6. Beversdorf D, Warner J, Davis R, et al. Donepezil in the treatment of dementia with Lewy bodies (letter). Am J Geriatr Psychiatry 2004;12:542–4.
7. Black S, Roman G, Geldmacher D, et al. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. Stroke 2003;34:2323–30.
8. Green RC. Advances in understanding dementia and its management: coverage of the AAN 55th annual meeting. Medscape 2003;www.medscape.com/viewarticle/453291.
9. Feldman H, Gauthier S, Hecker J, et al. A 24-week randomized double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001;57:613–20.
10. Gauthier S, Emre M, Farlow M, et al. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. Curr Med Res Opin 2003;19:707–14.
11. Mayo Clinic staff. Alzheimer's drugs. MFMER 2003;www.mayoclinic.com/invoke.cfm?id=AZ00015.
12. Winblad B, Poritis N. Memantine in severe dementia. Int J Geriatr Psychiatry1999;14:135–46.
13. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil. JAMA 2004 291:317–24.
14. Hsiung GR, Feldman H. Pharmacological management of Alzheimer's disease: an update. Geriatr Aging 2004;7:47–50.
15. National Institute for Aging. Alzheimer's Disease Cooperative Study. ClinicalTrials.gov, 2002; clinicaltrials.gov/show/NCT00043849.
16. Akhondzadeh S, Noroozian M, Mohammadi M, et al. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, ramdomized and placebo-controlled trial. J Clin Pharm Ther 2003;28:53–9.
17. Mendez M, Lim G. Seizures in elderly patients with dementia: epidemiology and management. Drugs Aging 2003;20:791–803.
18. Osterweil D. Alzheimer's disease in the long-term care setting—management of behavioral disturbances with cholinesterase inhibitors. Ann LTC 2004;12:18–24.
19. Sajatovic M, Mullen J, Sweitzer D. Efficacy of quetiapine and risperidone against depressive symptoms in outpatients with psychosis. J Clin Psychiatry 2002;63:1156–63.
20. Gauthier S, Feldman H, Hecker J, et al. Donepezil shows significant benefits in global function, cognition, ADL and behavior in patients with severe Alzheimer's disease. Neurol 2003;60:A413.
21. Alzheimer's Disease Management Clinical Consensus Panel. Alzheimer's disease: risk stratification, patient evaluation, and outcome-effective pharmacologic therapy—year 2004 clinical update. Geriatric nurse practitioner consensus reports, ADMCCP. U.S.A.: Thomson American Health Consultants, 2004.
22. Saltz B, Robinson D, Woerner MG. Recognizing and managing antipsychotic drug treatment side effects in the elderly. J Clin Psychiatry 2004;6(2 Suppl):S14–9.
23. Perez-Madrinan G, Cook S, Saxton JA, et al. Azlheimer disease with psychosis. Am J Geriatr Psychiatry 2004;12:449–56.
24. Leroi I, Voulgari A, Breitner J, et al. The epidemiology of psychosis in dementia. Am J Geriatr Psychiatry 2003;11:83–91.
25. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 2005;293:596–608.
26. Alexopoulos G, Streim JE, Carpenter D. Expert consensus guidelines for using antipsychotic agents in older patients. J Clin Psychiatry 2004;65(2 Suppl):S21–103.
27. National Institute on Aging. Treatment of agitation/psychosis in dementia/parkinsonism (TAP/DAP). ClinicalTrials.gov, 2004;clinicaltrials.gov/show/NCT00043849.
28. CME Consultants. Special report: update in the treatment of psychosis in the elderly. New York: McMahon Publishing Group, 2004.
29. Porsteinsson AP, Tariot PN, Erb R, et al. Placebo-controlled study of divalprex sodium for agitation in dementia. Am J Geriatr Psychiatry, 2001:58–66.
30. National Institute on Aging. Valproate in dementia (VALID). ClinicalTrials.gov, 2005; clinicaltrials.gov/show/NCT00071721.
31. Hawkins JW, Tinklenberg JR, Sheikh JI, et al. A retrospective chart review of gabapentin for the treatment of aggressive and agitated behavior in patients with dementias. Am J Geriatr Psychiatry 2000;8:221–5.
32. Mendelowitz AJ. The utility of intramuscular ziprasidone in the management of acute psychotic agitation. Ann Clin Psychiatry 2004;16:145–54.
33. Tulloch KJ, Zed PJ. Intramuscular olanzapine in the management of acute agitation. Ann Pharmacother 2004;38(12):2128–35.
34. Schrag A. Psychiatric aspects of Parkinson's disease—an update. J Neurol 2004;251:795–804.
35. Mohr E, Mendis T, Hildebrand K, et al. Risperidone in the treatment of dopamine-induced psychosis in Parkinson's disease: an open pilot trial. Mov Disord 2000;15:1230–7.
36. Alkhalil C, Tanvir F, Alkhalil B, et al. Treatment of sexual disinhibition in dementia: case reports and review of the literature. Am J Ther 2004;11:231–5.
37. Rosin RA, Levine MD, Peskind E. Transdermal nicotine for agitation in dementia. Am J Geriatr Psychiatry 2001;6:443–4.
38. Mayo Clinic staff. Vitamin E: helpful or harmful? Mayo Clinic, 2005;www.mayoclinic.com/invoke.cfm?id=AN00523.
39. Newcomer JW. Abnormalities of glucose metabolism associated with atypical antipsychotic drugs. J Clin Psychiatry 2004;65(18 Suppl):36–46.
40. Dunlop B, Sternberg M, Phillips L, et al. Disturbed glucose metabolism among patients taking olanzapine and typical antipsychotics. Psychopharm Bull 2003;37:99–117.
41. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601.
42. Iqbal M, Rahman A, Husain Z, et al. Clozapine: a clinical review of adverse effects and management. Ann Clin Psychiatry 2003;15:33–48.
43. Sachs GA, Shega JW, Cox-Hayley D. Barriers to excellent end-of-life care for patients with dementia. Jgen Int Med 2004 19:1057–63.
44. Fisher R, Connolly E. Artificial nutrition and hydration in the management of end-stage dementias. Geriatr Aging 2005;8:42–4.
45. Ballard CG, Margallo-Lana M. The relationship between antipsychotic treatment and quality of life for patients with dementia living in residential and nursing home care facilities. J Clin Psychiatry 2004;65(11 Suppl):23–8.
46. D'Andrea MR. Add Alzheimer's disease to the list of autoimmune diseases. Med Hypotheses 2005;64:458–63.
47. National Institute for Mental Health. Effects of an anti-inflammatory drug in Alzheimer's disease. ClinicalTrials.gov, 2004;www.clinicaltrials.gov/ct/gui/c/a2b/screen/ResultScreen/action/GetStudy?order=1.
48. National Institute for Mental Health. CATIE-Alzheimer's disease trial. ClinicalTrials.gov, 2004;www.clinicaltrials.gov/ct/show/NCT00015548?order=36.
49. Barclay L. Brain-penetrating ACE Inhibitors may be helpful in Alzheimer's disease. Neurology 2004;63:1324–5.
50. Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. NEJM 2003;348:1333–41.
51. Tune L. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001;62(21 Suppl):S11–14.
52. Jackson-Siegal J. Behavioral disturbances in the nursing home: an interdisciplinary approach to assessment and management. Presentation at the NCGNP Annual Convention, Phoenix AZ, Sept 2004.
53. AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial 363. Lancet 2004;9427:2105–15.