

# The Canadian

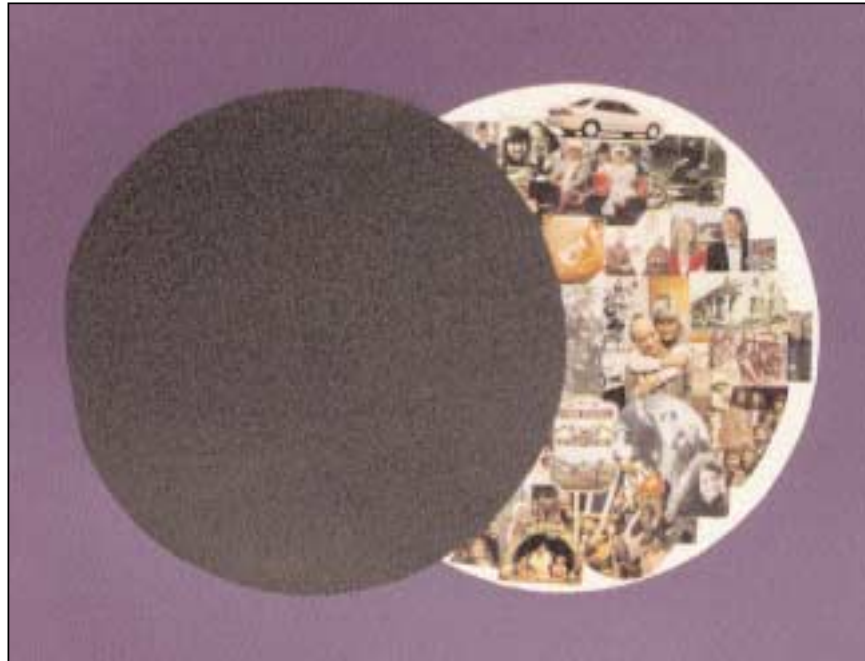
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# Alzheimer

## Disease Review

Volume 6, Number 1    September 2003

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Art by Crystal Doyle

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## ON THE COVER

### *Eclipse*, Paper collage by Crystal Doyle

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It is very difficult to describe the symptoms that a person with a mental illness experiences. As one who has watched family members and residents of a seniors' home progress through Alzheimer's, I had difficulty understanding what they were going through. At the age of about 10, I read the novel *What's Wrong with Daddy?* By Alida E. Young. In the novel, the father attempts to help his daughter understand what he was experiencing by describing his Alzheimer's as "an eclipse of the moon...my mind is the moon, and the darkness is slowly blotting out the light." Although it has been years since I read the book, that quote provided me with some insight while I was trying to understand the symptoms of Alzheimer's; it has helped me understand the anger and frustration that are prevalent in many Alzheimer's patients.

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# Vascular Dementia as a Treatable Illness

by *Kenneth J. Rockwood, MD, MPA, FRCPC*

In this issue, Dr. Inge Loy-English and Dr. Howard Feldman herald the beginning of a “new era” in vascular dementia (VaD), as evidence grows that it might be preventable (*e.g.*, by treating high blood pressure<sup>1,2</sup>) or treatable with cholinesterase inhibitors (ChEIs).<sup>3,4</sup> At the same time, however, as the entity comes under closer scientific scrutiny, questions are being raised and some closely held beliefs are being questioned.

One closely held belief that has started to wither is that multi-infarct dementia is the second most common cause of dementia, after Alzheimer’s disease (AD). Instead, it appears that much of the dementia seen in the setting of cerebrovascular disease is not due to multiple large strokes, but to subcortical ischemia and lacunar infarction.<sup>5,6</sup> Moreover, it is now widely appreciated that the classic dementia criteria are modeled on the dementia of AD.<sup>7</sup> Therefore, these criteria exclude people who have important and even progressive cognitive and functional impairment, but who do not conform to the AD model of dementia.<sup>8</sup> In consequence, there have been many calls for the development of criteria for what is increasingly known as “vascular cognitive impairment.”<sup>5,8</sup> However, at present, regulatory authorities are still debating the criteria and there are no drugs specifically approved for VaD.

Although it is not yet clear how to interpret the recent findings about the ChEIs donepezil and galantamine in the treatment of patients with dementia, for many physicians, details about disease nomenclature will be trumped by the possibilities for treatment. Some physicians may feel that, even if vigorous application of the NINDS-AIREN criteria<sup>8</sup> cannot exclude AD, if such patients still benefit, then it may be worthwhile to treat anyone with mild/moderate apparent AD or VaD. Other physicians may feel uncomfortable with any potential off-label prescribing, and will want to maintain a rigorous approach to dementia differential diagnosis. Some physicians may also

feel uncomfortable with arbitrarily translating measures used in clinical trials to those used in clinical practice.

What does seem clear from the recent trials is the merit in controlling vascular risk factors. Indeed, there is no evidence to suggest that, among patients with dementia, the stated guidelines for management of hypertension, diabetes and dyslipidemia<sup>9-12</sup> should not continue to be pursued. Physicians can therefore be encouraged to view VaD as a treatable illness.

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# Vascular Dementia: The Beginning of a New Era

Our concepts of vascular dementia (VaD) have been evolving rapidly during the past decade, and have broadened beyond the traditional understanding of VaD as being only a multi-infarct dementia (MID). It is now recognized that there are a broad range of cerebrovascular syndromes that can produce VaD, including strategic infarcts, subcortical VaD, and amyloid angiopathy. There has been emerging interest in the state of vascular cognitive impairment not dementia (vascular CIND) where it may be possible to intercede in treating vascular risk factors and stroke mechanisms before dementia becomes fully manifest. Indeed, there is evidence that treating vascular risk factors in asymptomatic individuals can lower the risk of developing dementia. Finally, the acetylcholinesterase inhibitors are emerging as a treatment option for the symptoms of VaD, with clinical trial evidence showing benefits on cognition, behaviour and functional disability.

*by Inge Loy-English, MD, FRCPC and Howard Feldman, MD, FRCPC*

## **Epidemiology**

In the Canadian Study of Health and Aging (CSHA), vascular dementia (VaD) was described as the second most common cause of dementia, affecting 1.5% of the population older than 65 years.<sup>1</sup> In a subsequent study, known as A Canadian Cohort Study of Cognitive Impairment and Related Dementias (ACCORD), 8.7% of individuals referred to dementia

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clinics in Canada were diagnosed as having VaD.<sup>2</sup> In addition to the patients who are clearly demented as a result of cerebrovascular disease, there also are those who have vascular cognitive impairment (VCI) without dementia. This group makes up a further 2.6% of the population in the CSHA,<sup>3</sup> and accounts for about 18% of those in the ACCORD study considered cognitively impaired but not demented.<sup>2</sup>

The risk of VaD increases with age—though less steeply than in Alzheimer's disease (AD)—and generally is found to be more prevalent in men than women.<sup>4</sup> The prevalence of dementia following a stroke is roughly 25%.<sup>5</sup> The magnitude of the burden of cerebrovascular disease and its impact on cognitive function represents a huge challenge in an aging society.

## **Classification and Clinical Features**

The definitions of VaD have been changing over the past few years. In VaD caused by cerebrovascular disease, early descriptions centered on multiple cortical and subcortical infarcts. In this type of VaD, the onset and worsening of the cognitive state is linked temporally to an episode of stroke or a transient ischemic attack (TIA). Current definitions of VaD describe it as a heterogenous disorder, as symptoms and signs are related to the cortical or subcortical area injured by the stroke. The pattern of deterioration usually is stepwise, and there are obvious focal neurologic deficits related to previous strokes.

The Hachinski Ischemic Score was developed to help differentiate between VaD and AD (see Table 1).<sup>6</sup> A scale is used in which

various features considered characteristic of VaD are assigned a value of 1 or 2. A score over 7 is diagnostic of VaD/multi-infarct dementia (MID), a score between 4 and 7 is diagnostic of mixed dementia and a score less than 4 is diagnostic of AD or other non-vascular causes of dementia.

Figure 1 presents examples of vascular disorders that are associated with both VCI and VaD:

**MID.** The concept of MID (Figure 1A) has gradually been expanded to include dementia associated with a larger variety of cerebrovascular disorders.

**Subcortical VaD** includes the terms Binswanger's disease and "état lacunaire," and is primarily characterized by an insidious onset in over 50% of patients, rarely with a clear stepwise progression. While having focal neurologic features on examination (e.g., subtle unilateral or bilateral weakness, Babinski signs, sensory deficits, dysarthria), patients often will not have a clear history of a TIA or stroke. Patients also may have an atypical gait (e.g., "marche-a-petit-pas"), resulting from frontal-subcortical damage. Cognitively, there is prominent frontal dysfunction with difficulty in executive functions, including planning, sequencing and organization. The memory impairment in VCI and VaD often is mild, especially compared to AD, with more impaired retrieval and better preserved recognition memory. Computed tomography (CT) scans and, more effectively, magnetic resonance imaging (MRI) show extensive ischemic lesions and lacunar infarcts in the deep and superficial white matter and grey matter bilaterally (Figure 1B).

**Strategic infarcts** are an increasingly recognized and important category of VCI and VaD. While in other types of VaD it is estimated that patients need a cumulative volumetric damage to 100 cubic centimetres of brain to produce dementia, in strategic infarct dementia, the required volume may be only one tenth that amount.<sup>7</sup> Examples of strategic lesions include thalamic, hippocampal and dominant angular gyrus lesions (Figure 1C). The clinical cognitive impairment depends entirely on the location of the strategic lesions. In the example of bilateral thalamic infarcts, there may be a dense amnesic syndrome associated with bilateral upgaze palsies. A severe dominant angular gyrus lesion can produce the classic Gerstmann's syndrome of right-left disorientation, finger agnosia, dyscalculia and agraphia. It is important to recognize the phenotype of the single strategic-area lesion, to facilitate early diagnosis and treatment.

**Global cortical hypoperfusion** post cardiac arrest is another subtype of VaD (Figure 1D).

**Hemorrhagic disorders** (Figure 1E) also are subtypes of VaD (e.g., cerebral amyloid angiopathy, or following subarachnoid hemorrhage).

**CADASIL.** There also are rare hereditary causes of multiple strokes leading to dementia. The recently described entity of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is becoming increasingly recognized as a cause of otherwise unexplained subcortical VaD in young and middle-aged patients (Figure 1F).

Table 1

**Hachinski Ischemic Score\***

Feature	Point Value
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History or presence of hypertension	1
History of stroke	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

\* A score of >7 is suggestive of VaD; a score of <4 is suggestive of AD or another non-vascular dementia; a score of 4-7 suggests mixed dementia.

Adapted from: Rosen WG, et al. Ann Neurol 1980; 7:486-8.

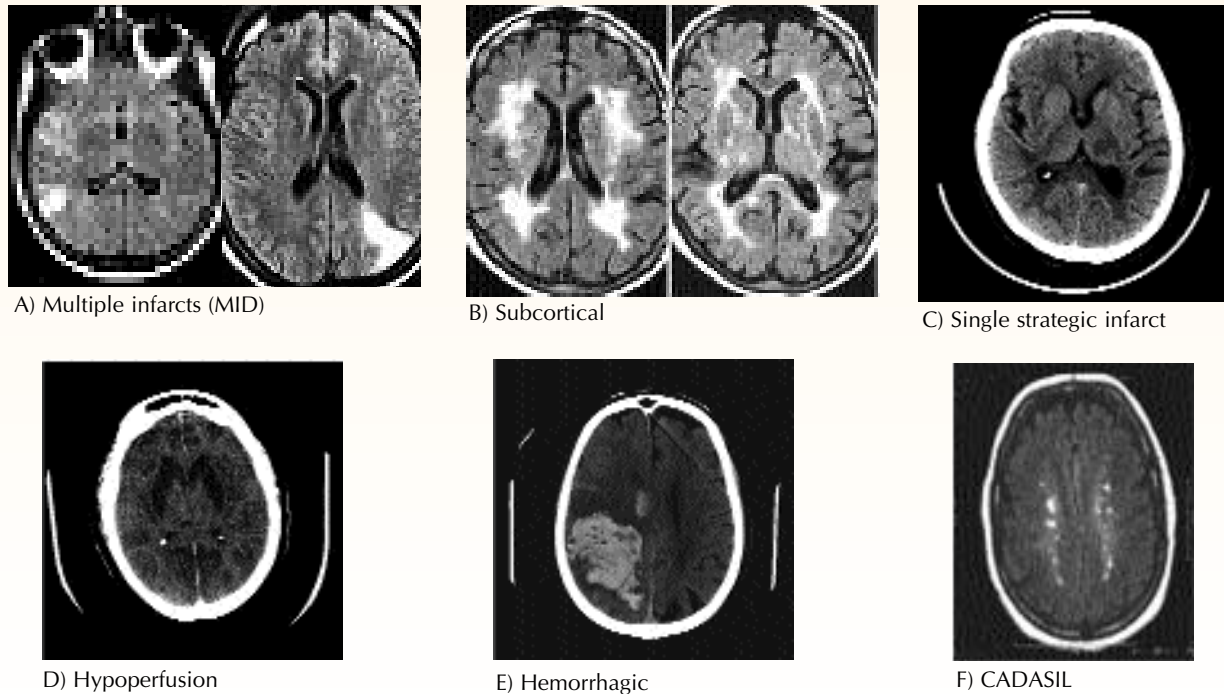
It is worth emphasizing that any of the above subtypes of VCI/VaD can coexist with AD, producing a mixed dementia. Mixed dementia of this type has been reported to account for 18.7% of all dementias diagnosed in the ACCORD study.<sup>2</sup>

**Diagnostic Criteria**

There are three sets of diagnostic criteria currently being used in research settings for VaD: 1) the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV); 2) the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10); and 3) the NINDS-AIREN criteria (NINDS = National Institute of Neurological Disorders and Stroke; AIREN = Association Internationale pour la Recherche et l'Enseignement en Neurosciences).<sup>8-10</sup> Although they

Figure 1

## Types of VaD



are not applied rigorously in clinical practice, it is worth considering some of the points of diagnostic emphasis (Table 2). The NINDS-AIREN criteria, which are the most widely used in recent clinical trials, require a temporal relationship with the onset of dementia occurring within three months of a recognized clinical stroke. They also specify that there be neuroimaging confirmation of ischemic lesions to make the diagnosis.

### Treatment

The fundamental approach to the treatment of VCI and VaD is centered on the prevention of further ischemic cerebrovascular disease. More recently, however, evidence has emerged supporting the use of acetylcholinesterase inhibitors in the treatment of VaD.

#### **Vascular risk factors:**

*a) Hypertension.* Hypertension has long been known to be a risk

factor for stroke and VaD, however the effects of treating hypertension on preventing dementia have been elucidated only more recently. The Systolic Hypertension in Europe (Syst-Eur) trial investigated the effects of treatment of systolic hypertension in mid-life.<sup>11</sup> This double-blind, placebo-controlled, randomized controlled trial (RCT) compared the ability of nitrendipine, +/- enalapril and +/- hydrochlorothiazide, with that of placebo to control systolic blood pressure to below 150 mmHg. Results demonstrated a 55% reduction in the incidence of dementia (95% CI, 24%-73%) and a 42% reduction in stroke (95% CI, 17%-60%) with active treatment.<sup>12</sup> There also were fewer cases of VaD and AD in the active treatment group.

In a recent article analyzing all the studies of the effects of treating hypertension on VCI,<sup>13</sup> the authors concluded that decreasing hyper-

tension in the elderly is safe and effective in reducing morbidity and mortality. Angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (especially nicardipine and nitrendipine) have the best supportive evidence with respect to preventing VCI associated with hypertension. There is less evidence to support the use of diuretics and beta-blockers in this regard.

*b) Diabetes mellitus.* The association between diabetes mellitus and stroke also is well known, with recent recognition of an association between diabetes and incident cognitive impairment. A recent Cochrane review<sup>14</sup> concluded that there was upwards of a two-fold increase in the risk of cognitive impairment in diabetics compared to the general population. Although the evidence remains uncertain with respect to diabetes treatment

Table 2

## Diagnostic Criteria for Probable VaD

	DSM-IV	ICD-10	NINDS-AIREN
Ischemic stroke and hemorrhagic stroke	Yes	Yes	Yes
Stepwise deterioration required	Yes	No	Yes (or temporal relationship between stroke and dementia)
Unequal distribution of cognitive defects	No	Yes	No
Focal neurologic signs	Yes (or radiographic evidence of significant cerebrovascular disease)	Yes	Yes
Focal neurologic symptoms	Yes	No	No
Etiologic relation of stroke to the disturbance in cognition	Yes	Yes	Yes
Temporal relation between stroke and dementia onset	No	No	Yes
Structural neuroimaging required	Yes (or clinical evidence of significant cerebrovascular disease)	No	Yes: multiple large vessel strokes or multiple lacunes or extensive white-matter lesions or a single, strategically placed lesion

reducing the incidence of dementia, there is evidence that treating hyperglycemia has a positive effect on cognitive function, at least in the short term.<sup>15,16</sup> This adds to the clear benefits of treating blood sugars tenaciously to prevent the spectrum of diabetic complications.

*c) Stroke.* The use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (*i.e.*, statins) has emerged as a common practice in the secondary prevention of stroke. There have been two recent meta-analyses evaluating the effect of statins primarily on the risk of stroke in patients with coronary artery disease.<sup>17,18</sup> These analyses showed a reduction in stroke rate of approximately 25% to 30% using pooled data.

The recently published Heart Protection Study<sup>19</sup> investigated the effects of simvastatin on vascular outcomes, including stroke, myocardial infarction (MI) and death. In this double-blind RCT, 20,536 pat-

ients were allocated to receive simvastatin or placebo. The risks of stroke, MI and death all were significantly decreased in the active treatment group, however there was no significant benefit of simvastatin on five-year cognitive outcomes.

*d) Homocysteine.* Homocysteine is a recently identified risk factor for cerebrovascular disease and dementia. It is known from previous studies that there is an independent linear relationship between the risk of TIA, stroke and increasing homocysteine levels.<sup>20</sup> The treatment for lowering plasma homocysteine levels is felt to be well tolerated: daily supplementation with vitamin B6 (25 mg), vitamin B12 (250 mg to 500 mg) and folic acid (2 mg to 3 mg). While there have been no studies to date looking specifically at the outcomes of lowering homocysteine levels in VCI or VaD, there are currently ongoing studies looking at the role of homocysteine in both reducing the risk of stroke and as a treatment for AD.

**Treatment with antiplatelet agents.** There has only been a single RCT evaluating the effects of antiplatelet agents in dementia.<sup>21</sup> In this three-year, single-blind study, 70 patients with MID were randomized to either treatment with acetylsalicylic acid (ASA) 325 mg or an untreated control group. There were significant improvements in cerebral perfusion values and cognitive performance scores for the patients treated with ASA compared to the untreated patients. This study has not been replicated and there have been no studies on the role of other antiplatelet agents (*e.g.*, ticlopidine, clopidogrel, dipyridole/ASA combinations) or warfarin in VCI or VaD.

**Symptomatic treatment for VaD.** The recognition of cholinergic deficits in VaD and VCI has led to the recent treatment trials with acetylcholinesterase inhibitors. In one double-blind, placebo-controlled study, donepezil was investigated for safety and

efficacy in probable VaD, as defined by the NINDS-AIREN criteria.<sup>22</sup> There was benefit in the 5 mg and 10 mg donepezil groups compared to placebo on the Clinician's Interview-based Impression of Change (CIBIC-plus; a global assessment measure) and on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog; a psychometric assessment).

Galantamine also has been evaluated in a double-blind RCT that included probable VaD and mixed AD-VaD.<sup>23</sup> The group treated with galantamine did significantly better at six months than

the placebo group on the CIBIC-plus and the ADAS-Cog.

There have been no published RCTs evaluating the efficacy of rivastigmine in VaD or mixed AD-VaD.

## Conclusions

VCI and VaD are a heterogeneous group of disorders that are becoming better understood with the advent of better diagnostic criteria and neuroimaging. The phenotypic identification of subtypes of VCI and VaD may allow more targeted therapy in the future. At present, diligent control of vascular risk factors clearly is important in

trying to prevent ongoing or increasing ischemic injury. The use of acetylcholinesterase inhibitors in the symptomatic treatment of VaD is emerging as a treatment intervention supported by level I evidence from recent RCTs.

## Acknowledgements

The authors gratefully acknowledge Dr. Doug Graeb and Professor Philip Scheltens for contributing the CTs and MRIs used in Figure 1. The capable assistance of Mr. Jacob Grand in the development of this manuscript also is acknowledged with appreciation.

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# Drug Interactions and Polypharmacy in the Elderly

With the seemingly constant flow of new therapeutic agents and new treatment indications for existing medications, polypharmacy is increasingly common, especially among elderly patients. While the benefits of comprehensive treatment are proven in well-designed trials, the risk of drug interactions (DIs) with each new combination in each patient must be carefully assessed. With a better understanding of pharmacodynamics and pharmacokinetics, these interactions can be predicted, prevented and minimized, allowing patients to benefit from a full spectrum of medical therapy.

by Peter Lin, MD, CCFP

**E**lderly patients often present with multiple medical conditions, and treating all of those conditions often necessitates polypharmacy. With each new guideline publication, increasing numbers of medications are shown to have benefits for our patients. In a post-myocardial infarction (MI) patient, for example, the current standard of care consists of using a statin, an angiotensin-converting enzyme (ACE) inhibitor, a beta-blocker and an antiplatelet agent. Each component of this quadruple therapy has been tested in large clinical trials and has been shown to have a significant benefit for the patient. In essence, this is the state-of-the-art, evidence-based medicine. But what about the risks of drug interactions (DIs) with polypharmacy?

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As the number of medications being taken by a given patient increases, the risk of DIs in that patient also increases. The risk of DIs can increase from approximately 6% in patients taking only two medications to 50% in those taking five medications and 100% in those taking 10 medications.<sup>1</sup>

Many DIs are avoidable, but those that are not require awareness of the interaction to allow for proper management and appropriate dosage adjustments. In reality, however, we must become knowledgeable not only about DIs; indeed, a broad understanding of how to use various drugs safely in our patients is essential. DIs comprise only one component of this complex issue.

For example, nonlinear pharmacokinetics may sound irrelevant to busy clinicians, but can have significant impact on their patients. Simply put, nonlinear pharmacokinetics means that doubling the dose of a given medication does not translate into just a doubling of

the blood level or effect of the medication. For many medications, dose increases can produce exponential rises in blood levels, so even a small change in dose could mean a significant rise in the drug's blood level and, hence, in potential side effects. This then becomes an important issue in prescribing safely to patients.

Similarly, it is important to be aware of medications employed in all therapeutic areas, because a medication prescribed by another physician or specialist can have effects on the medications a patient is already taking. This article focuses primarily on the DI aspect of these issues, with a particular emphasis on the cytochrome system. Examples are used to illustrate the method of the interactions discussed, and are not intended to provide an exhaustive list of all possible interactions.

## Types of Interactions

In pharmacology, two key words that need to be understood are

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“pharmacodynamics” and “pharmacokinetics.” Pharmacodynamics defines what a drug does to the body. Acetylsalicylic acid (ASA), for example, blocks platelet function, which results in increased bleeding time. Therefore, bleeding is the pharmacodynamic effect of ASA.

An example of a pharmacodynamic interaction is as follows: A patient takes over-the-counter ASA for his rheumatism and Ginkgo biloba for his memory. He develops atrial fibrillation (AF) and is prescribed warfarin by his cardiologist for stroke prevention. In this case, the ASA blocks the platelets and the warfarin affects the clotting factors. Both increase the risk of bleeding and, hence, the interaction is bleeding. Ginkgo biloba at high doses also increases bleeding.<sup>2</sup> The pharmacodynamic interaction of all these medications would result in bleeding for the patient.

Pharmacokinetics, on the other hand, defines what the body does to the drug. The body absorbs the drug, distributes it, metabolizes it and then eliminates it. Anything that affects these four steps would affect the drug levels in the body; DIs can occur at any of these steps. For example, many elderly patients take bisphosphonates for osteoporosis. They also take calcium supplements. If they take these two medications together, the calcium binds onto the bisphosphonates and thereby reduces the absorption of the bisphosphonates. Bisphosphonates have low absorption<sup>3</sup> to begin with, so this can almost eliminate any absorption of the drug. As a result, such patients are not getting the full

benefit (or perhaps even any benefit) of their bisphosphonate treatment.

By comparison, other pharmacokinetic interactions could cause significant problems. Take, for example, the case of cisapride (used to treat gastroparesis, ileus, chronic constipation and gastroesophageal reflux disease). This medication has a useful dosing of 40 mg per day. In some cases, an interaction may occur when another medication (*e.g.*, erythromycin) blocks the metabolism pathway of cisapride, which results in the accumulation of cisapride in the body.<sup>4</sup> At high levels, cisapride causes prolongation of QT intervals,<sup>5</sup> which could lead to *Torsade de pointes*.

longed period of time). The goal in prescribing safely is to keep our patients in the useful window and avoid the toxic window.

Unfortunately, however, not all medications are created equal. Some medications, like amoxicillin, can be given in doses of up to 2 g at once without any toxic effects. With medications like warfarin, on the other hand, even a 1-mg change in dosage could be disastrous. This is because each medication has its own unique set of useful and toxic windows. How close these two windows are to each other is known as the therapeutic index (TI). A narrow TI means the two windows are close together, so even a small change in drug levels can send the patient

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Basically, the four steps in pharmacokinetics will ultimately determine the amount of medication in the body. Affecting any of these steps changes the drug levels in the body by making them either too high or too low. An important concept to remember is that for all medications there is a useful dosing window and a toxic dosing window. In fact, this is true for any chemical that enters the body. Even oxygen has useful and toxic “windows” (*i.e.*, toxic effects are produced if a patient receives 100% oxygen over a pro-

from the useful window into the toxic window. A wide TI means the dose can be increased significantly before toxic effects are produced.

The TI for each medication is important in predicting DIs, as medications with narrow TIs are at higher risk for DIs. Hence, appropriately guiding the dosing of medications such as digoxin, theophylline, and warfarin requires careful blood monitoring. However, even with medications with wide TIs (*e.g.*, cisapride), an interaction that blocks the elimi-

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nation of a drug can drive blood levels up high enough to hit the toxic window. Therefore, care and knowledge must guide the use of any medicine.

### Cytochrome P450

The cytochrome P450 is a set of enzymes found in the small intestine, liver, kidney, lungs and brain. They process a variety of chemicals and play a role in the metabolism step of the pharmacokinetic profile. Their job is to make fat-soluble molecules more water-soluble so they can be eliminated

tion. St. John's Wort, for example, is an inducer of CYP 3A4,<sup>2</sup> through which some calcium channel blockers (CCBs) are metabolized. The addition of St. John's Wort speeds up the metabolism of such CCBs and, hence, the blood-pressure control of the CCBs may be adversely affected.

Finally, an interaction based on "competition" can occur. If too many drugs are sent to the same enzyme, the medications may compete for use of that enzyme. Warfarin is a perfect example. Any other drug that goes through

important, if the combination must be used, the doses need to be lowered to avoid any toxic effects. The knowledge of pharmacokinetics and pharmacodynamics outlined above allows the safe use of this new, fictitious medication.

Continuing with this example, suppose this new drug is an inhibitor of CYP 3A4. This means it will block CYP3A4 so all the drugs that normally go through CYP 3A4 will be processed slower and all of their blood levels will rise. If this medication is an inducer of CYP 2C19, then all the medications that normally go through CYP 2C19 will go through much more quickly. Hence, their blood levels will all fall. Phenytoin, for example, goes through CYP 2C19. This new medication would speed up phenytoin's metabolism and, hence, the phenytoin levels would fall and loss of seizure control would be a side effect of the combination.

Clearly, with an understanding of this terminology (substrates, inhibitors, inducers, competition), it is possible to predict DIs before they occur.

### Genetic Variation

Approximately 40 years ago, it was noted that the hydrolysis of the muscle relaxant succinylcholine by butyrylcholinesterase (pseudocholinesterase) was abnormal in some patients. It turned out that 1 in 3,500 white subjects had an atypical form of butyrylcholinesterase,<sup>8</sup> and that this form was unable to hydrolyze succinylcholine (thus prolonging the drug's effects on muscle relaxation). This discovery eventually evolved into the concept that there are genetic variations in

*Basically, the four steps in pharmacokinetics ultimately will determine the amount of medication in the body. Affecting any of these steps changes the drug levels in the body, making them either too high or too low.*

via the kidneys. Molecules that bind to these enzymes and are processed are called substrates of the enzyme. For example, cisapride is a substrate of the CYP 3A4 enzyme.<sup>6</sup>

Chemicals also can affect how the enzyme system functions. Some chemicals can block the enzyme. They enter the system and bind permanently to the enzyme so the enzyme no longer is able to process any other chemicals or medications. These are known as "inhibitors." For example, erythromycin is an inhibitor of CYP 3A4.<sup>7</sup> Cisapride needs CYP 3A4 to leave the body. When erythromycin blocks that enzyme, cisapride is unable to leave the body and the blood levels rise and cause the above-mentioned side effect (prolongated QT intervals).

"Inducers" are chemicals that accelerate the cytochrome func-

tion. The same pathway will displace warfarin and the warfarin will not be processed (resulting in higher levels of warfarin and associated side effects).

With the four words, "substrate," "inhibitor," "inducer" and "competition," it is easier to describe the effects of medications on the cytochromes. For example, consider the possibility that a novel treatment becomes available for Alzheimer's disease (AD), but no DI trials have been done with the agent in question. Some basic tests show that the medication is a substrate of CYP 2C9. This would mean that any medication that blocks CYP 2C9 will slow down the clearance of this new drug and, predictably, the drug's blood levels will increase. This would imply that inhibitors of CYP 2C9 should not be used together with this new drug. More

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different patient populations which would cause some patients to metabolize some drugs at different rates. Since then, there have been well-documented variations in several of the cytochromes, one of which is CYP 2D6.

CYP 2D6 is a very well studied enzyme. Its story began when researchers observed that some patients would metabolize certain drugs rapidly while other patients would metabolize those same drugs slowly. This greatly affected the blood levels of the drugs in these patients. Without any obvious explanation for this phenomenon, patients were classified as being fast metabolizers or slow metabolizers. This classification was not very useful, because it depended on the patient and on the specific drug. In other words, knowing that a patient was a fast metabolizer of metoprolol gave no insight into what other drugs he or she may be able to metabolize quickly.

With further research, and the advent of molecular genetics, it was discovered that there were different copies of the gene that codes for the CYP 2D6 enzyme. Some alleles made functional enzymes while other variants produced non-functional ones. Poor metabolizers had nonfunctional copies, while fast metabolizers had multiple copies of the functional gene.

This discovery made it much simpler to predict interactions. All that was needed was a list of all the medications that use the CYP 2D6 enzyme. Patients with multiple copies of the gene for CYP 2D6 would metabolize all of these medications faster, so higher doses would be needed to main-

tain the same blood levels. On the other hand, in patients with the defective allele, even a small dose could result in toxic blood levels. Seven percent to 10% of white people and 3% of black and oriental people are known to be deficient in the CYP 2D6 enzyme.<sup>9</sup> This is an example of how genetics may play a significant role in determining drug metabolism.

### AD Treatments

Because AD is predominantly found in the elderly, the issue of polypharmacy and DIs in this population group is very important. Still, it is important not to discard good medications because of the potential risk of DIs. Instead, knowledge of the interactions should be employed so that appropriate steps can be taken to manage those interactions. Awareness and knowledge of DIs are key in helping to manage our patients. If the interaction in ques-

tion raises the drug levels, the dosage needs to be reduced. If the interaction decreases drug levels, more medication is required. Such attention allows for the safe use of various medications in useful combinations.

In terms of cholinesterase inhibitors (ChEIs), donepezil, galantamine and rivastigmine are currently available in Canada for the treatment of AD. To use any medication properly, one has to be familiar with its characteristics, and all aspects of the medication

have to be considered before it is used in a given patient.

For example, donepezil is 100% absorbed and is not associated with any food interactions. It has a half-life of 70 hours, which makes it a true once-daily medication. Also, because of its long half-life, no discontinuation-type symptoms are expected if the drug is stopped abruptly.<sup>10</sup> All of these are important points, especially in this elderly population who may forget a dose and who may not remember to take medications more frequently than once per day. Galantamine and rivastigmine both have shorter half-lives and therefore need to be dosed twice per day.<sup>11,12</sup>

Donepezil and galantamine are metabolized by CYP 3A4 and CYP 2D6.<sup>9,13</sup> This means that inhibitors of these enzymes could theoretically increase the blood levels of these medications.

The common inhibitors of

*Clearly, with an understanding of this terminology (substrates, inhibitors, inducers, competition), it is possible to predict DIs before they occur.*

CYP 3A4 and CYP 2D6 are described elsewhere<sup>6</sup> and physicians who manage patients taking ChEIs (or other drugs, for that matter) metabolized by these enzymes should familiarize themselves with these inhibitors. For example, many elderly patients consume grapefruit juice, which is an inhibitor of CYP 3A4. Such patients should be told that this may increase their donepezil or galantamine levels. More important, this inhibition also may affect their CCB, statin or war-

farin levels. The interaction is not just a cholinesterase-inhibitor issue, but a CYP 3A4 issue that may affect many of a patient's medications. The same concerns surround the use of macrolides (e.g., erythromycin, clarithromycin), which also are inhibitors of CYP 3A4.

Many patients take selective serotonin reuptake inhibitors (SSRIs) for mood disorders. Paroxetine and fluoxetine, for example, are inhibitors of CYP 2D6. If these SSRIs are taken along with either of the ChEIs mentioned above, the blood levels of the

and inhibitors of these enzymes will help not only with the anticholinesterase treatment, but also in terms of any other medications the patient is taking that are metabolized by these enzymes.

Rivastigmine does not use the CYP 450 system, so it is not likely to have cytochrome-type interactions.<sup>14</sup> This is a very important characteristic. However, other aspects of this medication must be considered as well. For example, it has a short half-life and requires twice-daily dosing. Also, rivastigmine has a particular pharmacokinetic profile: it has

they can be effectively managed. Intelligent choices with respect to medication combinations can be made, and doses can be adjusted to keep patients in safe therapeutic zones. Finally, DIs represent just one aspect of the safe use of medications. Other aspects that must be considered include side effects, compliance, and pharmacokinetic profile. It is with an understanding of all these different aspects of each medication that we can prescribe these therapies safely for our patients.

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ChEIs may increase. The solution is to choose an antidepressant that has less effect on this enzyme, or to reduce the dose of the ChEI. If a patient is already taking an SSRI that inhibits this enzyme, the addition of the ChEI should begin with a lower dose and titrated upwards to the effective dose.

Inducers of these enzymes would reduce the blood levels of the ChEIs. For example, St. John's Wort is an inducer of CYP 3A4 and would speed up the metabolism (thereby reducing the levels) of these ChEIs. The patient would therefore need more medication to achieve the same clinical effect.

In general, avoiding inducers

linear pharmacokinetics at doses of up to 3 mg twice daily, but becomes nonlinear at higher doses. This means that doubling the dose from 3 mg twice daily to 6 mg twice daily results in a three-fold increase in AUC.<sup>12</sup> Because of this jump, there may be increased side effects, such as nausea and vomiting.

### **Conclusions**

With the general increase in the use of (and need for) polypharmacy, it is not uncommon to see patients taking eight or 10 medications. The issue of DIs is bound to come up. It is therefore prudent to learn about such interactions so

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# The Challenges of Medication Management in Patients with Alzheimer's Disease

Managing a number of medications is challenging for any patient, but seniors often have greater difficulty due to sensory impairment, multiple medical conditions, and/or financial restraints. In addition, if cognitive impairment is a factor, the complexity of managing a medication regimen is raised exponentially. Not only does caregiver administration and monitoring of the medications become more difficult, but the types of medications that can be safely used is decreased. Although these challenges cannot always be completely resolved, support can be provided through a healthcare team.<sup>1</sup> This article will demonstrate the integral role a pharmacist has in assisting patients with medication-related concerns.

by Cheryl Wiens, PharmD

The community pharmacist has frequently been touted as the “most accessible healthcare professional.”<sup>2</sup> Indeed, an appointment usually is not necessary and, in each community, pharmacies often are open long hours. The functions of a pharmacist can be summarized as “ABCS”—first suggested by Knowlton.<sup>3</sup> The “ABCS” are a helpful review of the pharmacist’s role and are defined as follows:

- **A**ssessment of medications and prescriptions
- **B**ottling of the pharmaceuticals
- **C**ounseling (of patients, caregivers, other clinicians)
- **S**urveillance, or monitoring, of medications

These roles also are described in other publications.<sup>4,5</sup>

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## Assessment

Patients with Alzheimer’s disease (AD) have a decreased cholinergic reserve and are therefore particularly susceptible to the risk of anticholinergic side effects with certain medications. Unfortunately, since medications with anticholinergic side effects are available without a prescription, many patients or caregivers may unknowingly purchase a harmful medication. Scopolamine patches, for example, are effective for reducing motion sickness but have been associated with delirium.<sup>6,7</sup> Also, antihistamines or antiemetics are frequently used products that have excessive cholinergic inhibition.<sup>8,9</sup> All patients with AD should be encouraged to discuss medication needs with their doctor and pharmacist. A pharmacist can assist in selecting a safe formulation, should a cough syrup or other over-the-counter (OTC) medication be required.<sup>10</sup>

Healthcare providers should not forget that many alternative and herbal products also have anticholinergic properties. These products often are overlooked. Patients and caregivers should be instructed to always bring all medications—including complementary supplements—to clinic visits. Pharmacists can conduct medication histories, counsel patients on the safe use of alternative products and provide information to patients, caregivers, and other clinicians. A drug-regimen review can be conducted by a pharmacist to determine medications that could be affecting cognition or behaviour.<sup>11</sup> In fact, pharmacists frequently recommend discontinuation of medications upon review.<sup>12,13</sup>

As AD progresses, many medications are discontinued because they are not expected to provide a tangible benefit and may be viewed as more of a burden for the patient. When discontinued,

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certain medications have to be carefully withdrawn. Based on knowledge of pharmacokinetics and pharmacodynamics, pharmacists may be able to suggest tapering regimens and can be of assistance in monitoring withdrawal complaints.

Adverse drug reactions also are very common, accounting for up to 20% of hospital admissions in the elderly.<sup>14</sup> Although age itself is not a risk for increased drug reactions,<sup>15</sup> seniors often are taking more medications because of chronic diseases and, therefore, would benefit even more from a pharmacist's drug-regimen review.<sup>13</sup>

Medication errors and adverse events are clinically significant and costly problems in our current healthcare system.<sup>16,17</sup> Pharmacists are able to provide advice on which medications are best tolerated in a senior population, and can assist in interpreting the significance of drug interactions and how to avoid those that are clinically significant. Working with pharmacists can therefore improve patient outcomes by reducing potentially harmful drug interactions and selecting medications that may be most appropriate for a specific patient.

Reducing costs may be a priority for certain patients since a co-payment—or even the full cost—is borne by the patient. Elderly families have a higher prescription out-of-pocket burden compared to younger families, and some patients may choose to go without filling prescriptions in order to save money.<sup>18</sup> In some cases, a pharmacist may be able to review a patient's medication

profile to assist the healthcare team in reassessing the need or potential benefits of continuing certain medications. Also, there often are less expensive medications which can be considered as substitutes for more expensive products. Pharmacists also can make suggestions about the use of OTC products which, when factored into the overall cost of a medication regimen, may dramatically increase costs.

### **Bottling**

Today, most dispensing functions are carried out by technicians. However, it may be helpful to think of “bottling” in terms of recommending appropriate administration devices (*e.g.*, calendar packaging). Calendar packaging (*e.g.*, dosette, blister package) may slightly increase cost, however it may be the most efficient and safest way to organize medications for a patient. Although there is little evidence to indicate that calendar packaging dramatically increases compliance, it does make it easier for caregivers and patients to administer medications and note whether the medications have been taken out of the package.

Calendar packaging is not necessarily appropriate for every patient. Although some devices have additional features, such as raised symbols for patients with poor eyesight, other devices are not easy to manipulate if a patient has arthritis. Discussing the different devices available can help a patient and caregiver select the most appropriate product to meet their needs.

Pharmacists also can advise patients on devices that assist with

the use of other products, such as eye drops, metered-dose inhalers or nasal sprays. These products often are difficult to administer, even if an individual does not have dementia, because of decreased coordination and dexterity.<sup>16</sup> Other important monitoring tools, such as glucometers or blood-pressure meters, may have been purchased through a pharmacy. The pharmacist can educate the patient and caregiver on appropriate use and handling of such devices in monitoring medical conditions.

Safe use of medications also is a primary responsibility of the pharmacist. Ensuring that child-proof containers are used may be necessary for the safety of a patient with AD. Discussing safety issues in the home with the patient and caregiver can result in the appropriate measures being taken.

### **Counselling**

Considering the number of medications available and the rapid rate at which new products are entering the market, it is not surprising that the Canadian Medical Association (CMA) has noted a deficiency in knowledge of medications.<sup>19</sup> Education of patients, caregivers, and other health professionals is an important role for pharmacists.

Patients may not be aware of OTC medications that should be avoided, and they may not be familiar with the complications that can arise as AD progresses. The pharmacy is an ideal place to make pamphlets and other educational materials available. Patients or caregivers often visit the pharmacy on a monthly basis. The

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pharmacist can then build on information already given to the patient, or provide him/her with information on new programs or services that could be of benefit. Education and support for patients and caregivers are primary concerns and are some of the most significant ways in which a pharmacist can reduce medication errors.<sup>16</sup>

Because the caregiver is ultimately responsible for the use of as needed (*pro re nata* or “prn”) medications, education of the caregiver is essential. Counselling the caregiver about appropriate use and the accepted frequency of use of a prn medication is important. Also, the caregiver may not be familiar with a medication if it is not given frequently. An accessible healthcare provider who is available to answer questions is a valuable resource.<sup>11</sup>

Education of healthcare providers also is an important task. Pharmacists spend their careers focusing on pharmaceutical products, and their expertise can be shared in a formal or informal setting. Ensuring that medication issues are dealt with prior to the medication being prescribed would be more efficient for everyone involved.

It is important to keep in mind that, while pharmacists are readily accessible to patients, they often have little information from a patient’s chart. It is helpful to communicate significant changes or indications to the pharmacist if he/she is to build on patient education that has already been initiated. In addition, the distribution of samples is commonplace in today’s competitive pharmaceuti-

cal market. If a prescriber decides to dispense a sample to a patient, that prescriber often is the only health professional to know the patient is taking that medication. Pharmacists, in contrast, must make decisions about drug interactions and addition of medications to calendar packaging, and/or provide medication lists to other specialists, without the knowledge of the dispensed samples. In order to provide seamless care, patients would benefit greatly if samples or other physician-dispensed items were noted on the pharmacy profile. Grissinger *et al*<sup>16</sup> noted that many medication errors occur because of poor order communication between the physician and pharmacist.

### Surveillance

A simple screening process that pharmacists often do is checking the refill dates for medications. If a patient is “late” picking up or ordering refills, pharmacists can follow up with the patient or caregiver. Nonadherence is common in all patient populations but ranges between 25% and 50% in seniors.<sup>2</sup> Verbal counselling and other visual reminders have been shown to improve compliance.<sup>2</sup> Pharmacists also can be involved in self-medication programs that assess adherence and medication-related problems in-hospital, before a patient is discharged.<sup>2</sup>

Pharmacists can monitor target symptoms by encouraging caregivers to document (*e.g.*, using a diary) behavioural problems or progression of dementia. Pharmacists frequently see patients in the pharmacy and can ask

about medication-related concerns (*e.g.*, side effects) or adherence.<sup>11</sup> Screening for problems can prevent minor issues from turning into major issues, and pharmacists may encourage a patient to see his/her physician earlier than scheduled if a problem has arisen. A follow-up telephone call also can be of benefit in providing education or resolving medication concerns.<sup>13,20</sup> Seevak *et al*<sup>13</sup> found a significant number of medication-related concerns in patients, however, these concerns may not have been discovered if the patients had not been specifically asked about them. Another important finding was that dealing with these patient concerns did not lead to an increased workload for physicians.

A number of pharmacists and/or pharmacy staff members also do home visits on a regular basis to deliver medications. A formal consult also can be requested. The pharmacist may be able to provide ample information about medication issues, such as hoarding or medication organization, in addition to a general description about the home situation. Information obtained from pharmacists who conduct home visits can be a valuable resource when designing a care plan for patients and their caregivers.

### Beyond the “ABCS”

Pharmacists can contribute to improved medication management in many other ways, including:

- Participating in formulary reviews at the institutional or provincial level;
- Participating in research; and



- Becoming involved with educational endeavors to improve knowledge and awareness of medication-related concerns for other healthcare providers. The *Drug Use in the Elderly Quarterly* newsletter, produced in Alberta by the Alberta Medical Association and the Alberta College of Pharmacy, is a great example of this type of educational endeavor. Newsletters are co-authored by a physician and pharmacist, which improves collaboration and ensures that information needs are met for both disciplines.

It also is important to keep in mind that the ABCS apply not only to community pharmacists, but also to hospital pharmacists. Pharmacists working on all wards, not just the Geriatric Assessment Unit,<sup>21</sup> can provide support for optimizing medication management in patients with AD.

Teamwork is the optimal approach to healthcare in seniors.<sup>22</sup> A Canadian study of community-dwelling subjects found that the majority of medication issues can be resolved when a multidisciplinary team is involved, leading to improved compliance,

reduced adverse drug reactions, and a trend toward reduced hospital visits and hospital admissions.<sup>23</sup>

Most recently, pharmacists have been recognized through the Romanow Commission report for helping Canadians achieve better results from their medications.<sup>24</sup> Both the Romanow Commission and the Mazankowski Report<sup>25</sup> highlight the need for pharmacists to play an important role in the healthcare of Canadians. Indeed, pharmacists continue to reduce the risks and improve outcomes for patients with AD.

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# Personal Revelations, Experiences and Reflections of an AD Caregiver

Roberta Bedard is a caregiver for her husband who has Alzheimer's disease (AD). She has written many humorous and touching vignettes about her personal experiences in dealing with the development of the disease, and has graciously agreed to feature these vignettes as a series in this and upcoming issues of the *Canadian Alzheimer Disease Review*. Roberta's writings enable readers to share in her journey with AD caregiving, provide valuable insight on the human aspect of disease and stimulate contemplation on the deeper meanings of life and love. In this feature, Roberta explains how she has come to understand the Retrogenesis Theory and reveals the joys and sorrows this understanding brings.

## CHAPTER 2

### *The Retrogenesis Theory*

by Roberta Bedard

It's taken a long time to settle down to write this chapter. Months. Not because I didn't understand the idea behind the Retrogenesis Theory. But I was determined to write these articles in the spirit of hope and joy. And before we can find the joy we have to come to terms with the sadness.

As I stated previously in Chapter 1, vastly simplified, the retrogenesis theory correlates the stages of AD to specific developmental stages in children. For example, a Stage 3 AD patient can be expected to function at the level of a teenager, whereas a Stage 5 AD patient can be expected to function at the level of a five- to seven-year-old child. In effect, retrogenesis is child development—only backwards.

In the "backwards" lies the sadness, although the Retrogen-

esis Theory can help caregivers understand what can realistically be expected from our loved ones. Because in our human understanding and socialization, from the time we are in the crib through to our adult lives, and then the lives of our children, the emphasis is on learning, developing, and moving forward.

When we strive to manage and love our way through the various stages of children's development, we are doing it with the idea of teaching and preparing for the next step forward—helping our children to become adults who will make and live in a better world.

In fully accepting the Retrogenesis Theory and in using the knowledge to help our loved one, we must first accept that we are not promoting growth. We are not moving forward, but backward.

To find the joy inherent in our loved one's current stage of awareness, we must let go of anticipation of the next higher level of accomplishment.

We are not teaching. But we are loving, interacting, managing.

We are not preparing for future depths of awareness. But we are constantly assessing where we are at the moment.

We are not holding on to the idea that tomorrow there will be a step into a greater future. But we are open to the pleasures to be found this day.

We must set aside mourning the adult we have lost and take pleasure in the child we have found.

**Please look for Chapter 3: Validation in the next issue of the *Canadian Alzheimer Disease Review*.**

## News from the Alzheimer Society of Canada

### Tough Issues in Alzheimer Care

On a regular basis, perhaps even a daily basis, family physicians (FPs) are required to make difficult and sometimes controversial choices when caring for their patients. Generally, FPs make these decisions based on prior experience, with consideration for the values and beliefs of the patient, and with reference to the principles outlined in the Hippocratic Oath and the Code of Ethics of the Canadian Medical Association.

Treating people with Alzheimer Disease (AD) also poses many ethical challenges. The recent publication of *Tough Issues: Ethical Guidelines* is designed to assist FPs in making tough decisions by raising issues and providing guidance pertinent to various situations that may arise during the treatment and care of people with AD.

*Tough Issues* was launched in April 2003 at the Alzheimer Society of Canada's (ASC) 25th national conference in Ottawa. The publication provides information and guidance for people living with AD, as well as families, healthcare professionals and researchers involved with AD. This publication is actually the second by the same name. The first set of guidelines was published by the ASC in 1997, and was not created specifically for people living with AD but for AD caregivers and health professionals.

The new ethical guidelines represent the culmination of nearly two years of consultations nationwide, with over 150 people connected to AD representing different interest groups. An advisory committee was formed with people representing various viewpoints and areas of expertise, including people with AD.

There are three significant differences between the 2003 and 1997 ethical guidelines:

- 1) People with AD are now directly addressed in the guidelines, as they are capable of participating more in their own care (thanks to better awareness and earlier diagnosis of AD);

- 2) Two new guidelines have been added: "Living Alone" and "Intimacy and Sexuality"; and
- 3) Existing guidelines have been revised to reflect the progress that has been made in caring for people with AD.

*Tough Issues* examines nine topics that affect people touched by AD. Each section provides background information, explores an issue, offers recommendations (when possible) and lists additional resources. The topics are: communicating the diagnosis; driving; living alone; decision-making; respecting individual choice; quality of life; participation in research; genetic testing; restraints; and intimacy and sexuality.

"The first set of ethical guidelines," said Ilona Horgen, Director of Support Services and Education for the ASC and Chair of the Advisory Committee for the Alzheimer Society's ethical guidelines, "was received with a great deal of interest and enthusiasm when it was published in 1997 and we hope the 2003 document will prove to be just as helpful to healthcare professionals and members of the public. It's a valuable reference guide for every doctor's office."

Although all of the topics are relevant to FPs, the issues discussed below may pose particular challenges in the care of patients with AD.

#### Communicating the Diagnosis

Communicating the diagnosis of AD to a patient is often a very difficult task. FPs may wrestle with the fear that delivering the news will jeopardize their relationship with the patient or that the patient will not be able to cope with the information. Other common situations for FPs include learning that family members disagree about the need to communicate the diagnosis, or that the patient does not want to be told the cause of his/her symptoms. The Alzheimer Society believes that people with AD and their families need to be sensitively informed

about the diagnosis. If, however, a patient has expressed the wish not to know the cause of his/her symptoms, the request should be honoured. Knowledge of the diagnosis helps people to be directed to appropriate treatment, care and support, and provides the opportunity to develop plans for the future.

### Use of Restraints

When is it appropriate to use chemical, physical or environmental restraints on a person with AD? Almost never, according to the new guidelines as well as “best-practices” research that exists on this subject. Although some aggressive behaviour may put others at risk of injury, there are preferred care strategies to assist in finding alternative solutions to restraints. The problem-solving approach advocated by the Alzheimer Society is described by the following steps:

1. Identify the problem prompting the behaviour.
2. Analyze the problem.
3. List possible strategies (solutions).
4. Choose a strategy (solution).
5. Take action.
6. Assess the results.

If it is deemed necessary to use restraints (*e.g.*, a lap belt at meal time) because restraint-free strategies are not possible, it is crucial that the least restrictive restraints are chosen and used appropriately, over the short-term, with regular monitoring and assessment. When minimal restraints are being considered, the positive and negative consequences for the person with AD and others must be carefully measured and monitored. The physical and mental well-being of a person in a restrained condition should not be compromised.

### Living Alone

An increasing number of older people live alone. If family members do not live close by, it becomes morally incumbent upon FPs to help determine whether a patient with AD is still capable of living in his/her own home. In some communities, additional support can be provided in the home. FPs should consider the following factors before making their recommendation:

- Overall well-being
- Health
- Nutrition
- Safety
- Finances

For more information on the above, as well as day-to-day strategies to enhance independent living, see the “Living Alone” section in *Tough Issues*.

A diagnosis of AD does not automatically mean that a person is incapable of living alone. Some of the barriers to making informed decisions about a person’s ability to live at home include: privacy and confidentiality regulations; the limited availability of services to support independent living; and competency legislation. With growing numbers of people with AD living alone, there is a need for more public discussion of these issues.

Today, an estimated one in 13 Canadians older than 65 years of age (or 364,000 people) has AD or a related dementia. This ratio increases to one in three in those older than 85 years of age. Because of aging baby boomers, these numbers will escalate. An estimated 750,000 Canadians will have AD or a related dementia by the year 2031 if a cure is not found. Each year, approximately \$5.5 billion is spent on caring for Canadians with AD. There is an urgent need to provide appropriate care for Canadians who have AD. Awareness of the ethical issues can be an important first step in providing quality care.

Some topics covered in the new guidelines are among those that appear consistently and frequently in the literature on ethical issues in AD. Other topics are breaking new ground. As more people are diagnosed with AD, and understanding of the disease increases, discussions surrounding ethical issues will continue to evolve.

Copies of *Tough Issues* are available from local Alzheimer Societies across Canada. The information is also posted on the ASC’s website in the Alzheimer Care section at [www.alzheimer.ca/english/care/ethics-intro.htm](http://www.alzheimer.ca/english/care/ethics-intro.htm).

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*The Alzheimer Society of Canada is a not-for-profit health organization dedicated to helping people affected by Alzheimer Disease. The Society provides support and educational programs for people with Alzheimer Disease and their caregivers. The Society also funds research into finding the causes and cure of the disease, and into improved methods of caregiving.*

*For more information on Alzheimer Disease and related dementias, Alzheimer Society programs and services, and how you can help, contact your local Alzheimer Society or visit the Society’s website at [www.alzheimer.ca](http://www.alzheimer.ca) or call 1-800-616-8816.*