FOCUS ON IMAGING

Potential Impact of Amyloid Imaging in Vivo on AD Treatment and Management
Nicolaas Paul L.G. Verhoeff, MD, PhD, FRCPC

Imaging and Alzheimer’s Disease: A Review
Christian Bocti, MD, FRCPC

Molecular Imaging of Alzheimer’s Disease Using PET
Pedro Rosa-Neto, MD, PhD; and Antoine Leuzy

Advocating for Change: Making Dementia a National Health Priority
The Alzheimer Society of Canada
On the Cover…

This watercolor was produced by Sylvia Sinclaire, a remarkable 83-year-old, who was diagnosed with dementia right after her retirement from teaching art. Creative expression allows us glimpses into Sylvia’s mind, and this same artistic expression offers her an avenue to us, if only temporarily. Her humour and positive attitude, in spite of her awareness of her disease, reminds us that we should not let our own preconceptions about illness blind us to the potential of the human spirit. She completed this work during an art session with Dr. Dalia Gottlieb-Tanaka, who developed the Creative Expression Activities Program, and has worked with and filmed Sylvia for five years.
Neuroimaging in Alzheimer’s Disease

By Peter Lin, MD, CCFP

This edition is devoted to the advances in neuroimaging for Alzheimer’s disease (AD). Broadly speaking, imaging can be put into three large categories:

• structural imaging;
• pathologic imaging; and
• functional imaging.

Dr. Bocti reviews the importance of structural imaging with computed tomography (CT) and magnetic resonance imaging (MRI) scans. These scans can help to rule out diseases as well as detect AD as they are able to detect atrophy in strategic locations which has become the hallmark sign for AD. As well, the presence of silent cerebrovascular disease is also important as it significantly worsens the dementia presentation. Futuristic MRI scans can even detect healthy versus unhealthy white-matter tracks which may allow for earlier detection of the diseased neurons.

Dr. Verhoeff discusses the use of tracers that can attach to amyloid or tau. This would allow us to image the location and to quantify the pathologic burden. This could be used to detect earlier stages of the disease, maybe even before significant neuronal death has occurred. This type of pathologic imaging will also play a critical role in assessing the efficacy of the newer therapies that target the amyloid pathways and, in turn, could accelerate the drug-discovery program for these disease-modifying agents.

Finally in this issue, Dr. Rosa-Neto explores the area of molecular imaging whereby the functioning status of neurons can be measured. Fluorodeoxyglucose (FDG), a glucose analog, can be followed with positron emission tomography (PET) to see where the metabolically active cells are and where they are not. Neurons that are dying use less glucose. In the coming years, using other molecular tags, we will be able to measure inflammation of the microglia and even neurotransmission of acetylcholine cells using this same technology.

In a sense, all of these imaging modalities are trying to do the same thing: help us to understand the disease process and to pick out patients at an earlier stage of the AD spectrum. Perhaps one day all scans can be combined together to identify patients of vulnerability, and targeted therapies can be administered to these patients to avoid the disease from ever materializing.
Potential Impact of Amyloid Imaging in Vivo on Alzheimer’s Disease Treatment and Management

Beta-amyloid (Aβ) modification therapies for Alzheimer’s disease (AD) are currently being developed that target Aβ production, aggregation, and/or degradation. Some of these medications are already in Phase 3 studies. It will therefore be most relevant to be able to quantify the neurobiological target of such therapies directly in vivo in the brain. This could permit a reduction in the required sample size for future clinical trials and will allow a more individually tailored approach once such treatments become clinically available. This article reviews the prevalence of AD amongst other dementias, the Aβ cascade, various Aβ positron emission tomography (PET) tracers that are being developed, and the potential application of these tracers for Aβ-modification therapies.

By Nicolaas Paul L.G. Verhoeff, MD, PhD, FRCPC

Dementia is common in older adults and approximately doubles in frequency every five years, from about 1% of people aged 60 years to 30% to 40% of those aged 85 years of age and older.1,2 AD3 is the leading neurodegenerative disorder, accounting for approximately one third to two thirds of dementia cases.2,4 Improving early detection of AD and studying the effects of new treatments for AD are of epidemic importance. Studies indicate that, on average, acetylcholinesterase-inhibitor (AChEI) treatment delays cognitive decline in AD patients by nine to 12 months and the need for institutionalization by 18 months.5-9 Moreover, at one year, superior cognitive performance was observed in patients who started AChEI treatment at the beginning than in those who started six months after the beginning in trials with rivastigmine,10 galantamine11 and donepezil.12 Therefore, it would be prudent to apply functional neuroimaging within six months of identifying progressive cognitive decline that could represent incipient AD.

Although the accuracy of the clinical evaluation for AD can be further improved with [18F]fluorodeoxyglucose ([18F]FDG) glucose metabolism positron emission tomography (PET),13,14 or perfusion single photon emission computed tomography (SPECT),15 further improvements can be expected from imaging in vivo of more specific pathological processes for AD: extraneuronal Aβ plaques,16-19 intraneuronal neurofibrillary tangles (NFT),16,20-22 and interneuronal synapse loss.23,24 To our knowledge, no NFT-specific or synapse-loss-specific tracers have been developed for imaging in vivo. Therefore, this article focuses on Aβ-specific tracers.

The β-amyloid Cascade
Mechanism of Aβ production.
The Aβ1-40 and Aβ1-42 (peptides of 40 to 42 amino acids) are derived from a transmembrane protein named amyloid precursor protein (APP).25 There are two APP cleavage pathways:18

- The non-amyloidogenic
pathway: APP cleaved by α-secretase into fragments that do not contain intact Aβ; this pathway does not result in amyloid deposition in the brain; and,

- The amyloidogenic pathway: APP is cleaved by β-secretase (or β-amyloid cleaving enzyme, [BACE]), followed by γ-secretase cleavage. BACE cleavage liberates β-APP that contains the Aβ peptide fragment, and γ-secretase cleavage liberates the Aβ peptide from β-APP. The Aβ peptides aggregate to senile plaques in the brain parenchyma and to cerebral amyloid angiopathy (CAA) in the blood-vessel walls.26

Aggregation of Aβ into senile plaques. Senile plaques are a form of Aβ accumulation and are one of the earliest pathological changes that appear before neuronal loss occurs in the aging and the AD brain.17 Senile plaques have two histologically different forms, which are thought to impact on disease symptoms and progression:17

- Diffuse plaques consist of amorphous Aβ, lack the β-sheet structure and are not surrounded by dystrophic neurites.27 They are associated with normal aging.
- Dense-core (or neuritic) plaques consist of fibrillar Aβ and are found mostly in patients with AD, but also in a small amount in the normal aging brain.28 Fibrillar Aβ has the conformation of a β-sheet structure, which is specifically detected by Congo red or Thioflavin T staining.29 Most of the PET Aβ radioligands discussed below have been derived from these two dyes and are thought to be mainly binding to fibrillar Aβ.

Dementia is common in older adults and approximately doubles in frequency every five years, from about 1% of people aged 60 years to 30% to 40% of those aged 85 years of age and older.
The Canadian Review of Alzheimer's Disease and Other Dementias

This could increase the ability of this tracer to detect presymptomatic AD, but it also suggests that [18F]FDDNP is not a solely Aβ-specific radiotracer, complicating its use in monitoring the effectiveness of Aβ-reducing medication. Moreover, [18F]FDDNP PET may also be positive for tau aggregation in frontal-lobe dementia dementia and for prion pathology.

The second successful in vivo attempt to image Aβ plaques in the AD brain used the benzothiazole aniline derivative [11C]2-(4’-(methylaminophenyl)-6-hydroxybenzothiazole ([11C]6-OH-BTA-1, also referred to as [11C]PIB), which has been reported to bind specifically to fibrillar Aβ at tracer concentrations in vivo (Figure 1). Compared with nine healthy controls, 16 mild-AD patients typically showed marked retention of [11C]PIB in areas of association cortex known to contain large amounts of amyloid deposits in AD, such as frontal, parietal, temporal, and occipital cortices and the striatum. [11C]PIB retention was equivalent in AD patients and healthy controls in areas known to be relatively unaffected by amyloid deposition, such as subcortical white matter, pons, and cerebellum. Of note, significant and high correlations were observed between in vivo [11C]PIB PET and postmortem [3H]PIB and Aβ Enzyme-

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<th>Table 1</th>
<th>Radioligands for Aβ Imaging By PET or SPECT</th>
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<td><strong>Modality</strong></td>
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<td><strong>Positron Emission Tomography (PET)</strong></td>
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<td><strong>Single Photon Emission Computed Tomography (SPECT)</strong></td>
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Linked Immunosorbent Assay (ELISA) uptake in 14 brain regions examined, in one 63-year-old female severe-AD patient. A significant negative correlation between [18F]FDG and [11C]PIB retention was observed in the parietal cortex but not in the frontal cortex at initial and two-year follow-up evaluations. This is interesting as in vitro studies have suggested that the neurotoxicity of fibrillar Aβ is related to impaired glucose transport and is enhanced under conditions of reduced glucose metabolism, while in vivo [18F]FDG PET and postmortem neuropathology data only suggested correlations with NFT but not with Aβ deposition.

The relationship between glucose metabolism and Aβ pathology may be different in distinct brain regions of AD patients, and Aβ plaque formation may not be directly responsible for neuronal dysfunction in all brain regions. Simplified quantification methods have been validated for [11C]PIB against kinetic modeling using arterial input data and graphical and compartmental approaches, and parameters derived from 60 minutes may be similar to those from 90 minutes acquisition time. Voxel-based analyses of [11C]PIB PET data have confirmed the previously obtained region-of-interest data and have shown that [11C]PIB PET was superior to [18F]FDG PET in discriminating mild-to-moderate AD patients from healthy controls. Also, [11C]PIB provided better contrast between three AD patients and three controls than [18F]FDDNP.

The third successful in vivo attempt to image Aβ plaques in the brain of AD patients compared the novel stilbene derivative [11C]4-N-methylamino-4’-hydroxystilbene ([11C]SB-13) with [11C]PIB in five female AD patients versus six matched healthy controls (Figure 2). The two radiotracers demonstrated similar binding properties with respect to regional distribution of retention (increased retention in the frontal and posterior temporal-inferior parietal association cortices in the AD patients, but not in...
the controls). The data indicated that [11C]SB-13 may be similar to [11C]PIB in discriminating AD patients from healthy controls.

The fourth successful in vivo attempt to image Aβ plaques in the brain of AD patients used the benzoxazole derivative [11C]2-[2-(2-dimethylaminothiazol-5-yl)ethenyl]-6-[2-(fluoro)ethoxy]benzoxazole ([11C]BF-227) and showed retention in the frontal, temporal and parietal cortices in 10 AD patients, who could be distinctly differentiated from 11 healthy controls.55

The fifth successful in vivo attempt to image Aβ plaques in the brain of AD patients was made with a SPECT radioligand: [123I]6-iodo-2-(4’dimethylamino)phenyl-imidazo[1,2-]pyridine ([123I]IMPY).56,57 In one study, the average cortical:cerebellar equilibrium distribution volume ratios were 1.25 in eight AD patients versus 1.06 in seven healthy controls,57 and 1.22 in four AD patients versus 0.85 in three healthy controls in another study.56 However, [123I]IMPY may not be selective for Aβ only, as it has also been reported to bind to prion deposits in scrapie-infected mice.58 Additional studies are in progress to more fully validate [123I]IMPY as a potential tool for assessing AD onset and progression. Given the longer radioactive half-life of 123I (13.2 hours), such tracers could be synthesized at one location and transported to a nuclear-medicine facility with a SPECT scanner at another location, greatly increasing the accessibility of this Aβ imaging method.

Aβ Modification Therapies

Aβ modification therapies target amyloid production, amyloid aggregation, and/or amyloid degradation. Some of them are being tested in ongoing clinical trials.61-64 Alpha-secretase activators include statins and estrogen. It has been suggested that some AChEIs may stimulate the non-amyloidogenic α-secretase cleavage of APP as well.65 Beta-secretase inhibitors include TAK-070.66 Gamma-secretase inhibitors include LY45-0139,67 nonpeptidic isocoumarin compounds (JLK inhibitors),68 STI571 imatinib mesylate,69,70 and NSAIDs.70 Gamma-secretase modulators include R-flurbiprofen (MPC-7869 or tarenflurbil).71,72 Especially, tarenflurbil has finished its Phase 2 trials in Canada and England in 2005, and presently Phase 3 trials in AD patients are ongoing in the U.S. and Canada. Tarenflurbil has shown apparent effect on activities of daily living, CDR score, and the Alzheimer’s Disease Assessment Scale-cognitive items (ADAS-cog) test.73

Amyloid-aggregation-targeting therapies by antifibrillization
include the glycosaminoglycan mimetic NC-531 (tramiprole), PBT-2, PPI-1019, and TTP-448. Tramiprole was originally developed by Neurochem in Montreal, Canada. The results of a Phase 3 trial have been collected but—to our knowledge—not yet been reported.

The very latest drug is a cyclohexanehexol stereoisomer, which blocks the accumulation of Aβ oligomers and reduces AD-like behavioral deficits, AD-like neuropathology, and accelerated mortality in a transgenic mouse model of AD. Because this drug is able to alter Aβ pathology even after the symptoms appear, it seems very useful to be applied not only to preclinical-AD subjects but also to AD patients.

Immunization is one Aβ modification therapy option that has been studied in transgenic mice and AD patients. Although immunization improves cognitive function in APP transgenic mice and may slow cognitive decline in AD patients, and although it reduces Aβ plaques in APP transgenic mice and possibly also in AD patients, the studies in AD patients had to be terminated prematurely owing to brain hemorrhage and/or meningoencephalitis. Pathological evidence of the post-immunization patients showed that, although there is no effect on the frequency and severity of CAA per se, hemorrhages could clearly be attributed to amyloid-laden blood vessels, and bleedings only occurred in brain areas affected by CAA. Antibody responders to active immunization with AN1792 had better cognitive function but more brain volume loss. Passive immunization has been tested in PDAPP transgenic mice but to our knowledge, no clinical studies have been performed.

**Potential Impact of Aβ Imaging on AD Management**

As cerebral fibrillar Aβ deposition may occur decades before the manifestation of the clinical AD syndrome, imaging of this pathology in vivo may gain considerable amount of time for therapies that intend to prevent Aβ accumulation, (e.g., by inhibiting fibrillar Aβ production or aggregation). A syndrome of amnestic mild cognitive impairment (MCI) has been identified for which subjects are at an increased risk of progression to AD. MCI subjects have—depending on the definition and group from which the subjects have been recruited—an annual incidence of about 12% progressing to AD in contrast to 1% to 2% for cognitively normal subjects from the same community. These increases in Aβ production or aggregation-inhibiting treatments may be the most effective at earlier stages, (i.e., as preventive rather than curative therapies). There are several in vivo Aβ neuroimaging data that, when combined, suggest that treatment needs to start as early as possible:

2. Amnestic MCI subjects as a group have an [18F]FDDNP uptake between that of cognitively normal subjects and mild-AD patients.
4. These increases in [11C]PIB uptake in non-demented subjects may be related to performance decline in cognitive tests that are highly sensitive to AD-like memory changes.

Of interest, the pattern of Aβ deposition in subjects with autosomal dominant PS1 mutations, predisposing to early onset familial AD, is different from sporadic late onset AD, with earlier and higher [11C]PIB retention in the striatum.
Cerebral $[^{11}C]PIB$ binding was inversely correlated with cerebrospinal fluid (CSF) $A\beta$-42 levels in a mixed group of subjects with Clinical Dementia Ratings varying from zero (no dementia) to two (moderate dementia). Of note, three cognitively normal subjects showed high $[^{11}C]PIB$ uptake with low CSF $A\beta$-42, suggesting preclinical AD. It may therefore be that subjects at risk will have to be identified even at a stage prior to amnestic MCI for these preventive therapies to be fully effective.

Since CAA is assumed to be a contraindication to $A\beta$ immunization (vide supra), screening for contraindication to $A\beta$ immunization was inversely correlated with reactivity to prevent post-immunization brain hemorrhage. Moreover, $[^{11}C]PIB$ PET might also be able to detect CAA in the absence of cerebral $\beta$-amyloidosis.

Given the fact that there appeared to be no change in $A\beta$ binding measured with $[^{11}C]PIB$ PET over two years in mild-AD patients, and that the test-retest reliability of $[^{11}C]PIB$ PET is about 3% to 7%, it has been estimated that anti-$A\beta$ therapy needs to induce at least a 15% decrease in $A\beta$ load before its effect can be detected. Incorporating in vivo $A\beta$ PET may make clinical trials more efficient, as the target patient population group can be better defined and a relevant neurobiological outcome measure can be assessed that may be more sensitive than, and predictive of, assessments of clinical outcome.

Conclusions

$A\beta$ PET can contribute to the management of AD by helping to:

- establish whether there is a cerebral $\beta$-amyloidosis underlying the dementia syndrome, which can help with the differential diagnosis of the potential cause(s) of the dementia;
- identify patients at risk of developing AD, who would be suitable candidates for anti-$A\beta$ therapies (particularly medications that target $A\beta$ production or aggregation);
- select patients for anti-$A\beta$ therapies that could have serious adverse effects, such as $A\beta$ immunization; and
- monitor the efficacy of anti-$A\beta$ therapies.

Acknowledgements:

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References


Imaging and Alzheimer’s Disease: A Review

Neuroimaging in Alzheimer’s disease (AD) has moved beyond the stage where it was used purely to exclude other disease processes. Structural brain magnetic resonance imaging (MRI) is useful to assess hippocampal atrophy on coronal slices; clinicians can use a simple visual rating scale, which can help to confirm the diagnosis of AD. Another useful indication for neuroimaging is to assess the contribution of cerebrovascular disease (CBVD) to the clinical syndrome of dementia. It has become clear in recent years that the most common situation in the general population is the combination of AD and CBVD. A neuroimaging procedure (CT scan or, preferably, MRI) can detect silent CBVD, which would modify management of modifiable risk factors. The recent Canadian Consensus on Dementia recognized this indication.

Christian Bocti, MD, FRCPC

Neuroimaging has traditionnally been recommended as a way to exclude potentially reversible causes of dementia, even though the prevalence of treatable causes of dementia in typical referral clinics is very low. This traditional view was largely held until the previous Canadian Consensus in 1999, where specific guidelines were stated to restrict the indications of neuroimaging in dementia. However, there has been much development since those guidelines were published. The most recent Practice Parameter from the American Academy of Neurology recommends that at least one neuroimaging procedure should be done in every patient with a dementing disorder. This article reviews structural and functional imaging in the diagnosis of Alzheimer’s disease (AD). Future developments of imaging hold great promise and are briefly overviewed.

Background

The process that leads to AD probably begins decades before we can detect it clinically. At one point, the functional connectivity and molecular changes that occur within cells result in neuronal loss and brain atrophy. This atrophy follows a specific, systematic anatomical pattern for reasons that are still a matter of debate. One hypothesis holds that the AD process follows brain regions in decreasing order of “neuroplasticity potential.” This view states that the hippocampus and its connections in the entorhinal cortex (the part of the medial temporal lobe just adjacent to the hippocampus) remain the most active in terms of plasticity throughout the lifespan. Indeed, the forming of new memories occurs during adult life, and is supported by structural changes in the hippocampal-entorhinal complex: these structural changes are termed neuroplasticity. Neuroplasticity failure would affect the medial temporal lobe first, then its connections within the limbic and para-limbic regions, then the multimodal associative cortex. It is this topographical selectivity that allows early detection of atrophy in the medial temporal regions.
Structural Neuroimaging: Brain Atrophy

Several studies using CT and MRI scans have shown significantly smaller hippocampi in subjects with AD compared with normal controls, with accuracy of classification in the 85% range. There is a whole spectrum of tools with varying degrees of technological intensity, ranging from the simplest visual rating scale to the most sophisticated 3D shape-deformation analysis of the hippocampus, which require advanced hardware, software and statistical knowledge. Visual rating scales (Figure 1) can be performed by clinicians quickly (one to two minutes), with minimal training, and have been validated against volumetric measures.

For reasons of ease-of-use and availability, this simple type of imaging analysis is probably the one with the most potential usefulness in clinical practice for now. Recent developments have brought automated measures closer to clinical practice, but even “simple” techniques require registration to standardized 3D templates, which is not likely to be widely available.

It should be kept in mind that hippocampal atrophy alone may not be sufficient to diagnose AD in cohorts comparing different diagnostic groups: the addition of a Mini Mental State Examination (MMSE) score to a visual rating of medial-temporal-lobe atrophy was found to be necessary to discriminate between AD and non-AD in one study, and other temporal-lobe structures were assessed in another. There are several reports where medial-temporal-lobe atrophy is found in non-AD dementias, such as fronto-temporal dementia. Nevertheless, a group of experts recently recommended that research criteria for AD be revised, and that assessment of medial-temporal atrophy should be a part of the new criteria, which also include cognitive information and other biomarkers.

In conclusion, although medial-temporal atrophy does contribute to diagnostic specificity in expert hands, it has yet to be translated into widespread clinical and radiological practice. According to a recent stringent evidence-based review, there is insufficient data on MRI in general-practice settings to recommend its widespread use.

Structural Neuroimaging: Cerebrovascular Disease

In recent years, CBVD has been reconceptualized as a major factor in cognitive decline and dementia, including AD. Ischemic lesions such as lacunar infarcts greatly influence the clinical syndrome of dementia; this could be an additive or a synergistic effect. It appears that the most common pathological substrate of dementia in population-based autopsy series is combined CBVD and AD pathology; mixed dementia could be more frequent in the general population than “pure” AD. It is also well known from large-scale, population-based imaging studies that the prevalence of...
“silent” brain infarcts is quite high in the general population and has an impact on cognitive decline.\(^{25,26}\) In light of these data, it is quite surprising to find that until recently, there were no official recommendations to include neuroimaging as a means to detect CBVD in dementia assessment. Although neuroimaging evidence of what constitutes “significant” CBVD in dementia is still not agreed on, there is a general agreement on the fact that detection of silent CBVD should lead to a more pro-active management of modifiable vascular risk factors.\(^{27}\) These considerations have resulted in a statement from the 3rd Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD):\(^{28}\) “There is fair evidence to support use of structural neuroimaging to rule in concomitant CBVD that can affect patient management.”

Ever since neuroimaging was integrated in clinical routine,\(^{29}\) there has been much controversy about the white-matter changes (or leukoaraiosis) that appear ubiquitous in aging.\(^{30}\) Recent years of research have finally crystallized knowledge on this phenomenon, and there is an emerging consensus that confluent lesions (as opposed to punctate lesions) do progress with time,\(^{31}\) and are associated with certain cognitive deficits as well as motor and functional disability.\(^{32-34}\) Moderate-to-severe leukoaraiosis is thus far from benign, and can easily be assessed with simple rating scales (Figure 2).\(^{35}\)

**Advanced Structural Neuroimaging Techniques**

Until now we have dealt with traditional neuroimaging techniques that are in common clinical use. Recent developments in MRI technology have revealed that structural damage can be detected in areas outside of visibly abnormal regions on the standard images: several techniques are available, but will not be reviewed in detail here. One of the most promising techniques is diffusion tensor imaging (DTI), where integrity of the white-matter tracts can be assessed by analyzing the movement of free water molecules within the tracts.\(^{38}\) More degraded tracts will result in increasingly random movements, which can be detected by DTI; such abnormalities can be correlated with cognitive functions.\(^{39}\) Studies have now shown that AD is associated with degradation of white-matter tracts.\(^{40}\) It is still a technical challenge to obtain such data and thus routine availability of DTI will not happen in the foreseeable future.

**Functional Neuroimaging**

Nuclear medicine has been used in the study of dementia for many years, with single photon emission computed tomography (SPECT) and positron emission tomography (PET) scans tested as diagnostic tools in AD and other dementias. There are reports on PET imaging that show it is more sensitive and specific compared with clinical assessment in the early diagnosis of dementia. The value of PET in the differential diagnosis of frontotemporal dementia versus AD has recently been demonstrated in a well designed study that looked at added benefit over clinical information alone, notably with a simple visual rating by the (experienced) clinician.\(^{41}\) SPECT is more
widely available, but is generally less sensitive and specific than PET. Nevertheless, it has some value in the diagnosis of AD and differential diagnosis of dementias, including frontal and anterior temporal hypoperfusion in fronto-temporal dementias, and occipital hypoperfusion in dementia with Lewy bodies.

**Advanced Functional Neuroimaging Techniques**

Direct imaging of neuropathological hallmarks of AD is becoming possible with the development of specific tracers in PET imaging. This has some potential to help in the early diagnosis of AD, but unfortunately correlations between amyloid on neuropathology and cognition have been far from compelling. Also, there is a substantial proportion of elderly without cognitive impairment who also have high amyloid burden on pathology. The specificity of an amyloid imaging technique remains to be proven in light of these known pathological correlates. Future development in tau imaging might contribute more substantially to this field since tau and neurofibrillary tangles are more robustly associated with cognition in AD.

**Conclusion**

In summary, the diagnosis of dementia will likely remain clinical for most purposes in the next few years. However, there are potential benefits and diagnostic utility of some widely available imaging techniques. In particular, systematic rating of medial-temporal atrophy on MRI has the potential of increasing diagnostic certainty for AD in specialty clinics. Similarly, identification of lacunes and application of a simple rating of leukoaraiosis on CT scans of the brain can provide prognostic information and alter management of patients.

The real challenge facing clinicians will be increasing pressure to diagnose AD earlier and with more accuracy and diagnostic confidence. This pressure will become much more important when efficient disease-modifying therapies are available. Neuroimaging perhaps will have to be used in that early period of the disease, where it is likely to be more useful. New research criteria have been proposed for that purpose, and rightfully include medial-temporal-lobe atrophy as a neuroimaging biomarker. These criteria will certainly give an impetus to the systematic rating of medial-temporal-lobe atrophy by radiologists and clinicians in the next few years. A large-scale, open-access database is currently being developed in the U.S. and Canada and will likely be very useful to further delineate the diagnostic value of neuroimaging in AD.

**References**


Molecular Imaging of Alzheimer’s Disease Using PET

Research indicates that positron emission tomography (PET) aids in assisting specialists in the early and differential diagnosis of Alzheimer’s disease (AD). In this article, Dr. Rosa-Neto and Mr. Leuzy discuss how PET reveals critical information on various aspects of the brain physiology altered by dementia.

Pedro Rosa-Neto, MD, PhD; and Antoine Leuzy

Molecular Imaging Techniques
Molecular imaging of the brain aims to quantify various biological processes via the modeling of interactions between a molecular probe and a molecule of interest naturally occurring in a living organism. Brain molecular-imaging techniques such as positron emission tomography (PET) and single photon emission tomography (SPECT) allow clinical investigators to record and analyze such interactions in vivo. PET and SPECT associated with specific molecular probes are sensitive to detecting biological processes in the order of pico-molar ($10^{-12}$), however these techniques have limited spatial resolution. In contrast, magnetic resonance imaging (MRI) has a tremendous spatial resolution (sub-milliliter range) but lower sensitivity (micromolar; $10^{-6}$) relative to PET and SPECT (Table 1). Together, these techniques reveal critical information with regards to the alterations in the brain’s anatomy and physiology witnessed in dementia, as well as canalizing diagnostic methods and therapeutic interventions.

The Nature of PET Imaging
The goal of a PET study in dementia is to quantify important biological processes altered in the brains of patients with dementia, such as glucose metabolism, cerebral blood flow, the availability of neuroreceptors and the detection of disease-related molecules (i.e., amyloid deposits, tangles, inflammation). PET is a complex evaluation requiring expertise in many fields such as nuclear medicine, radiochemistry, imaging, kinetics and neuroscience. A PET scan likewise encompasses various activities such as:
1. production of a radioisotope;
2. synthesis of a radiopharmaceutical;
3. data acquisition;
4. imaging reconstruction; and
5. estimation of a biologically relevant outcome by the analysis of the brain radioactivity distribution maps recorded during the course of the study (Figure 1).

The production of a radioisotope is generally obtained with a particle accelerator known as a medical cyclotron (Figure 1A), which produces a beam of high-energy protons or deuterons directed against a target consisting of the nuclei of stable atoms. This process results in transmutation of the target nucleus into a short-lived positron-
emitting radioisotope (Figure 1B). Spontaneous decomposition of the produced radioisotope occurs within a specific half-life ([15O], two minutes; [11C], 20.4 minutes and [18F], 109.8 minutes). The product of decomposition of these radioisotopes is an anti-electron, known as a positron. Once produced at the cyclotron facility, positron-emitting radioisotopes are chemically incorporated into radiopharmaceuticals (Figure 1C). Positrons emitted by the radioisotope present in the radiopharmaceutical collide with surrounding electrons. The resultant collision between the emitted positron and any electron located in its vicinity releases the rest-mass energy of the two particles \( (E = mc^2) \) as two high-energy photons (gamma rays) of 511 keV each. The photons are released at an angle of 180 degrees. If this annihilation event occurs within the PET field of view, a ring of detectors converts the coincident photons into light, which is subsequently amplified by photo-multipliers. Finally, the events computed by the scanner are analyzed by algorithms, which reconstruct the data as maps of the radioactivity concentration in the brain as a function of time (Figure 1F).

**PET records the interactions between radiopharmaceuticals and molecules of interest.** In essence, PET is a technique that computes patterns of spatial-temporal distributions of positron-emitting radioisotopes in the brain or any other part of the body (Figure 1F). With few exceptions, positron-emitting radioisotopes administered to dementia patients are associated with molecular probes called radiopharmaceuticals (Figure 1C), and thus, one may assume that the distribution of radioactivity recorded by the PET camera refers to the distribution of the radiopharmaceuticals in the brain or any other organ. The use of mathematical models allows for the extraction of biologically relevant information from the spatial-temporal distributions of positron-emitting radioisotopes recorded during the PET scan. However the mathematical models provide accurate results if:

1. the radiopharmaceuticals specifically interact with only one molecule of interest in the brain during the time frame of the PET scan; and
2. the radiopharmaceuticals are in “tracer concentration” (minute doses incapable of causing any pharmacologic effect).

Typical biological outcomes of interest for clinical research in dementia include the biodistribution of pharmaceuticals, the identification of disease-related molecules and the estimation of rates of molecular transport and energy metabolism.
PET Imaging Outcomes of Interest for Alzheimer’s Disease (AD)

Post-mortem studies indicate that the pathophysiologic process involved in AD begins long before the clinical symptoms develop.2,3 Thus, due to its high sensitivity and noninvasive nature, PET can identify the presence of the pathological molecules. Indeed, a number of imaging studies using longitudinal designs have shown the potential of PET to detect presymptomatic or prodromal AD in a population with elevated genetic risk and in subjects with mild memory impairment.4-8 In general, PET studies on AD focus on the quantification of abnormal metabolic changes, the detection of disease-specific abnormal proteins (tau and amyloid deposits) as well as declines in neurotransmission.9,10 PET associated with various molecular probes has the potential to diagnose and monitor disease progression and treatment. Table 2 summarizes several PET radiopharmaceuticals applied to AD research.

Imaging abnormal cerebral blood flow and metabolism in AD. Pioneer studies of brain metabolism performed by Kety and Lassen3,10 in the mid 1950s showed that a global decline of brain perfusion and metabolism is present in patients with dementia. The advent of tomographic imaging revealed that cerebral blood flow and metabolic consequences of dementia are not widely diffused through the brain; rather they are associated with a major dysfunction of certain brain regions (Figure 2 and 3).11,12

Brain regional glucose metabolism is typically estimated using the PET and the molecular probe 2-fluoro-2-deoxy-D-glucose ([18F]FDG), which is an analogue of glucose normally consumed by the brain.13,14 In brief, the accumulation of [18F]FDG in a given brain region is proportional to its glucose metabolic rate (Figure 2),13,15 In typical cases of AD, declines of brain glucose metabolism (hypometabolism) and cerebral blood flow initially occur in the posterior parieto-temporal cortex and posterior cingulate cortex (Figure 3).11,12,16 During the evolution of AD, metabolic declines progressively spread to other brain regions initially spared during the early phase of the disease. The hypometabolism revealed by PET in AD patients possibly reflects several pathological processes underlying AD pathology, such as loss of synaptic activity, gliosis and deposits of amyloid.
plaques. Recent studies also link the hypometabolism in the posterior parieto-temporal cortex and posterior cingulate cortex with various vulnerability factors for AD, such as the presence of the genetic polymorphism for the apolipoprotein E epsilon 4. Furthermore, several independent studies strongly suggest that PET [18F]FDG is sensitive in detecting the presence of hypometabolism in the brain several years before the onset of AD symptoms. Thus, the quantification of brain metabolism in AD has potential clinical relevance, since an early diagnosis of AD allows for early interventions with disease-modifying therapies, which aim to delay the onset and progression of AD.

Today, a PET [18F]FDG is typically indicated by a specialist for patients with a documented cognitive decline of at least six months and a recently established diagnosis of dementia, meeting the diagnostic criteria for AD. Although the accuracy of a PET [18F]FDG as a diagnostic tool for AD may be superior to a baseline clinical evaluation, the diagnostic value of a PET [18F]FDG is limited since regional hypometabolism is not a specific finding of AD. PET associated with radioligands designed to target specific aspects of AD neuropathology constitutes a research field with high translational value.

**Imaging brain pathology in AD.** Advances in radiochemistry permits the use of new radioligands specifically designed for the quantification of pathological aspects of AD. Much attention has been given to imaging of amyloid deposition and neuroinflammation associated with AD. Imaging brain pathology using PET may have important impact on disease-modifying therapies as this therapeutic approach focuses on specific mechanisms such as the formation of amyloid plaques, neuroprotection and neurorestorative approaches.

**Imaging disease-related abnormal molecules.** Progressive accumulation of abnormal protein aggregates including amyloid or tau deposits are pathological hallmarks of AD. Abnormal amyloid deposits in AD brains are found as neuritic plaques, amyloid angiopathy and diffuse amyloid deposits. The amyloid cascade hypothesis of AD predicts that the neurofibrillary tangles, cell loss, vascular damage, and dementia follow as a direct result of progressive abnormal amyloid deposition. Thus, quantifying the amyloid burden (amyloid accumulated) in the brain of AD patients may aid in the diagnosis and monitoring of disease progression. Another important application for imaging disease-related abnormal proteins is to improve the specificity and accuracy of the diagnosis of AD and predementia states.

Though several PET molecular agents for amyloid plaques have been tested, the [11C]PIB and the [18F]FDDNP have thus far proved to be the most effective radiopharmaceuticals in the demonstration of AD pathology. While [11C]PIB seems to be more specific to amyloid deposits, it has been suggested that [18F]FDDNP has an affinity for amyloid and tangle pathology. Preliminary studies indicate that these lead compounds exhibit high binding in brain areas affected by AD pathol-

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**Table 1**

<table>
<thead>
<tr>
<th>PET</th>
<th>SPECT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Pico-molar concentration</td>
<td>Pico-molar concentration</td>
</tr>
<tr>
<td>Typical anatomical resolution</td>
<td>5 mm³</td>
<td>10 mm³</td>
</tr>
<tr>
<td>Quantification</td>
<td>Absolute</td>
<td>Semiquantitative outcome</td>
</tr>
<tr>
<td>Typical radioisotopes utilized</td>
<td>[18F]FDG, [11C], [15O]</td>
<td>[99mTc]</td>
</tr>
</tbody>
</table>

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ogy, such as the frontal, temporal and parietal lobes. However, deposition in the brain is not unique to clinically apparent AD and has been found in normal aging as well as in patients in the presymptomatic stages of AD.28-31

The concept of amyloid imaging is currently being tested and hopefully PET imaging using amyloid agents will be available for clinical purposes in the near future.

**Imaging neuroinflammation in AD.** [11C]PK11195 is a radiopharmaceutical that selectively binds to the peripheral benzodiazepine receptor present in the activated microglia, which is a cell involved in brain inflammatory responses. In vivo studies carried out in various degenerative diseases, including AD, indicate that the inflammation is an active process underlying AD. The binding of [11C]PK11195 is enhanced in the entorhinal cortex, hippocampus and posterior cingulate cortex in patients with AD. In fact, neuroinflammation, as revealed by high [11C]PK11195 binding, was also present in AD patients with a mild clinical presentation of the disease.19,43,44 The clinical value of inflammation and amyloid imaging techniques is still under evaluation.

**Imaging abnormal neurotransmission in AD.** Abnormalities in various neurotransmission systems such as those utilizing serotonin, glutamate and acetylcholine, have been described extensively in AD. In vivo quantification of such abnormalities may help clinical researchers to understand the mechanisms underlying AD and to propose new therapeutic targets, the exploitation of which will hopefully translate into improved quality of life for AD patients.

**Imaging cholinergic neurotransmission.** Declines in cholinergic neurotransmission have significant clinical relevance since the mechanisms of action of three FDA-approved medications for the treatment of AD aim to enhance brain acetylcholine neurotransmission through the inhibition of acetylcholinesterase (AchE), the enzyme responsible for the breakdown of acetylcholine. In fact, post-mortem studies in AD patients indicate important declines in cholinergic innervation as well as a global reduction of acetylcholine synthesis capacity. These findings, together with the degeneration of the nucleus basalis of Meynert, strongly support that acetylcholine neurotransmission is impaired in AD. However, it has been argued that in vivo quantification of presynaptic cholinergic neurotransmission in AD patients

### Table 2

<table>
<thead>
<tr>
<th>Biological Process of Interest</th>
<th>Molecular Agents</th>
<th>Typical Findings in AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism</strong> (References: 12,16-18, 48-52)</td>
<td>Glucose metabolism</td>
<td>[18F]FDG</td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>[15O]O2</td>
<td>Hypometabolism</td>
</tr>
<tr>
<td>[15O]H2O</td>
<td>Reduction of blood flow</td>
<td></td>
</tr>
<tr>
<td><strong>Pathology</strong> (References: 19,21 17,18,25,26,29,30)</td>
<td>Neuroinflammation</td>
<td>[11C]PK11195</td>
</tr>
<tr>
<td>Amyloid plaques</td>
<td>[11C]PIB</td>
<td>High amyloid load</td>
</tr>
<tr>
<td>Amyloid plaques + tangles</td>
<td>[18F]FDDNP</td>
<td>High amyloid load</td>
</tr>
<tr>
<td><strong>Neurotransmission</strong> (Hippocampus/cortex) (References: 2,35,36,41-44,53,54)</td>
<td>Serotonin 5-HT1A</td>
<td>[18F]MPPF</td>
</tr>
<tr>
<td>Serotonin 5-HT2A</td>
<td>[18F]altanserin</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Dopamine D2</td>
<td>[18F]setoperone</td>
<td>Low binding</td>
</tr>
<tr>
<td>GABA</td>
<td>[11C]FLB</td>
<td>Low binding</td>
</tr>
<tr>
<td>Acetylcholinesterase (AchE) activity</td>
<td>[11C]flumazenil</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

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using PET is of limited value due to peculiarities of the cholinergic neurotransmission. Therefore, it is expected that eventual progress in radiochemistry would allow adequate quantification of cholinergic neurotransmission in the living human brain. Studies using [$^{11}$C]physostigmine, [$^{11}$C]methyl-4-piperidyl-acetate ([$^{11}$C]MP4A) and [$^{11}$C]methylpiperidin-4-yl-propionate ([$^{11}$C]PMP) confirm the declines in cholinergic neurotransmission reported by post-mortem studies; some of these studies found correlations between cholinergic dysfunctions and cognitive deficits of AD patients. Cholinergic, muscarinic and nicotinic receptors have been studied in patients with AD, however the interpretation of these studies is limited due the low specificity of most muscarinic and nicotinic neurotransmitters. In brief, studies using radiopharmaceuticals such as [$^{11}$C]nicotine suggest a decline in cholinergic nicotinic receptors in AD; studies with the muscarinic receptor radiopharmaceuticals [$^{11}$C]benztropine, [$^{11}$C]-N-methyl-4-piperidyl benzilate and [$^{18}$F]A85380 also indicate declines in acetylcholine neurotransmission in AD. So far no PET radiopharmaceutical could properly quantify the presynaptic aspects of cholinergic neurotransmission.

**Imaging serotonin and dopamine neurotransmission in AD.** In contrast to cholinergic radiopharmaceuticals, most of the current serotonergic and dopaminergic PET molecular agents allow for selective, reliable and accurate quantification of various aspects of serotonin and dopamine neurotransmission. Serotonin 5-HT$_{1A}$ receptors are abundant in brain regions affected by AD. Although there are conflicting results regarding the 5-HT$_{1A}$ binding in the hippocampus of patients with predementia, it seems that AD patients have substantial declines in hippocampal 5-HT$_{1A}$ receptor binding. Declines in hippocampal dopamine D$_2$ receptor binding are also reported in AD patients. In contrast, hippocampal and neocortical binding of gamma-aminobutyric acid (GABA) receptors remains unaltered in AD. Information regarding the availability of serotonin 5-HT$_{2A}$ receptor is conflicting and remains to be clarified. In the striatum, while dopamine D$_2$ receptors are unaffected by AD, dopamine D$_1$ receptors are slightly decreased. Together these findings highlight the role of hippocampal dopamine and serotonin neurotransmission in the etiology of AD, however further research is necessary in order to evaluate the clinical significance of these findings.

**Future directions of PET imaging in AD**

Certainly, the main mission of imaging in AD is the development of new techniques capable of accurately diagnosing pre-dementia states. Moreover, new radiopharmaceuticals for imaging cholinergic presynaptic terminals, imaging agents for glutamate synaptic function and efficient molecular probes for tau protein are amongst the

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**Figure 3**

Typical Declines of Brain Glucose Metabolism in AD Patients

This is a composite plate showing an MRI (A,D), a PET [$^{18}$F]FDG (B,E) and the combination between PET and MRI images (C,F) obtained from a patient (female; 70 years of age) with the diagnosis of probable AD. Note that in the fusion images (C,F), the MRI add spatial resolution to the PET. The indication (*) shows the posterior temporo-parietal junction (B,C) and the posterior cingulate gyrus (E,F), which are areas typically hypometabolic in AD.
important goals to be achieved by radiochemistry research. However, it is possible that single-mode imaging methods may not provide sufficient diagnostic accuracy for pre-AD dementia. Thus, multimodal imaging diagnostic platforms with multiple molecular probes may constitute an alternative for the current single-mode imaging methods.

Conclusions
Current literature indicates that only PET [18F]FDG has clinical relevance in assisting specialists in the early and differential diagnosis of AD.

Molecular imaging of AD patients using PET associated with various radiopharmaceuticals provides valuable information regarding the numerous aspects of the neurobiology of dementia. Furthermore, PET has potential research applications such as early diagnosis, following the evolution of certain biomarkers during the course of dementia, and in monitoring treatment efficacy. Hopefully these research applications will be rapidly translated into benefits for patients living with AD.

References:

To access this article’s full reference list please visit: www.stacommunications.com/adreview.html.
A Beacon of Hope

www.alzheimer.ca
Help for Today. Hope for Tomorrow.

It’s been called an “insidious fog”… and “sailing into the dark”...
Alzheimer Disease affects the brain, erases memory and eventually takes life itself.

The Alzheimer Society provides a beacon of hope to people with the disease and their families. The Society provides information, support and funds research into the cause and cure of the disease. We’re fighting back.
The safety of ARICEPT during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or in nursing mothers unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus or the infant.

ARICEPT tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of AD.

CONTRAINDICATIONS
ARICEPT (donepezil hydrochloride) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives.

SPECIAL POPULATIONS
Use in pregnant or nursing women
The safety of ARICEPT during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or in nursing mothers unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus or the infant.

Use in children
There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT in any illness occurring in children. Therefore, ARICEPT is not recommended for use in children.

Use in elderly patients (%65 years of age)
In AD patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age, and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as AD can be associated with significant weight loss, caution is advised regarding the use of ARICEPT in low body weight elderly patients, especially in those ≥85 years old.

Use in elderly patients with comorbid disease
There is limited safety information for ARICEPT in patients with mild-to-moderate or severe AD and significant comorbidity. The use of ARICEPT in AD patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and include close monitoring for adverse events (AEs). Caution is advised regarding the use of ARICEPT doses above 5 mg in this patient population.

In severe AD, the possibility of comorbid vascular disease and risk factors for vascular AEs and mortality should be considered.

Use in patients with vascular dementia
Three clinical trials, each of 6 months duration, were conducted to evaluate the safety and efficacy of ARICEPT for the symptomatic treatment of individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients with dementia that appears to be due solely to vascular causes, and to exclude patients with AD. ARICEPT was not shown to be an effective treatment for patients with vascular dementia in two of these clinical trials.

The safety profile from these controlled clinical trials in VaD patients indicates that the rate of occurrence of treatment-emergent AEs overall was higher in VaD patients (86%) than in AD patients (75%). This was seen in both ARICEPT-treated subjects and placebo-treated subjects, and may relate to the greater number of comorbid medical conditions in the VaD population.

In two of the clinical trials, there was a higher rate of mortality among patients treated with ARICEPT, during double-blind treatment; this result was statistically significant for one of these two trials. For the three VaD studies combined, the mortality rate in the ARICEPT group (1.7%, 25/1,475) was numerically higher than in the placebo group (1.1%, 8/718), but this difference was not statistically significant (see Supplemental Product Information below).

There is no evidence of an increase risk of mortality when ARICEPT is used in patients with mild-to-moderate AD.

ARICEPT (donepezil hydrochloride) is indicated for the symptomatic treatment of individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients with dementia that appears to be due solely to vascular causes, and to exclude patients with AD. ARICEPT is therefore recommended.

ARICEPT, as a predictable consequence of its pharmacological properties, has been shown to produce, in controlled clinical trials in patients with AD, diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg dose than with the 5 mg dose. In most cases, these effects have usually been mild and transient, sometimes lasting 1 to 3 weeks and have resolved during continued use of ARICEPT (see ADVERSE REACTIONS section).

Treatment with the 5 mg/day dose for 4-6 weeks prior to increasing the dose to 10 mg/day is associated with a lower incidence of gastrointestinal intolerance.

When monitoring for adverse events (AEs) in patients with hepatic disease being treated with ARICEPT, close monitoring for AEs in patients with hepatic disease being treated with ARICEPT is therefore recommended.

Neurologic
Seizures: Some cases of seizures have been reported with the use of ARICEPT in clinical trials and from spontaneous Adverse Reaction reporting. Cholinomimetics can cause a reduction of seizure threshold, increasing the risk of seizures. However, seizure activity may also be a manifestation of AD. The risk/benefit of ARICEPT treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

ARICEPT has not been studied in patients with Parkinsonian features. The efficacy and safety of ARICEPT in these patients are unknown.

Peri-operative considerations
Anesthesia: ARICEPT, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.
Renal
There is limited information regarding the pharmacokinetics of ARICEPT in renally impaired AD patients. Close monitoring for AEs in patients with renal disease being treated with ARICEPT is therefore recommended.

Respiratory
Because of their cholinomimetic action, cholinesterase inhibitors should be prescribed with caution to patients with a history of asthma or obstructive pulmonary disease. ARICEPT has not been studied in patients under treatment for these conditions and should therefore be used with particular caution in such patients.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE

Mild-to-moderate Alzheimer’s disease
A total of 747 patients with mild-to-moderate AD were treated in controlled clinical studies with ARICEPT (donepezil hydrochloride). Of these patients, 613 (82%) completed the studies. The mean duration of treatment for all ARICEPT groups was 132 days (range 1-356 days).

The rates of discontinuation from controlled clinical trials of ARICEPT due to AEs for the ARICEPT 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received the 10 mg/day dose after only a 1-week initial treatment with 5 mg/day ARICEPT was higher at 13% (see Table 1).

The most common AEs, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, were diarrhea, nausea, vomiting, decreased appetite, and aggression. Each of these AEs led to discontinuation of ARICEPT treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common AEs may be affected by the duration of treatment with an initial 5 mg daily dose prior to increasing the dose to 10 mg/day (see Table 2 and Supplemental Product Information below).

Severe Alzheimer’s disease
A total of 573 patients with severe AD were treated in controlled clinical studies with ARICEPT. Of these patients, 441 (77%) completed the studies. The duration of double blind treatment in all studies was 24 weeks. The mean duration of treatment for all ARICEPT groups was 148.4 days (range 1-231 days). The mean daily dose of ARICEPT was 7.5 mg/day.

In clinical trials of patients with severe AD, most patients with significant comorbid conditions were excluded. The use of ARICEPT in AD patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and should include close monitoring for AEs.

In controlled clinical trials in severe AD, the rate of discontinuation due to AEs was 11.3% in patients treated with ARICEPT, compared to 6.7% in the placebo group. The most common AEs that led to discontinuation, more often in patients treated with ARICEPT than placebo, were diarrhea, nausea, vomiting, urinary tract infection, decreased appetite, and aggression. Each of these AEs led to discontinuation of less than 2% of patients treated with ARICEPT.

The incidence profile for AEs for severe AD was similar to that of mild-to-moderate AD (see Table 4).

The most common AEs, defined as those occurring at a frequency of at least 5% in patients and twice the placebo rate, were vomiting, diarrhea, nausea, and aggression. Overall, the majority of AEs were judged by the investigators to be mild or moderate in intensity.

Results from the controlled clinical trials indicate that the incidence of AEs, such as vomiting, urinary tract infection, urinary incontinence, pneumonia, falls, decreased appetite, aggression, restlessness, hallucination and confusion, may be higher in ARICEPT- and placebo-treated patients with severe AD than in patients with mild-to-moderate AD.

Postmarket adverse drug reactions
Voluntary reports of AEs temporally associated with ARICEPT that have been received since market introduction that are not listed above, and for which there is inadequate data to determine the causal relationship with the drug, include the following: abdominal pain, cholecystitis, convulsions, heart block (all types), hemolytic anemia, hepatitis, hypertension, pancreatitis, and rash.

DRUG INTERACTIONS

Concomitant Use with Other Drugs
Use with anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with cholinomimetics and other cholinesterase inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists, such as bethanechol.

Use with other psychoactive drugs: Few patients in controlled clinical trials received neuroleptics, antidepressants or anticonvulsants. There is thus limited information concerning the interaction of ARICEPT with these drugs.

Drug-drug interactions
Pharmacokinetic studies, limited to short-term, single-dose studies in young subjects, evaluated the potential of ARICEPT for interaction with theophylline, cimetidine, warfarin and digoxin administration. No significant effects on the pharmacokinetics of these drugs were observed. Similar studies in elderly patients were not done (see Supplemental Product Information below).

Health Canada may be notified by phone of serious or unexpected reaction to this drug at: 1-866-234-2345.

Administration

Dosing considerations
ARICEPT (donepezil hydrochloride) or ARICEPT RDT should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of AD.

Special populations: The use of ARICEPT in AD patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for AEs. It is recommended that ARICEPT be used with caution in these patient populations. AEs are more common in individuals of low body weight, in patients ≥85 years old and in females.

Recommended dose and dosage adjustment
Adults: The recommended initial dose of ARICEPT or ARICEPT RDT is 5 mg taken once daily. Therapy with the 5 mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug (see ADVERSE REACTIONS section) and to allow plasma levels to reach steady state. Based on clinical judgement, the 10 mg daily dose may be considered following 4-6 weeks of treatment at 5 mg/day. The maximum recommended dose is 10 mg taken once daily.

Following initiation of therapy or any dosage increase, patients should be closely monitored for AEs.

Special populations: AEs are more common in individuals of low body weight, in patients ≥85 years old and in females. In elderly women of low body weight, the dose should not exceed 5 mg/day.

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

Administration
ARICEPT should be taken once daily in the morning or evening. It may be taken with or without food.
ARICEPT tablets should be swallowed whole with water.
ARICEPT RDT should be placed on the tongue and allowed to disintegrate before swallowing with water.

Study References
**Warnings and Precautions**

Use in pregnant and nursing women.

Teratology studies conducted in pregnant rats at doses of up to 63 mg/kg/day and in pregnant rabbits at doses of up to 10 mg/kg/day did not disclose any evidence for a teratogenic potential of ARICEPT.

Use in elderly patients (≥75 years of age).

In controlled clinical studies with 5 and 10 mg ARICEPT in patients with mild-to-moderate AD, there were 836 patients between the ages of 65 to 84, and 37 patients aged 85 years and treated with ARICEPT. In controlled clinical trials of patients with severe AD, there were 167 patients who were ≥75 years of age. 726 patients between the ages of 75 and 84, and 138 patients aged ≥85 years treated with ARICEPT.

Use in patients with vascular dementia.

**Mortality Rates in ARICEPT Vascular Dementia Clinical Trials**

Table 3. Mortality Rates in ARICEPT Vascular Dementia Clinical Trials

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Placebo (n=355)</th>
<th>ARICEPT (n=747)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Patients with any Adverse Event</td>
<td>72%</td>
<td>74%</td>
</tr>
</tbody>
</table>

Body System/Adverse Event

- Body as a Whole
  - Headache 9 10
  - Pain, various locations 6 9
  - Migraine 6 7
  - Fatigue 3 5

- Cardiovascular System
  - Syncope 1 2

- Digestive System
  - Nausea 6 11
  - Vomiting 3 5
  - Anorexia 2 4

- Hemic and Lymphatic System
  - Ecchymosis 3 4

- Metabolic and Nutritional
  - Weight decrease 1 3

- Musculoskeletal System
  - Muscle cramps 2 6

- Nervous System
  - Incontinence 6 9
  - Dizziness 6 8
  - Depression <1 3
  - Abnormal dreams <1 2
  - Somnolence <1 2

- Urogenital
  - Urinary incontinence 1 2

Other adverse events observed during clinical trials in mild-to-moderate Alzheimer’s disease.

During the premarketing phase, ARICEPT has been administered to over 1,700 individuals with mild-to-moderate AD for various lengths of time during clinical trials worldwide. Approximately 1,500 patients have been treated for at least 3 months, and more than 1,000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In patients for the highest dose of 10 mg/day, this population includes 650 treated patients for 3 months, 475 treated patients for 6 months and 115 patients treated for over 1 year. The range of patient exposure is from 1 to 1,214 days.

Table 4. Severe Alzheimer’s disease

Table 4 lists treatment-emergent signs and symptoms (TSS) that were reported in at least 2% of patients from placebo-controlled clinical studies who received ARICEPT, and for which the rate of occurrence was greater for ARICEPT than placebo-assigned patients.

Table 5. Mild-to-Moderate Alzheimer’s disease:

**Adverse Events Referred to Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT and at a Higher Frequency than Placebo-Treated Patients**

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Placebo (n=465)</th>
<th>ARICEPT (n=573)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Patients with any Adverse Event</td>
<td>74</td>
<td>83</td>
</tr>
</tbody>
</table>

Gastrointestinal

- Diarrhea 4 10
- Vomiting 9 8
- Nausea 3 6

Fecal incontinence 1 2

Skin:

- Skin rash 1 2

Infections and infestations

- Urinary tract infection 7 8
- Nasopharyngitis 6 8
- Pneumonia 3 4

- Injury, Poisoning, Procedural Complications
  - Full 9 10
  - Contraction 2 4
  - Skin ulceration 1 2

Investigations

- Blood-creatine phosphokinase increased 1 2

- Metabolism and Nutrition
  - Anorexia 2 4
  - Decreased appetite 1 1
  - Defaturation 1 2

Musculoskeletal and Connective Tissue

- Back pain 2 6
- Osteoarthritis 1 2

- Nervous System
  - Headache 9 11
  - Somnolence 0 2

- Psychiatric
  - Agitation 3 4
  - Insomnia 3 4
  - Restlessness 2 3
  - Hallucinations 1 1
  - Confusional state 1 2

Renal and Urinary

- Cardiac Function 2 3

Respiratory

- Cough 1 2

- Vascular
  - Hypertension 1 2

A frequency of 1% was used when frequencies were <0.5%.

Other AEs listed in Table 3 occurred in at least 2% of ARICEPT treated patients, and at an equal or lower rate than in placebo-treated patients, included: abdominal pain, fatigue, gastroenteritis, excoriation, dizziness, and anxiety and depression.
Long-term safety for severe Alzheimer’s disease

In Study 315, which was a 24-week, randomized, placebo-controlled study in severe AD patients, at the end of double-blind treatment, 239 patients entered open-label ARICEPT treatment for up to an additional 12 weeks. Therefore, at the end of the open-label phase, 111 patients had received up to 36 weeks of ARICEPT treatment and 118 patients had received up to 12 weeks of ARICEPT treatment. The most commonly affected body systems, types and frequencies of AEs reported during 12 weeks of open-label ARICEPT treatment were similar to what was observed during 24 weeks of double-blind treatment. Gastrintestinal AEs (diarrhea, nausea, vomiting, anorexia) were reported at a higher frequency in patients who received up to 12 weeks of ARICEPT treatment. Other AEs reported at higher frequencies in patients treated with ARICEPT for up to 12 weeks included infection, pneumonia, fever, dizziness, hypertension, asthma, tremor, pharyngitis, hallucinations, convulsions and cysts. In patients treated with ARICEPT for up to 36 weeks, accidental injury, urinary incontinence and urinary tract infections were reported at higher frequencies.

DRUG INTERACTIONS

Drug-drug interactions

Drugs highly bound to plasma proteins: Drug displacement studies have been performed in vitro between donepezil, a highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil at concentrations of 0.3-10 μg/mL did not affect the binding of furosemide (5 μg/mL), digoxin (5 ng/mL) and warfarin (5 μg/mL) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin.

Effect of ARICEPT on the metabolism of other drugs: In vitro studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6. Donepezil (mean Ki about 50-130 μM) affected the binding of warfarin (3 μg/mL) and digoxin (2 ng/mL) to human albumin. The binding of donepezil to CYP 3A4 and CYP 2D6 was not affected by donepezil.

Effect of ARICEPT on the metabolism of other drugs: Effect of ARICEPT on the metabolism of other drugs: In a pharmacokinetic study involving 18 healthy volunteers, the administration of ARICEPT at a dose of 5 mg/day for 7 days had no clinically significant effect on the pharmacokinetics of ketoconazole. No other clinical trials have been conducted to investigate the effect of ARICEPT on the clearance of drugs metabolized by CYP 3A4 (e.g., cyclosporine, terfenadine) or by CYP 2D6 (e.g., imipramine).

Effect of other drugs on the metabolism of ARICEPT: Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism in vitro. In a pharmacokinetic study, 18 healthy volunteers received 5 mg/day ARICEPT together with 200 mg/day ketoconazole for 7 days. In these volunteers, mean donepezil plasma concentrations were increased by about 30%-36%.

Drugs metabolized by CYP 2D6 and CYP 3A4 (e.g., paroxetine, carbamazepine, dexamethasone, rifampin and phenytoin) could increase the rate of elimination of ARICEPT.

Some pharmacokinetic studies demonstrated that the metabolism of ARICEPT is not significantly affected by concurrent administration of donepezil or valdecoxib.

Drug-food interactions

Food does not have an influence on the rate and extent of donepezil hydrochloride absorption.

Drug-herb interactions

Interactions with herbal products have not been established.

Drug-laboratory interactions

Interactions with laboratory tests have not been established.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms: Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Treatment: The elimination half-life of ARICEPT (donepezil hydrochloride) at recommended doses is approximately 70 hours. Thus, in the case of overdose, it is anticipated that prolonged treatment and monitoring of adverse and toxic reactions will be necessary. As in any case of overdose, general supportive measures should be utilized.

Tertiary anticholinergics, such as atropine, may be used as an anticholinergic for ARICEPT overdose. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Appropriate responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity observed in animals included: reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, fasciculation, and lower body surface temperature.

Product Monograph available on request.
Advocating for Change: Making Dementia a National Health Priority

As the national voice for people affected by dementia, the Alzheimer Society has an important role to play in advocating for change within our provincial and federal governments.

With approximately half a million Canadians affected by dementia, or one in every 13 people older than 65 years, this is more than just an important health concern. This disease has the potential to overwhelm the healthcare system if fundamental changes are not made in research funding and care delivery.

By working to influence the programs and initiatives that directly affect people living with Alzheimer’s or a related disease, the Alzheimer Society is helping to improve the quality of life for everyone touched by dementia.

“The Alzheimer Society believes that research remains the key to finding a cure, and that a significant investment in science is essential if we are to eradicate dementia,” says Scott Dudgeon, CEO of the Alzheimer Society of Canada. “We also believe that there must be better support, care and treatment for people living with Alzheimer’s or a related disease.”

With this in mind, the Alzheimer Society of Canada is building on the success of previous federal-government initiatives and advocating the Government of Canada to sponsor the development of a Canadian Dementia Management Strategy.

**Canadian Dementia Management Strategy**

The purpose of the strategy will be to guide policy development and care delivery, and it will draw upon the collaborative efforts of policymakers, healthcare-system managers, clinicians, researchers and healthcare providers.

It will encompass those aspects that most directly impact the lives of those touched by Alzheimer’s or a related disease, including: research, prevention, diagnosis, improved treatment, improved care and care for caregivers.

“We know that tremendous strides are being made in the development of biomarkers, and in the use of neuroimaging to facilitate rapid reliable diagnosis and early intervention,” says Dr. Jack Diamond, scientific director for the Alzheimer Society of Canada. “Part of this strategy would be to ensure that policy is in place to expedite adoption of these emerging diagnostic technologies.”

**Raise Your Voice**

Time is of the essence. As the population demographics shift in Canada, it becomes paramount that preventive measures are put into place to avoid the epidemic of dementia.

“Already, many Canadians have taken up the challenge and become Alzheimer advocates. People living with Alzheimer’s and related diseases, caregivers, healthcare professionals and researchers are joining their voices together to become a powerful tool for change, working to create a future without Alzheimer’s disease,” adds Dudgeon. “You too can make a difference. Let your voice be heard by becoming an Alzheimer’s advocate today.”

The Alzheimer Society of Canada is a not-for-profit health organization dedicated to helping people affected by Alzheimer’s disease. The Society provides support and educational programs for people with Alzheimer’s disease and their caregivers. The Society also funds research into finding a cure for the disease, and into improved methods of caregiving. For more information, or to become an Alzheimer Advocate, please contact your local Alzheimer Society, or visit www.alzheimer.ca
Mindscapes 2008, an exhibition of art produced by seniors with dementia, will be featured from June 2 to June 16, 2008 at Emily Carr Institute of Arts and Design on Granville Island in Vancouver. The exhibition follows the opening of the Third International Conference on Creative Expression, Communication and Dementia which will take place on May 30 and 31, 2008 at Emily Carr. The exhibition is open to the public; admission is by donation.

These events are hosted by the Society for the Arts in Dementia Care and the Institute of Neurosciences, Mental Health and Addiction to bring attention to the creative abilities of seniors with dementia and to spotlight the research that is underway to improve the quality of life for these seniors.

The program includes invited speakers who are international leaders in their fields. They come from the United States, Australia and universities on the east and west coasts of Canada, and will discuss their research and practical approaches to dementia care.

In addition, an elegant dinner is planned for conference participants at the Granville Island Hotel, followed by a piano concert featuring the celebrated artists, Tami and Yuval Admony, which is open to the public (tickets online).

Visit the conference website at: www.cecd-society.org for more information. Professionals, practitioners and the interested public are welcome to attend.

For more information, contact:
Dr. Dalia Gottlieb-Tanaka at 604/986-6408
or at info@cecd-society.org
ARICEPT is indicated for the symptomatic treatment of patients with mild, moderate and severe dementia of the Alzheimer’s type. ARICEPT does not change the underlying course of the disease.

In patients with mild-to-moderate AD, the most common adverse events with ARICEPT 10 mg/d after proper dose escalation include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia (occurring in at least 5% of patients and at twice the placebo rate). These events are usually mild and transient, resolving with continued ARICEPT treatment without the need for dose modification.

In patients with severe AD, the most common adverse events were vomiting, diarrhea, nausea, and aggression (occurring in at least 5% of patients and at twice the placebo rate). Overall, the majority of adverse events were judged by the investigators to be mild or moderate in intensity.

† In a 24-week, randomized, double-blind, placebo-controlled study of ARICEPT in 153 mild AD patients (MMSE 21-26). Patients received either ARICEPT 5 mg/d for the first 6 weeks and 10 mg/d thereafter, (n=96), or placebo (n=57). 37% of ARICEPT-treated patients experienced a 4 point ADAS-cog improvement and 10% experienced a 7 point improvement vs. 16% and 7% respectively with placebo.

‡ In a 24-week, multicentre, randomized, double-blind, placebo-controlled trial, 473 patients (MMSE 10-26) were randomized to receive ARICEPT 5 mg/d, ARICEPT 10 mg/d or placebo. Following the 24-week, double-blind phase, all patients underwent a 6-week, single-blind placebo washout. Patients treated with either dose of ARICEPT demonstrated significantly less decline on the CIBIC-plus vs. placebo (CIBIC-plus value at endpoint for ARICEPT 5 mg/d and 10 mg/d were 4.15 and 4.07 respectively vs. 4.51 with placebo, \(p=0.0047\) and \(p<0.0001\)).