

PROGRESS IN CLINICAL NEUROSCIENCES: Canadian Guidelines for the Development of Antidementia Therapies: A Conceptual Summary

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ABSTRACT: The magnitude of the problems faced by an aging Canadian society has been clearly identified. Perhaps the single most important problem is the increasing incidence of dementia. Alzheimer's disease (AD) accounts for 50-60% of the dementias in later life within a spectrum of other contributing dementias. Regulatory approval has been given to Acetylcholinesterase inhibitors for the symptomatic treatment of mild to moderate AD, and conditional approval to memantine for the symptoms of moderate to severe AD. There has been no regulatory approval for the treatment of the degenerative dementias beyond AD. The very rapid progress in the past decade in biotechnology and in the molecular biology of the dementias is supporting a new generation of innovative treatment strategies that will more directly target the underlying disease pathogenic mechanisms. Such treatments will foreseeably include immunotherapies, anti-aggregants that may prevent misfolding and deposition of proteins, and neuroregenerative interventions. These Guidelines follow the 2nd Canadian Conference on the Development of Antidementia Therapies, held in 2004, which covered a range of design, methodological and ethical issues facing clinical researchers and regulatory authorities. They are intended to provide a common point of reference and guidance in Canada for therapeutic development of the dementias.

RÉSUMÉ: Lignes directrices canadiennes pour le développement de traitements de la démence: sommaire conceptuel. L'amplitude du problème auquel fait face la société canadienne vieillissante a été clairement identifiée. Le problème le plus important est l'incidence croissante de la démence. De 50 à 60% des cas de démence chez les gens âgés sont dus à la maladie d'Alzheimer (MA). Des inhibiteurs de l'acétylcholinestérase ont été approuvés pour le traitement symptomatique de la MA légère ou modérée et la mémantine a reçu une approbation conditionnelle pour le traitement des symptômes modérés ou sévères de la MA. Aucun traitement des démences dégénératives autres que la MA n'a été approuvé. Les progrès très rapides de la recherche sur les démences en biotechnologie et en biologie moléculaire pendant la dernière décennie sont à l'origine d'une nouvelle génération de stratégies novatrices de traitement qui cibleront plus directement les mécanismes pathogéniques de la maladie sous-jacente. Il est probable que différentes stratégies seront utilisées dont l'immunothérapie, les anti-agrégants qui préviennent le pliage erroné de protéines et leur dépôt et les interventions neurorégénératrices. Ces lignes directrices sont émises suite à la deuxième conférence canadienne sur le développement de traitements anti-démence en 2004. Cette conférence a examiné plusieurs questions de modèles, de méthodologies et d'éthique auxquels sont confrontés les cliniciens chercheurs et les organismes réglementaires. Elles offrent un point de référence commun et une orientation pour le développement de traitements des démences au Canada.

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Dementias are now recognized to present some of the most important challenges to face medicine in the 21st century. The Canadian Study of Health and Aging (CSHA) reported that, in 1991, the prevalence figures for all types of dementia were 80/1,000 in those over the age of 65 and 345/1,000 in those over the age of 85 in this country. The study projected that by 2011 there would be 475,000 individuals over the age of 65 affected with dementia.¹ Of those affected with dementia, 50-65% have a diagnosis of Alzheimer's Disease (AD), while mixed causes of dementia are increasingly recognized. The direct and indirect cost of care for each patient with AD has been estimated to vary between \$16,000 to as much as \$37,000 per year (1998, CAD), with increasing costs tied to disease severity.² This estimate

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means that billions of dollars are spent on the care of AD patients at the present time in Canada. To meet this challenge, both government and the private sector will need to make major investments in research on the prevention of dementia, its treatments and on the community infrastructure needed to manage these illnesses.

Major advances in both molecular neurobiology and biotechnology hold considerable promise in translating basic neuroscientific findings into more definitive therapies aimed at treating the pathologies of the dementias. This rapid growth of research, however, requires careful consideration of the range of ethical issues that come up almost continually. As well, the development of new treatment approaches for dementia will require position papers to be published and disseminated to stimulate the public discussion needed on these very important issues related to antedementia treatments. The existence of an integrated network of investigators from within the Consortium of Canadian Centres for Clinical Cognitive Research (C5R), the Canadian Neurological Society, the Canadian Academy of Geriatric Psychiatry (CAGP), and the Canadian Geriatrics Society (CGS), allow Canada to play a significant role in addressing this important global problem.

The goal of this Guidelines paper is to provide a broad conceptual summary that can serve as a point of common reference to clinicians, clinical researchers, government agencies, and the pharmaceutical, biotechnology industries in Canada who all face the important challenge of the dementias together in the coming decades. It is presented in a similar form of draft statements and recommendations to the Guidelines for Antedementia Therapies that were published in this journal in 1995.³

METHODS

The 2nd Canadian Conference on Antedementia Drug Guidelines was convened October 28-29, 2004, in Montreal. The conveners of the conference (H. Feldman and S. Gauthier) established a steering committee with the chairs of each of the major Canadian medical societies involved in the care of patients with dementia, including H. Chertkow (C5R), D. Conn (CAGP), C. MacKnight (CGS), and M. Freedman (Canadian Neurological Society). An agenda was developed to cover the range of diagnostic and treatment standards, study designs, ethical issues related to the development of therapies, outcome measures, biological markers, and the broad spectrum of the dementias. Emphasis was placed on both the current state of the art as well as on the anticipated future issues around each topic. Each participating organization was asked to recommend five representatives with recognized expertise for each topic area, to ensure the highest level of contribution to the conference. Selected consultants were then added to the conference to cover specialized areas outside of the expertise of the working group, including D. Streiner who spoke on design and methodologic issues, and J. Poirier who provided a future vision of the development of therapies. Important regulatory guidance was provided by three participating members of the Central Nervous System (CNS) Division of the Therapeutic Products Directorate (TPD) of Health Canada. The Alzheimer Society of Canada sent three representatives to the Conference to ensure that the

perspective of patients and caregivers was fully considered. Finally, there were a number of international external consultants invited, including the Chair of the International Working Group on the Harmonization of Antedementia Drug Guidelines (Dr. J.-M. Orgogozo), and a member of the United States Food and Drug Administration Advisory Panel on Dementia (Dr. S. DeKosky).

In preparation for the conference, all of the medical society representatives were asked to submit a 500-word summary statement and potential recommendations for their assigned topic. Participants working within specific topic areas met with the conveners via teleconference to review their progress and discuss their perspectives before the conference. Each participant was also asked to submit a more expanded 2,000-word background paper to capture the basis of their summary statements and recommendations. At the time of the conference each topic was presented in a short plenary format, followed by an open-session discussion of the recommendations that had been proposed. The summary of the conference and its recommendations were finalized and prepared for publication by the authors of this paper.

During the conference, all participants provided statements of disclosure of their involvement with pharmaceutical and biotechnology companies, which are held on file. Funding for the conference was received through a workshop grant of the Canadian Institutes of Health Research (CIHR) Institute on Aging and through grants-in-aid to the meeting from a large number of pharmaceutical companies who were invited in an observer role (see Acknowledgements for details). All meeting funding was received and administered by MedPlan who was responsible for the logistics and organization of the meeting.

DIAGNOSTIC CRITERIA AND APPROACHES FOR RESEARCH STUDIES

Dementia

The syndrome of dementia consists of cognitive and functional decline and is frequently associated with behavioural symptoms and personality changes.⁴ For the effective evaluation of treatment strategies, a consistent diagnostic framework must be adhered to. While a number of diagnostic criteria have been proposed worldwide, in Canada, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) is the most widely used framework for the general definition of dementia.⁵ This diagnostic standard continues to be revised and will be updated.

There are some noted deficiencies in the DSM-IV-TR criteria. Of particular concern is the central emphasis on the memory domain, whereas some forms of dementia frequently present without a prominent memory deficit. The provision that there be a progressive decline in any two cognitive domains, each resulting in impairment in social or occupational function, would allow a broader range of dementias to be captured beyond those that can be identified by the DSM-IV-TR. Furthermore, there is no requirement for neuroimaging within the diagnostic research criteria, yet it is standard that neuroimaging be performed in all subjects participating in dementia therapeutic trials. This is viewed as an essential part of determining vascular elements

within dementia and should be included in proposed criteria to allow the highest degree of diagnostic accuracy and characterization of persons entering into therapeutic trials.

Alzheimer's Disease

The DSM IV-TR and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD provide the clinical diagnostic standards for research studies.^{4,5} These criteria have been validated both clinically and pathologically. While their diagnostic sensitivity has ranged from very good to excellent, their specificity has been problematic in many studies,⁶⁻⁸ and their inter-rater reliability has ranged from only fair to very good.⁷ There are inherent limitations in measuring the accuracy of diagnostic criteria where the gold standard neuropathology that is most widely used is based on a probabilistic likelihood and where more than one pathological process may contribute to dementia.⁹ Within the NINCDS-ADRDA criteria, the distinction between "possible" and "probable" AD has been difficult to apply particularly in the presence of multiple comorbid pathologies. It is now recognized that cerebrovascular dementia and AD co-exist clinically at a frequency in 30-40% of all dementia cases.^{10,11} Other subgroups within possible AD have also been identified.¹² "Possible AD" has been generally removed from AD clinical trials research focus and the licensing of AD treatment for "probable" AD leaves a significant percentage of patients with mixed disorders being treated off of labeled indication and without sufficient supportive data on efficacy and safety. The deficiencies of the NINCDS-ADRDA criteria in addressing comorbid and mixed AD pathologies need to be addressed in future AD diagnostic criteria, as will the need to include study groups with mixed pathologies within the clinical trial development of therapies.

With the emergence of naturalistic and treatment studies focusing on earlier AD identification beginning with the stage of mild cognitive impairment (MCI), there is also a current need to develop more sensitive formal diagnostic criteria for early disease. These criteria will need to be shown to reliably identify disease in patients who do not meet current standard criteria. Criteria for earlier AD diagnosis are an important priority area for research and development.

Vascular Dementia

For vascular dementias (VaD), traditional classification has been based on the Hachinski Ischemic Score and its modified versions.^{13,14} Currently it is the 1993 National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria that are used most frequently in randomized clinical trials of VaD, with both the "probable VaD" and "possible VaD" subgroups.¹⁵⁻¹⁸ The NINDS-AIREN criteria have been reported in clinical pathological correlative studies to have high specificity but low sensitivity.¹⁹⁻²¹ Whereas this is advantageous in the initial acquisition of clinical trials data for VaD therapy, it leaves an unfulfilled need for criteria with greater sensitivity and broader generalizability to the problem of VaD in its various forms.

Some of the issues surrounding the sensitivity of these VaD diagnostic criteria likely result from the reliance or specification

that there is a core memory disorder where executive dysfunction is more often the prominent core symptom and where medial temporal lobe structures need not be involved as is the case more typically in AD.

Dementia with Lewy Bodies (DLB)

The criteria developed by McKeith et al²² have become a standard for studies in DLB. These criteria, have been shown to generally have high specificity (in the range of 85-90%), while reports have shown them to have substantially lower sensitivity.^{23,24} However, the inter-rater reliability of DLB criteria remains significantly lower than for other sets of dementia criteria, likely resulting from the heterogeneity of clinical presentation.²⁵ Within the symptom cluster of DLB there have been recognized difficulties in defining fluctuations within the core criteria. There is a need to improve diagnostic sensitivity of the DLB criteria, without losing their high specificity, however this may not be resolved until there is a biological test.

Parkinson's Disease Dementia (PDD)

There are no standard criteria for the diagnosis of PDD. There has been much debate and uncertainty over the relationship between the timing of onset of cognitive decline and the motor Parkinsonian signs. Recent publications have proposed that PDD be defined as having at least one year of motor Parkinsonism before the onset of symptoms of dementia.^{24,26} The biological plausibility of this distinction is uncertain. The necessary understanding of the relationship between DLB and PDD is apparent as both disorders are characterized by an indistinguishable neuropathology, and revised clinical diagnostic criteria will likely be needed to reflect the neuropathological continuum that exists between these disorders.

Frontotemporal Dementia (FTD)

Two current sets of criteria for the clinical spectrum of disorders related to frontotemporal dementia have been proposed: the Neary criteria of 1998, which have superseded the older Lund Manchester diagnostic checklist,^{27,28} and the criteria published by the Workgroup on Frontotemporal Dementia and Pick's Disease.²⁹ The Neary criteria recommend the term "Frontotemporal lobar degeneration" (FTLD) as the overarching single category that includes three clinical syndromes: frontotemporal dementia, progressive non-fluent aphasia and semantic dementia that are each defined by core and supportive criteria. With their detailed characterization of these recognized subtypes, the Neary criteria have some advantage for use in clinical trials research. Although it is not currently known whether patients within these different phenotypic subtypes respond differently to pharmacological treatment, the availability of these well-defined operational criteria should facilitate such an evaluation. However, there is still no broad consensus presently on FTD/FTLD diagnostic criteria,²⁸⁻³¹ and terminology^{32,33} and this is needed to facilitate the development of therapeutic trials that will optimally evaluate emerging therapies.

Mixed Dementia

There has been a growing recognition that a significant

proportion of dementia cases have multiple overlapping neuropathological processes, including vascular, amyloid, tau, and synuclein abnormalities. Clinically this has resulted in mixed dementia diagnoses occurring in increasingly large numbers within dementia cohort studies.¹⁰ Alzheimer's disease and vascular dementias are the two dementias that most commonly coexist. There is a need for a diagnostic framework on mixed dementia to be developed for research studies and treatment trials.¹²

Mild Cognitive Impairment (MCI)

The term Mild Cognitive Impairment (MCI) has emerged in the past decade as the most frequently used term to describe the condition of individuals with aging who fall outside of the normal range of cognitive functioning, but do not reach criteria for a diagnosis of dementia. The spectrum of overlapping, but slightly different, conditions in MCI includes Benign Senescent Forgetfulness, Age Associated Memory Impairment (AAMI), Age Associated Cognitive Decline (AACD) and Cognitively Impaired Not Demented (CIND). Common to a number of these defined states, such as MCI, AACD and CIND, are a consistently reported and increased rate of longitudinal progression to dementia diagnosis.³⁴⁻³⁷ Petersen et al have operationalized MCI to include individuals with both subjective and objective memory impairment, with generally normal cognitive function outside of the memory domain, and with normal activities of daily living (ADL).³⁸ By definition these individuals do not meet the DSM IV TR criteria for dementia; however, there is considerable debate as to whether this form of MCI is a high risk state of progression to AD or the earliest stage of the disease.³⁸ It has been proposed that the constructs around MCI might be better clarified by refinement of ADL assessments,³⁹ by careful subclassification of neuro-psychological domains involved,⁴⁰ or by the inclusion of neuroimaging or biomarkers.⁴¹ The best approach remains a matter of some controversy.^{42,43} An amnesic form of MCI (MCIa) is one clinically defined phenotype of particular interest as a target of therapy. Although intervention at the earliest point in the dementia pathway is clearly desirable, there are a number of issues surrounding MCI that will need resolution to allow it to be an acceptable condition for regulatory approval. In particular, the multiplicity of MCI definitions, the heterogeneity of MCI cohort outcomes based on settings of care, the role of etiological subtypes and the generalizability of the MCIa subgroup to the much larger group of MCI, both in efficacy as well as safety, all need to be further addressed.

Recommendations on Diagnostic Criteria and Approaches for Research Studies

The current diagnostic standard for dementia, the DSM-IV-TR, would benefit from movement away from a prerequisite amnesic disorder and towards a set of criteria that might better apply to VaD, PDD, DLB and FTD. Patients with AD and multiple associated disorders, including cerebrovascular disease or Lewy bodies where clinically definable, should also be included within AD drug development to allow sufficient collection of safety and efficacy data for patients with mixed causes of their dementia. As a priority, diagnostic criteria for the earlier identification of AD are required to support earlier

treatment interventions. The diagnostic criteria for DLB and VaD both have high specificity but insufficient sensitivity, which underscores the need for further refinement, while PDD and FTD criteria are still in evolution and would benefit from efforts to establish international consensus criteria. Whether MCI and its amnesic form will be a useful construct for randomized controlled trials (RCTs) remains to be fully evaluated.

THERAPEUTIC APPROACHES FOR DEMENTIA

Symptomatic Approaches

In proposing a medication as a putative symptomatic treatment for dementia, it is essential that several issues be addressed. The first is the identification of which symptomatic domains of cognition, behaviour, or function, are the object of treatment. Second, it is mandatory that symptomatic treatment effects be both clinically apparent and meaningful.

The drugs for the symptomatic treatment of AD that are currently available have been approved by the CNS Division of the Therapeutic Products Directorate (TPD) of Health Canada on the basis of meeting dual primary outcomes, that include a target symptom domain (cognition or behaviour) and a global impression of change. They include the Acetylcholinesterase inhibitors (AChEIs) (donepezil, rivastigmine, and galantamine) for the symptoms of mild to moderate AD; and memantine, the uncompetitive NMDA-receptor antagonist, which has been conditionally approved for the treatment of the symptoms of moderate to severe AD. This same regulatory approach is likely to continue in the future for symptomatic treatments, though targets, including ADLs, should be considered where appropriate, particularly in more advanced disease.

At present, there is no regulatory specification to include a measure of quality of life (QOL) associated with symptomatic improvement, however, it is appreciated that this is an important aspect for patients and their caregivers and its measurement should be encouraged.

Therapies for Disease Modification

Currently there is a lack of agreement on the methodology to demonstrate disease modification. Proposals have included a delayed start and early withdrawal, however, these have numerous and serious limitations. Proof of a disease-modifying effect would require biological plausibility, a convincing and meaningful change in the disease progression, supported by beneficial effects on biological or imaging markers of the disease.

It is appreciated that symptomatic drugs may also have disease-modifying properties; however, this has yet to be demonstrated. For currently available treatments, a sustained symptomatic benefit is a more realistic target for long-term studies. The methodology for demonstrating a disease modification still requires more development. At the present time the long-term impact of treatment in dementia is best evaluated within survival study designs to the clinical milestones.

Therapies for Disease Prevention

With the projected growth in the number of dementia patients over the next three decades,¹ dementia prevention will likely

become a primary focus of research. The concept of dementia prevention is currently described as delaying the time to onset of diagnosable disease.⁴⁴ Current trials are being conducted in the United States and Europe with a range of three to 12 years.⁴⁴ The number of subjects within these current studies and their associated costs have been prohibitive and are unlikely to be sustainable. Enrichment strategies such as positive family history, apolipoprotein E genotype (E4) will be needed to allow sufficiently high numbers of incident cases to develop within the reasonable timeframe for studies. Prevention studies will also need to be large, take into consideration high drop-out rates, pay particular attention to simple, valid, reliable measures, and to safety. Studies can be nested in other endeavours (e.g., Syst-Eur) which can decrease costs.⁴⁵ The adherence rate to protocol over long periods of study is an important issue within prevention studies.

Recommendations on Therapeutic Approaches for Dementia

An indication for symptomatic treatment of dementia should be supported by a demonstration of efficacy within at least one of the individual domains of cognition, behaviour, or function in conjunction with a significant benefit on a clinical global measure. Whereas it may be possible to demonstrate a sustained symptomatic benefit at the present time, there is no agreed methodology for a disease-modifying study. Prevention trials are required as they may have the largest public health impact, though there are methodological challenges to make these studies practical and affordable within the Canadian context.

ETHICAL ISSUES

Standards of Care

The AChEIs are considered the standard of care for mild to moderate AD in Canada,⁴⁶⁻⁵² although only approximately 25% of patients with AD are reportedly treated at the current time.⁵³ A recent survey found that investigators in 82% of Canadian dementia clinical research units did not believe that it was possible to recruit to placebo-controlled studies of longer than three months, while 73% reported that they considered it ethically unacceptable to recruit drug-naïve patients with mild to moderate AD to a placebo-controlled clinical trial. (Personal communication Dr. Howard Chertkow)

Risk/Benefit Ratio

With the increasing prevalence of dementia there is pressure to develop therapies more rapidly and to allow their general use as early as possible. As the discussions of the risks and benefits to patients in this process are intensifying, a number of dilemmas are apparent. The progressive nature of these illnesses requires intercession as quickly as possible, while non-judicious use of inadequately tested treatment with doubtful efficacy and significant toxicity can be injurious and is clearly undesirable.

A further concern with respect to emerging biotechnological therapies for AD is the absence of reliable animal models for investigation. The "new biology" of immune therapies, nerve growth factors, genetically-engineered tissues, and other tissue modifying techniques pose both ill-defined risks and considerable opportunity. While showing therapeutic promise they may also have significant risks. For example, one AD

immunotherapy trial with amyloid beta (Ab) was initiated, then discontinued in Phase II when an important and serious meningoencephalitis occurred in 6% of subjects.⁵⁴ Consideration should be given to testing beyond murine models before taking novel putative disease-modifying treatment into human studies to assist in ascertaining a signal of safety and, where possible, efficacy.

The Canadian Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans (TCPS, 2003) embodies principles for ethical decision-making, with some more clearly defined than others.⁵⁵ The TCPS is the basis upon which Canadian research review boards review their submissions, though it is unclear in its discussion of consent, assent, and proxy-decision-making in dementia. It will also need to be updated and clarified with regard to its consideration of the risk/benefit ratio of specific trials and the participation of vulnerable individuals. Ethical review is a dynamic process, particularly as applications are surfacing with higher risk and a need for more intense ethical debate.

Placebo Use

The use of placebos in medicine and in medical research has a long and complex history. The legal, ethical, and scientific debate around placebo use is equally complex.^{56,57} Recently, Health Canada and the CIHR established a National Placebo Initiative and a National Placebo Working Committee that recommended that whenever possible "... research subjects in the control group of a trial of a diagnostic, therapeutic, or preventative intervention should receive an established effective therapy."⁵⁸ Their document points out that there can be clear distinctions between a treatment that has met regulatory approval and an "established effective therapy". Even when an established effective therapy exists, the possibility of designing an ethically acceptable placebo-controlled trial is not precluded.⁵⁸ However, in practice, with an established standard of care of AChEIs for AD, placebo trials will be used in most circumstances within add-on-designs, where standard therapy is provided to all subjects and either placebo or experimental therapy is added on for the period of research study.

Recommendations on Ethical Issues

AChEIs represent the standard of care in Canada. The scientific community and industry can no longer rely on a presumed necessity for demonstration of absolute efficacy through a placebo-controlled trial by a regulatory agency as sufficient justification for the study design without provision of a standard of care. Investigators and sponsors will need to carefully and thoughtfully justify the use of a placebo when it is proposed and seek alternative study designs.

DESIGN AND METHODOLOGY ISSUES

The prevalence of AD makes it the main target of experimental therapeutic intervention in dementia. Much of the discussion that follows is therefore centered on AD, though many of the general concepts outlined will also apply to the other dementias.

Phases of Drug Development

Traditionally, Phase I studies have been conducted with healthy volunteers, young and old, for the purpose of elucidating kinetics, pharmacodynamics, toxicity and tolerance to pharmacological agents. With treatments targeting the biology of the disease directly, Phase I trials will usually require individuals with the disease rather than healthy volunteers. The traditional role of Phase II studies has been the evaluation of the safety and efficacy of drugs in small, well-defined, restricted patient groups, as well as to obtain signal of efficacy as proof of principle. This usually involves multiple doses, looking for maximum tolerated dose (MTD). For treatments targeting the biology of the disease directly, alternative research pathways to MTD seem likely to be pursued. These may center around the treatment dose that can provide both a biological and clinical response in Phase II, as a prelude to a larger scale Phase II-III trial looking for a clinically-meaningful response in a representative population.⁵⁹ The dose selected may not be related or determined by the MTD. The success of this alternative approach remains to be demonstrated. Open-label extension studies on the active drug after Phase II would be useful sources of the necessary safety data for regulatory approval to proceed to Phase III. Pharmacovigilance after marketing (or a structured Phase IV trial concentrating on safety) is essential to detect unexpected and important adverse effects. There is currently no structured program in Canada for this and this represents an unmet need.

Study Designs

New agents for the treatment of AD are most likely to be developed with randomized, controlled trials that allow for the use of the standard of care treatment for all subjects, with the experimental agent or placebo added on. This design will restrict the new indication to add-on therapy, while new monotherapy claims will foreseeably require alternative approaches to add-on designs, including testing for superiority, equivalence and non-inferiority. The use of a placebo design without a usual care background will likely be restricted to those patients who are intolerant, those with a non-response to standard pharmacological treatment, or those who give an informed refusal of standard pharmacological care. Each of these scenarios is anticipated to occur infrequently. A further design option is a three-arm trial where there is an experimental treatment, an AChEI and a placebo arm. The size of the placebo arm would be as small as possible, with as short duration of placebo exposure as necessary to demonstrate the requisite efficacy. Some studies have attempted an enrichment technique through a defining of early responders who then continue on a more extended protocol;⁶⁰ however, this is not a currently recommended approach.

Most studies are designed to compare the results on a particular test at time X between groups. Survival studies (time to a clinically relevant event) will be seen more often, and may be simpler for patients, families, third-party payers and non-expert professionals to interpret. These types of studies have been tried in AD.⁶¹

For disease modification the randomized withdrawal design that has been proposed has particular ethical problems, while the randomized start design assumes that the response to an agent

(either symptomatic or disease-modifying) is independent of the stage at which the agent is started.⁶²⁻⁶⁴ Designs based on survival to a clinically meaningful endpoint might solve some of these problems; however, there are a number of considerations that must be resolved to establish widely accepted and appropriate disease milestones. To date, studies have used time to nursing home placement, decline in Clinical Dementia Rating (CDR) stage, loss of ADLs, and death.⁶¹ Nursing home placement as a disease milestone is complex, as it is determined not only by disease progression but by bed availability, caregivers and other socioeconomic factors that have little to do with pharmaceutical treatment. Death may not be a suitable outcome in dementia if there is prolonged suffering and incapacity in a poor state of health. The delay in losses of ADL may be a suitable outcome; however, there are stage-specific changes and confounding factors can enter into consideration based on settings of care. The emergence of neuropsychiatric symptoms (NPS) has been proposed but phenomenologically NPS may be recurrent and not a suitable permanent dementia milestone. The United States Food and Drug Administration has stated that delaying a clinical milestone in a parallel-group, controlled trial would not be viewed as sufficient evidence for disease modification.⁶⁵ This leaves the unresolved question of whether in the absence of a surrogate biological marker, the demonstration of disease modification is a realistic goal.

Other study designs for dementia also have pitfalls. Multiple cross-over trials are inappropriate for a progressive disease, given that the response at one point in time would not be expected to be the same as the response at a different point in time, precluding the pooling of results from each phase. The use of historical controls is also inappropriate because of the rapid changes in the management of the whole patient with AD, making subjects from even just a few years ago very different from those today.

Statistical Considerations

Until recently, the gold standard for assessing the efficacy and effectiveness of new medications has been the placebo-controlled, RCT. With a need to advance monotherapy claims in the presence of a standard of care, other study design options include superiority, equivalence, and non-inferiority trials.⁶⁶

In superiority trials, the goal is to establish that the new drug is better (i.e., more effective or with a more benign side-effect profile) than the standard. Because such trials require much larger sample sizes than placebo-controlled studies and are rarely required to bring a drug onto market, they are infrequently done. In equivalence trials, the aim is to show that the new and standard agents have similar degrees of effectiveness or adverse events; however, due to sample size requirements, most studies of new drugs are non-inferiority trials in which it is sufficient to demonstrate that the new drug is not significantly worse than the existing ones.⁶⁷ There are methodological considerations with equivalence and non-inferiority trials, including (a) an inability to determine if the drugs were equally good or equally bad; (b) poorly executed trials with low power can be mistaken for "proving" equivalence or non-inferiority; (c) the equivalence interval is arbitrary; (d) successive non-inferiority trials may lead to a gradual reduction in effectiveness; and (e) often larger trials are necessary.⁶⁷

At the analytic level a strict adherence to intention to treat analyses carries difficulties when applied to AD and other dementias. In dementia trials, subjects often die or withdraw for reasons unrelated to their dementia, and analyses only of completers or with an ITT approach using Last Observation Carried Forward can significantly bias the results. The use of retrieved drop-outs, though theoretically helpful, is difficult to carry out in practice. Studies will need to be designed and analyzed keeping these particular analytic challenges in mind.

Recommendations on Design and Methodology Issues

It is anticipated that most future placebo controlled RCTs in Canada will allow for a background treatment with current standards of care. The trial designs that involve active controls will change the design and goals of the studies. Although superiority trials are not often performed with the requirement of very large sample sizes, non-inferiority trials and equivalence trials carry risks, such as downward drift of effectiveness and low power being mistaken for 'proof'. Such trials will need to be carefully designed and openly interpreted, with critical consideration by regulatory agencies.

TARGET SYMPTOMS AND OUTCOME MEASURES

The phenomenology of dementia demands that reliable measurement indices be established for cognitive, behavioural, and functional symptoms. For use in trials, measurements should be both ecologically valid and clinically meaningful.

Cognition

The cognitive section of the Alzheimer's Disease Assessment Scale (ADAS-cog) remains the most widely used cognitive measure in dementia trials^{68,69} and is available in several languages.⁷⁰ It takes 20 to 50 minutes to administer. Memory, orientation, language, construction, and praxis are assessed, while executive function and agnosia are not. Designed for use in AD, the scale may not be ideal for assessing patients with other dementia diagnoses. The ADAS-cog is useful for differentiating AD patients from controls⁶⁹ and for stratifying dementia severity.^{71,72} Worsening on the ADAS-cog is not linear across disease severity, having both a ceiling and a floor effect.⁷³ Patients with moderately severe AD deteriorate more on the ADAS-cog over a year than patients with mild or very severe disease.⁷⁴

Mohs et al⁷⁵ have investigated some additions to the ADAS-cog and found that a cancellation task is sensitive across a range of dementia severities. A word learning task with delayed recall and a maze task may be useful additions in studying patients with early dementia or MCI.

The ADAS-cog has been used within a number of recent MCI studies where its utility as an outcome measure will be evaluable.^{76,77} It has also been used in drug trials for vascular and mixed dementia and has demonstrated sensitivity and reliability to measure change longitudinally in these conditions.^{17,78,79}

In more advanced dementia the most widely used assessment tool is the Severe Impairment Battery (SIB).^{80,81} The domains tested are analogous to those assessed by the ADAS-cog. The SIB is reliable and valid and its utility has been demonstrated in

moderate to severe dementia.⁸²⁻⁸⁶

The Mini-Mental State Exam (MMSE)⁸⁷ is often used to classify dementia severity. Floor and ceiling effects are limiting,^{88,89} with scores being affected by both age and education.⁹⁰ Although the MMSE has been included as an outcome measure in trials,⁹¹⁻⁹³ its main use has been as an inclusion criterion. It is part of the lexicon that allows an understanding by the wider clinical community around subjects selected for trials.

Remarkably little is known about the specificity of symptomatic medications for particular cognitive domains, even though this may provide important insight into treatment response. As medications are developed in the future it is foreseeable that more focused testing of specified cognitive domains with neuropsychological testing may be a preferred approach to investigate potential treatment benefits. Inclusion of more fine-grained neuropsychological testing, particularly of executive function, should be encouraged at least as secondary outcome measures in trials.⁹⁴

Recommendations on Cognition

The ADAS-cog remains the most widely used cognitive outcome measure in dementia trials of mild to moderate severity and is likely to remain so, particularly for AD. The SIB is useful in studying patients with advanced dementia facilitating measurement where floor effects of the ADAS cog and MMSE are encountered. The MMSE remains useful for stratifying AD patients for trial entry. The best cognitive outcome measure for MCI and for the other dementias remains a matter for future elaboration. For clinical trials, measures of symptomatic domains should be valid, and should sample from the cognitive domains relevant to the clinical expression and likely to respond to treatment.

Neuropsychiatric Symptoms

Neuropsychiatric symptoms (NPS) are common in dementia. They increase in prevalence with severity and are a major source of disability, patient distress, caregiver burden, and cost, and are an important determinant of nursing home placement.^{95,96} This grouping of symptoms includes disorders of mood, behaviour as well as psychosis. Given both their clinical and social importance, antidementia therapies should be directed at NPS including aggression, psychosis and mood as specific treatment targets.⁹⁷

Mood assessment is of particular importance, yet the actual diagnosis of depression in dementia is complex and requires a high level of clinical knowledge and acumen, as well as second party collateral information. Instruments that have been specifically developed to assess mood in the non-demented population, such as the Hamilton Depression Rating Scale⁹⁸ and the Montgomery-Asberg Depression Rating Scale,⁹⁹ may be useful in mildly demented individuals, but they are not reliable in the later stages of dementia when language and comprehension have declined significantly. The Geriatric Depression Scale, which is widely used in clinical practice, has been shown to be unreliable in those with increased cognitive impairment.¹⁰⁰⁻¹⁰² Many of the global neurobehavioural rating instruments do include mood items; however, their clinical significance has not been established.

In studies where the assessment of mood in dementia is of major importance, it is preferable to use an instrument that has been developed specifically for dementia, and which integrates caregiver information into the rating. Two useful instruments for clinical trials that focus on mood as an outcome measure are the Dementia Mood Assessment Scale and the Cornell Scale for Depression in Dementia.^{103,104} The Dementia Mood Assessment Scale was developed for rating the severity of depressed mood in mild to moderate AD.¹⁰³ It was modelled on the Hamilton Depression Rating Scale but excludes items that are more subjective and therefore prone to error. For patients who are more severely demented, the Cornell Scale is a better choice, as it is a caregiver-rated scale that is particularly suited to differentiating between cognitive and mood symptoms, and is sensitive to treatment effects over a wide range of depression and dementia severity.¹⁰⁴

Outside of depression, rating instruments designed specifically to measure the spectrum of NPS in dementia are generally caregiver-rated. The Neuropsychiatric Inventory (NPI) is particularly useful as it is brief and addresses a wide range of symptoms.¹⁰⁵ It measures 12 domains and has been validated with evidence of reliability and sensitivity to measure change within clinical trials. Concerns about the NPI scale include some difficulties in the metrics of the scale as well as the wide variance that is seen within the trials that have included it.^{106,107} The Behavioural Pathology in AD Scale (BEHAVE-AD) is also considered to be a valid and reliable scale that measures 25 behaviours in seven clusters.¹⁰⁸ It includes a global assessment of caregiver distress and has been used within a number of RCTs demonstrating both reliability and sensitivity to change.^{109,110} The behavioural rating scale for dementia of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-BRSD) is another useful instrument that measures 46 items in eight clusters.¹¹¹ Unlike the BEHAVE-AD, it evaluates the frequency of behavioural symptoms as opposed to their severity.

The Cohen-Mansfield Agitation Inventory (CMAI) is the best-known instrument for the detailed evaluation of agitation.¹¹² The original version assesses 29 different items and was developed for use in nursing homes although its use has been extended to other settings. It is particularly useful when a study is being considered around the target symptom of agitation.

Recommendations on Neuropsychiatric Symptoms

Neuropsychiatric symptoms in dementia are both highly prevalent and an important cause of distress to patients and families. They represent an important symptomatic target of therapy and they merit consideration of regulatory labeling where data demonstrating therapeutic efficacy and safety can be demonstrated. For both depression and other NPS, there are dementia-specific scales that have been validated and have been shown to be responsive and reliable at measuring treatment effects.

Functional Disability

Functional decline and loss of activities of daily living (ADLs) are core features of dementia.⁵ In AD, this decline begins insidiously and deteriorates gradually. It usually progresses hierarchically, starting with demanding occupational tasks,

followed by instrumental activities of daily living (IADLs), and finally affecting the basic ADLs (bADLs), such as dressing, personal hygiene, and continence.¹¹³ The ADL status can also be used to chart the course of the disease, having utility as a prognostic marker, and significantly contributing to caregiver burden and institutionalization.⁹⁶ For these reasons, functional assessment has been widely used as an outcome measure in treatment trials of dementia and is emerging as a useful co-primary outcome measure particularly in more advanced dementia.

Functional decline results from a complex interaction of factors, including cognitive decline (particularly executive dysfunction), behaviour, motor skills, perceptual and sensory abilities, medical comorbidities, and social variables.¹¹⁴ The loss of functional autonomy does not, however, invariably parallel the loss of cognitive function.

The ADL scales have been specifically developed for use in the assessment of AD, and have been integrated as outcome measures in clinical trials with cholinesterase inhibitors and memantine. The most widely used scales are the Alzheimer Disease Functional Assessment and Change Scale (ADFACS),¹¹⁵ the Disability Assessment for Dementia (DAD),¹¹⁶ the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL),¹¹⁷ and the Progressive Deterioration Scale (PDS).¹¹⁸ These scales share some common features. They each assess both ADLs and IADLs, are based on an interview with the caregiver, and can be completed within 15-20 minutes. Only the DAD assesses the hierarchical manner with which function declines cross referenced to the cognitive processing involved for each item.¹¹⁶ All of these scales have been validated and have been used in trials involving predominantly patients with AD. Their utility and continuing validation will be needed for use in other types of dementia.

Recommendations on Functional Disability

There are ADL scales that have been developed and validated to measure functional disability across the spectrum of diagnosed dementia. The ADLs are an essential outcome for inclusion within the investigations of treatments for dementia. In more advanced dementia ADLs are a suitable target as a co-primary outcome measure, while further research is still needed relating to functional disability at the mild cognitive impairment stage.

Global Assessments

Global assessment measures particularly using the Clinician's Global Impression of Change (CGIC) or the Clinician's Interview Based Impression of Change (CIBIC) have long been a mainstay in dementia drug trials. Though they have been a regulatory specified primary outcome measure in antidementia trials for the FDA, they also have found acceptance from clinicians. They require skilled judgments to be made by experienced clinicians about whether treatment has been associated with clinically detectable change at the individual patient level. As a dual primary outcome measure within dementia RCTs, they ensure that in addition to a statistically significant effect on a primary objective psychometric or other outcome, there is also a clinically detectable global change. The

CIBIC-plus assessment, which requires caregiver input as well as patient assessment, has been validated and has been shown to have both measurement sensitivity and reliability in AD.¹¹⁹

Other global measures, such as the CDR and the Global Deterioration Scale (GDS),^{120,121} which consist of descriptions of patient characteristics in a variety of symptomatic domains (e.g., memory, behaviour, functioning), as well as social domains (e.g., home and hobbies, community affairs, personal care, ADLs), allow an alternative approach to the CGIC/CIBIC-plus.¹²² To judge where a patient falls on these various domains, clinicians either conduct a semi-structured interview with ratings of each domain or complete an aggregate rating with all clinical information available following the assessment. The CDR allows both an overall stage as well as a sum of the individual domains to be determined, while the GDS provides a specified stage. These global assessments have been used in many clinical trials, particularly in those longer than six months.

The experience with global clinical measures to date suggests that the above approaches both can identify treatment effects of about the same order of magnitude as the ADAS-Cog;¹²³⁻¹²⁵ but they do not identify the same patients as benefiting.¹²⁶ However, there are important limitations to the use of global assessments that should encourage refinements in future research studies. The currently available global rating scales do not consider patient preferences in evaluating the clinical meaningfulness of antedementia drugs. Furthermore, there have also been recent data demonstrating that the CIBIC-plus, as it is currently operationalized, has a limited ability to detect improvement as opposed to decline, a deficiency that will need to be addressed as treatment opportunities with larger effect sizes become available for testing.¹²⁷

Recommendations on Global Assessments

The use of global assessments as a primary outcome measure has both clinical and ecological validity. Beyond objective measures of benefit on psychometric testing, the global assessment establishes that treatment effects are clinically identifiable. Refinements to global assessments are needed to allow patient improvement to be reliably captured as there are larger treatment effect sizes in the coming generation of therapeutic interventions.

Quality of Life

There is a growing consensus that QOL is an important outcome for assessing the effectiveness of dementia interventions, but, to date, there is no agreement about how to measure it.^{97,128-134} Generally, disease-specific measures are more responsive (i.e., sensitive to disease-related changes over time), while generic measures facilitate comparisons across disease states and are more useful for policy decisions.¹³⁵ Several dementia-specific QOL measures have been developed (e.g., QOL-Alzheimer's Disease and Dementia QOL), and these, along with various generic QOL instruments, have been used to assess QOL in dementia patients. The QOL measures vary with respect to content, respondent, method of administration, and target population.

Until recently, there was a focus on proxy and observational QOL measures, because it was believed that dementia patients could not rate their own QOL,^{136,137} however, there is now

substantial evidence to suggest that a majority of mild-moderate dementia patients can meaningfully rate their own QOL.¹³⁸⁻¹⁴³ In addition, data from studies using a variety of QOL measures have consistently shown significant differences between patient rated and caregiver proxy rated QOL, and between ratings by different proxy sources.^{141,144-150}

Although some QOL measures have evidence supporting their reliability and validity for use in dementia populations, there are virtually no data about the responsiveness of these measures to change with treatment intervention.¹³⁴ In addition, little is known about the impact of various potential confounders (e.g., comorbidity, patient's living circumstance) on patient and proxy QOL ratings. To date, few dementia clinical trials have included patient QOL as an outcome.¹⁵¹ A number of AChEI trials used a poorly validated generic QOL measure that exhibited marked variability and inconsistent results,^{93,152-154} while other trials used The Progressive Deterioration Scale (PDS), which was developed as a dementia-specific QOL measure.¹⁵⁵⁻¹⁵⁹ Most consider the PDS to be a measure of daily activities rather than of QOL.

Since dementia interventions may also affect the QOL of caregivers, this should also be measured in dementia trials.¹⁶⁰⁻¹⁶⁴ Some generic QOL measures have been used to assess caregiver QOL, with little known about their responsiveness to intervention studies.

Recommendations on Quality of Life

Patient and caregiver QOL outcome measures should be included in studies of antedementia therapies, though at this time, no specific measures can be recommended. Disease-specific measures will likely be more responsive to treatment effects, while generic measures may be necessary to address policy issues, such as cost-effectiveness. For patients with mild to moderate dementia, both patient- and proxy-rated QOL measures are encouraged, as they appear to provide different information. For patients with severe dementia, proxy and/or observational QOL measures are recommended. Future studies are needed to clarify the criteria for inclusion of patients for self-rating and for identifying the most appropriate proxy informants; to identify the characteristics of patients and proxies that influence their QOL ratings over time; and to determine which QOL measures are the most reliable, valid, and responsive for specific dementia populations.

Biological Markers

There are important potential roles for biomarkers within antedementia treatment studies. The Consensus Report of the Working Group on Molecular and Biochemical Markers of AD outlined many of the issues surrounding the use of biomarkers within research studies and created a reference framework that is still the most influential.¹⁶⁵ The forthcoming Alzheimer Disease Neuroimaging Initiative (ADNI) is the largest National Institutes of Health (NIH)-funded research study yet undertaken to advance the development of dementia biomarkers.

Biomarkers have the potential to assist in the accurate identification of suitable patient populations for inclusion within trials and to reduce sample sizes through the collection of more homogeneous study groups. They may allow the diagnostic distinction to be made between elderly normals, subjects with

MCI at high risk of progressing to dementia, and individuals with dementia of differing etiologies. They may allow study populations to be enriched with those at high risk of progression or with a particularly distinctive course. Ideally they will also allow for the measurement of response to both symptomatic and disease modifying therapy. As biomarkers mature they will certainly complement clinical and neuropsychological evaluations, but they may also eventually evolve into useful surrogate endpoints in AD research. These markers may also provide important mechanistic clues to the pharmacological action of anti-dementia compounds. At the present time, however, their place within antidementia drug trials is adjunctive to the necessary clinical outcomes.

CSF and Blood Biomarkers

There is a long list of putative cerebrospinal fluid (CSF) and blood biomarkers that have generated interest as diagnostics for AD and other dementias. Virtually all of these are at the level of research interest still requiring additional confirmation. The greatest current interest in CSF markers are those that are most fundamental to the pathological footprint of AD. The CSF phosphorylated tau (CSF p-tau) proteins are the only biomarkers with currently demonstrated sensitivity and specificity sufficient to serve as a useful diagnostic biomarker.¹⁶⁶ Specificities and sensitivities are reported in the 85-90% range at distinguishing AD from other dementias as well as distinguishing MCI that will progress.¹⁶⁷ Ab 1-42 has been measured in both plasma and CSF with poor correlation between CSF levels and disease duration and severity. Its utility in distinguishing AD from other dementias is still uncertain. CSF p-tau (alone or with CSF Ab measures) could potentially enhance the homogeneity of patients entering MCI trials;¹⁶⁷ however, there is no proven utility of any blood or CSF marker in monitoring disease progression at this point.

It is foreseeable that a panel of disease markers might prove advantageous. It will also be important to develop “non-invasive” markers utilizing readily obtainable tissue samples to monitor disease progression or regression. The assays themselves will need to be reproducible, reliable, and relatively inexpensive. To facilitate future biomarker development, it will be highly advantageous to collect and store biological specimens as an adjunct to current clinical trials research in AD.

Recommendations on Biological Markers, CSF and Blood Biomarkers

Development of surrogate disease markers – from imaging, CSF samples, and blood tests – has the potential to stimulate drug development and clinical trials in the dementias. There are a set of highly promising current biomarkers that have the potential to reach the level of disease surrogates in the future, but all require shared collection of data, standardization, and longitudinal assessment of their relationship to disease progression and treatment. Data must be amassed not only at the group level, but anticipating the individual variability (largely genetic) which may influence drug response. Collection of such data in the course of RCTs should be encouraged as complementary endpoints. They are not at present recommended to replace clinical outcomes but only to provide supportive

evidence. The DNA banking and genotype profiling during trials will open the way to more effective pharmacogenomics in the future.

Neuroimaging: PET, MRI, MRS, SPECT

Use of neuroimaging parameters as outcome measures in the development of new therapies is continually advancing and this pace will continue to accelerate in the coming decade. The MRI is currently being tested in RCTs, particularly using volumetric measures.¹⁶⁸ However, these measures remain non-standardized and variable between centres. Centralized reading and extensive efforts to standardize the neuroimaging at each site, including scanning phantoms, may reduce some of the variability and increase reliability. While the technologies for cerebral functional measurement are available through the use of positron emission tomography (PET) or functional MRI (fMRI), their routine use has been restricted by technical complexity, cost, and lack of sufficient experience to establish correlations to clinical outcomes. Recent technological advances, including novel ligands for PET, and increasingly standardized scientific data collection and interpretation, may allow for their use in antidementia drug development.^{169,170}

Recommendations on Neuroimaging

Promising neuroimaging cannot be accepted as a surrogate endpoint in antidementia drug trials at the present time. However, further research to validate, standardize and establish sensitivity and specificity of these neuroimaging markers may advance these modalities. The variability among labs awaits improvement, and the whole range of possible neuroimaging modalities currently remains as a set of biomarkers rather than surrogate endpoints. Measures such as hippocampal volumetrics, fMRI memory activation in AD and quantitative MRI lesion measurements in VaD, are steadily improving.

Pharmacogenomics

Pharmacogenomics holds the potential to predict which individuals have a greater chance of either benefit or harm from pharmacological intervention. If this working hypothesis were to be verified through research in dementia, this would be particularly significant as it is the large constituency of elderly patients on multiple medications that are the major users of antidementia treatments. To date, there are no reliable pharmacogenomic predictors of response to currently available dementia therapies. The apolipoprotein E genotype has been investigated in some detail with the acetylcholinesterase inhibitors, but has lacked consistent predictive ability across studies and remains of uncertain utility. In their draft guideline on this topic entitled: Guidance for Industry: Pharmacogenomic Data Submission,¹⁷¹ the FDA indicated their belief that pharmacogenomic analyses can be smoothly integrated into drug development processes while there has been an expressed interest by the European regulatory authorities to include a DNA banking program with apoE genotype profiling in dementia RCTs.

THERAPEUTIC APPROACHES TO ALZHEIMER'S DISEASE**Mild to Moderate Alzheimer's disease**

Mild to moderate AD has most often been operationally defined for RCTs by MMSE total scores of 10 to 26, inclusively.⁸⁷ This definition does not take into account the many dimensions of dementia that fall outside of the MMSE scale's ability to define severity. Revised definitions of mild to moderate that do not exclusively rely on the MMSE or other cognitive tests and which take into account levels of functional disability and neuropsychiatric symptoms are needed.

The criticisms of the existing Phase III trials have been that they have included too highly selected populations, with outcomes measures that are useful in trials but have no clinical applicability outside of the trial setting. The RCTs including only NINCDS-ADRDA "probable AD" subjects exclude a significant percentage of individuals with "possible AD" whose trajectory of disease course is probably similar and whose inclusion would improve study generalizability. Subjects with significant NPS are most often systematically excluded. There are other opportunities to develop and include more clinically meaningful outcomes, with pre-specified minimally significant clinical differences. Exclusion criteria (e.g., comorbid conditions, medications) should be minimized in an effort to improve the generalizability of results. Cognitive rehabilitation interventions in AD are a potential treatment approach that require an evidence base to be developed through research studies to define their utility.

Recommendations on Therapeutic Approaches to Mild to Moderate AD

Both subjects with NINCDS-ADRDA "possible" and "probable" AD should be evaluated in AD clinical trials. Subjects with a potential second etiology contributing to their dementia need to be studied as well. A balance between study sample homogeneity and the generalizability of study results is needed through the development process of antedementia treatments. There is still a need to develop valid, reliable, sensitive, relevant and comprehensive measures of treatment effects. Minimal clinically significant differences should be pre-determined and used in evaluating the results of these studies. Subjects with significant NPS should be included in RCTs.

Moderate to Severe Alzheimer's disease

The clinical features of more advanced AD, in the moderate to severe stages, include greater functional losses, increased levels of neuropsychiatric symptoms and an increasing burden of illness for caregivers.^{95,121,164} The neuropathological and neurochemical changes of advanced AD may distinguish the moderate to severe stages from earlier disease stages, however, the distinctions are not readily made with current in vivo technologies. From a societal perspective, data from the Canadian Study of Health and Aging (CSHA) have suggested that the costs of the illness rise very significantly in transition from mild to severe disease.² Despite the obvious importance of moderate to severe AD, there have been few treatment trials in this population. In Canada, memantine has received conditional regulatory approval for the symptomatic treatment of moderate to severe AD. There is a strong rationale for attention to this

stage of dementia severity as CSHA estimated that the prevalence of moderate to severe dementia was 50% of all cases of dementia.¹

For the purposes of RCTs, subjects with moderate to severe AD can be distinguished from milder disease through the combination of a global staging instrument and a screening cognitive measure. The GDS stage 5-7 or CDR stage 2-5 are recommended for global staging.¹²⁰⁻¹²² For cognitive screening in moderate to severe trials, average MMSE scores should be no higher than 12, and should have a range of inclusion from 0 to 15. Until there is an approved standard of care for severe AD, trials should be randomized and double-blind with placebo controls. In the future, when a standard of care for severe AD is established, a design to allow all patients being treated with "standard care" and then an add-on design will likely be needed with the provision that for a monotherapy claim there will be a need for direct head-to-head designed RCTs.

Outcome measures in moderate to severe AD trials must address stage specific symptoms. Since small changes in cognitive function may have questionable clinical relevance at this stage, primary outcomes should include a global rating, and might alternatively include a functional or behavioural co-primary outcome measure. The CIBIC-plus has been successfully used in previous RCTs in this population.¹⁰⁷ There is some suggestion that it relies heavily on ADLs and behavioural changes, which is appropriate for moderate to severe AD. Function can be measured with the ADCS/ADLSEV or DAD, though both scales are limited in long-term care settings. NPS at these stages can be measured with the NPI and efforts to include subjects with significant NPS in RCTs are well justified. The SIB is currently recommended as a cognitive outcome measure.

Stabilization of function, behaviour, and cognition are all reasonable goals of therapy, and potentially more realistic than significant improvement at this stage. Pharmacoeconomic outcomes are important and might focus on indirect costs, such as caregiver time, which make up a significant proportion of costs for community dwelling patients.

Recommendations on Therapeutic Approaches to Moderate to Severe AD

The methodology and outcomes in moderate to severe AD trials face different issues than those of milder stages. The inclusion criteria require both a functional and a cognitive global measure to define the target study group. Until there is a standard of care for moderate to severe AD, placebo-controlled parallel group trials are recommended. When a standard of care becomes available, add-on therapy designs or non-inferiority to the standard of care are most likely to be used to demonstrate efficacy of new therapies. For a symptomatic indication in moderate to severe AD, functional disability or behavioral symptoms are an alternatively suitable primary outcome measure beyond cognition, while global ratings are an important co-primary outcome in this patient group.

THERAPEUTIC APPROACHES TO MILD COGNITIVE IMPAIRMENT

Recently, there have been trials of therapeutic interventions targeted at slowing the rate of progression in MCI. The MCIa has been used within a current generation of randomized placebo

controlled parallel group clinical trials of the AChEIs and rofecoxib.^{76,172,173} The anticipation within these trials was that the use of MCIa as a diagnostic construct would allow the accrual of homogeneous MCI study samples and predictably high rates of conversion ranging from 10-15% per annum. From the preliminary presentations of these studies, as well as from previous population studies,¹⁷⁴ it has become apparent that small differences in the MCIa inclusion criteria, in the cut-off points on neuropsychological tests of episodic memory, in the exclusion criteria or in the AD diagnostic conversion criteria, all impact on the rates of progression to dementia in RCTs. Careful interpretation of this variability will be required in determining whether this is a problem with the validity of the MCIa construct, the treatments being used or the underlying heterogeneity of MCIa that have yet to be reconciled.

It was estimated in a study of Canadian dementia referral clinics that only 25% of MCI is MCIa. This leaves the largest group of referred subjects with MCI outside of the MCIa studies.¹⁰ From a regulatory perspective, it can be anticipated that were a successful MCIa RCT to be reported, there would still be the need to address the clinical heterogeneity and efficacy of the therapy of MCI more broadly within a usual care setting, as it would need to be demonstrated that treatment is both safe and efficacious in usual care settings.

Recommendations on Therapeutic Approaches to MCI

There is recognition and general acceptance that MCI represents an intermediate state of cognitive function that falls outside of normal without meeting criteria for dementia. Still unresolved is its utility as a suitable target for antedementia therapy to delay the progression of cognitive impairment to dementia. The first generation of RCTs using MCIa as the diagnostic construct have demonstrated that apparently small differences in inclusion, exclusion and conversion to dementia criteria are associated with variable outcomes. This has raised some controversy about the validity of the MCIa as a construct for use in clinical trials, and the way that this might be advanced or improved. It can be anticipated in future drug development targeted at MCI that a positive study in MCIa done in dementia research settings will need to be replicated within usual care settings to ensure safety and efficacy of treatment before it would be appropriate for approval in usual care community settings.

THERAPEUTIC APPROACHES TO VASCULAR DEMENTIA

Vascular dementia (VaD) is an etiologically heterogeneous disorder arising from a variety of cerebrovascular diseases (CVD), and resulting in cognitive impairments that reflect the degree and location of the underlying vascular damage. The term Vascular Cognitive Impairment (VCI) has been proposed as an alternative nosology that may gain a foothold in future clinical trials. Vascular Cognitive Impairment is a term that is inclusive of VaD and its subtypes, Vascular Cognitive Impairment No Dementia (VCIND), and mixed AD and CVD (AD/CVD).^{175,176} It reflects the important and diverse causes of vascular injury and the related patterns of cognitive impairment. Within VCI particular attention has been directed at the subcortical ischemic vascular subtype that results from ischemic injury associated with small vessel disease.^{177,178}

It can be readily appreciated that with this heterogeneity of mechanisms of cerebrovascular injury and related subgroups, the design and methodology of clinical trials will be challenging particularly as it may relate to regulatory approval for a vascular indication. Though great strides have been made in developing neuroimaging for VCI/VaD, there are still gaps in lesion identification, including the detection of microinfarcts, which are an important correlate of cognitive impairment. Advances in neuroimaging do hold the promise of better definition to the VaD disorder and improved diagnostic sensitivity. However, there is currently no readily available imaging technique that can identify the presence of mixed AD and CVD, which may be the most common form of VaD.

Clinical trials to date have focused on “clinically probable” and “possible” VaD by the NINDS-AIREN criteria with some beneficial effects evident for different drug classes, including the AChEIs and memantine.^{17,18,179,180} The lack of converging and consistent results to achieve regulatory approval of any of these drugs for VaD has raised the question of whether it is the therapy or the study methodology that is lacking. These RCTs have adapted cognitive test instruments and outcome measures from AD studies. While these instruments were developed and validated in AD, their measurement sensitivity and reliability in VaD are uncertain. The placebo groups in these RCTs have not declined as predicted, suggesting that their decline is slower and their course different than AD. The value of tests of executive function and neuropsychiatric symptoms in VaD has been largely overlooked and need to be included in future trials. To date it has been difficult to address the etiological heterogeneity within the VaD/VCI framework where different mechanisms of vascular injury might also have differential response to treatment. The RCTs to date have had insufficient power to examine the etiologically relevant CVD subgroups.

Among the other lessons learned from the recently completed generation of clinical trials is the advantage of using well-defined neuroimaging criteria with centralized reading and standardized protocols, including advanced techniques, such as diffusion tensor imaging. Follow-up scanning to quantify changes in tissue atrophy, and lesion burden is becoming feasible, though not yet validated as a surrogate outcome. Akin to blood storage, scans can also be archived for future analysis.

Recommendations on Therapeutic Approaches to VaD

Designs and approaches for future trials will depend on the evolving concepts of VCI and VaD which are etiologically heterogeneous and may have differential potential to respond to particular interventions. The methodology of VaD trials has suffered from a dependence on AD outcome measures with an unmet need to develop sensitive and valid VaD outcome measures. It is recommended that more sensitive measures of executive functioning be included, as well as ADL and behavioural assessments. The advantages of centralized reading and standardized neuroimaging entry criteria to RCTs are now recognized and will benefit future trials. Longer trial periods may be required to discern clinically meaningful benefits.

THERAPEUTIC APPROACHES TO PARKINSON'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

Parkinson's Disease Dementia and Dementia with Lewy Bodies are pathologically overlapping conditions. They represent a spectrum of dementias that is very challenging for clinician management as they face a unique mix of neuropsychiatric symptoms including hallucinations/delusions, progressive cognitive impairment and movement disorders. They are uniquely sensitive to the negative effects of dopamine-blocking neuroleptic medications that are associated with increased morbidity and increased mortality.²⁴

Within the last decade the first placebo controlled RCTs have been undertaken in these disorders. These studies have underscored some of the important conceptual and methodological challenges. "Probable DLB" as defined by the McKeith criteria is an infrequent disorder for which RCT recruitment has been very difficult.²³ A large scale RCT did not meet its recruitment targets citing both administrative delays and recruitment difficulties in some centers.¹⁸¹ For PDD there is still a lack of consensus definition.²⁶ There are unanswered questions over the natural history of these disorders and there are a lack of validated outcome measures. As with vascular dementia, there is a tendency to call on outcome measures that have been validated for use within AD trials, though there are important differences in the cognitive and neuropsychiatric symptoms that would make the AD outcomes more insensitive probes than those that might be developed and validated for DLB/PDD. The use of biomarkers, including neuroimaging with PET, MRI and SPECT and CSF markers as outcome measures in PDD and DLB, require further investigation to determine their sensitivity and reliability within clinical trials and their use within RCTs is encouraged to advance their development. Clinical scales that evaluate autonomic function and motor parkinsonism may be useful adjuncts.

Beyond open-label and case series reports of the AChEIs in PDD and DLB, the double-blind randomized placebo-controlled trials in DLB and PDD have been performed with positive outcomes allowing that regulatory submissions might be forthcoming.^{181,182} In an RCT of rivastigmine in PDD the primary outcomes were the ADAS cog and the CGIC while in a DLB trial the primary outcome measures were the NPI total scores and a combined score from selected tests from the cognitive drug research computerized cognitive assessment system.¹⁸²

Anti-psychotic agents, such as clozapine and quetiapine, have been reported to benefit both DLB and PDD.¹⁸³⁻¹⁸⁶ Two randomized placebo-controlled trials of clozapine have shown benefit for psychotic symptoms in PD, but only included patients with mild PDD. There have been no published placebo-controlled RCTs of PDD or DLB with atypical anti-psychotic agents. Additional studies of these and other agents are necessary in these patient groups.

To advance the future designs of clinical trials in PDD and DLB, there will be a need to orient outcome measures around clinically important milestones such as time to onset of dementia in PD, the loss of function abilities, falls, nursing home placement, QOL and mortality.

Recommendations on Therapeutic Approaches to PDD and DLB

Parkinson's Disease Dementia and Dementia with Lewy Bodies are both significant causes of dementia for which there is an important unmet need for treatment. The pitfalls and limitations of current therapies should drive the pursuit of therapies with outcomes that are clinically important including the time to onset of dementia, cognitive and behavioural impairment, functional decline, falls, nursing-home placement, mortality, and QOL. It may become both necessary and desirable to combine PDD and DLB with Parkinsonism in large scale RCTs. Motor impairment has been the focus of PD trials and must be assessed in patients with PDD and DLB. Conversely, cognitive impairment should be assessed in trials targeting motor impairment in PD. The move away from AD outcome measures to validated measures for PDD and DLB is needed.

THERAPEUTIC APPROACHES TO FRONTOTEMPORAL DEMENTIA

Notwithstanding the different proposed nosologies for the spectrum of disorders related to FTD or FTLT,¹⁸⁷ it is generally agreed that these dementias most commonly occur under age 70 years, and account for an estimated 12% of dementia cases with onset under 65 years of age.¹⁸⁸⁻¹⁹⁰

Despite their recognized importance as a cause of dementia and the rationale for therapies targeting serotonergic and dopaminergic systems, there have been no large-scale treatment trials in FTD.¹⁹¹⁻¹⁹³ A wide variety of drugs have been reported to have benefits including trazodone,^{194,195} idazoxan,¹⁹⁶ lithium plus fluoxetine¹⁹⁷ and paroxetine,¹⁹⁷ fluoxetine,^{198,199} sertraline,^{198,199} fluvoxamine,²⁰⁰ paroxetine,^{198,199,201} l-deprenyl,²⁰² moclobenide,²⁰³ and methylphenidate.²⁰⁴ However, only two studies are double-blind, placebo-controlled trials: a case study using idazoxan and a group trial using trazodone.^{195,196}

Although the general principals for therapeutic trials in AD will be applicable to FTD, there are no standards of care for FTD allowing that for FTLT, placebo-controlled trials will be both ethical and necessary.

Early FTD affects primarily social cognition, which may reflect orbitofrontal involvement; however, most standard frontal neuropsychological tests are sensitive to dorsolateral frontal function and relatively insensitive to orbitofrontal function.^{31,205} Therapeutic trials in FTD in turn will need to include measures of social cognition, such as Theory of Mind tasks, and tests of orbitofrontal function that are also sensitive to FTD but that are outside the social cognitive realm, such as Object Alternation.²⁰⁵⁻²⁰⁷ Ideally, a single global measure of social cognition/orbitofrontal function should be developed to minimize the number of primary outcome measures. Candidates for tests of other frontal functions to supplement the social cognitive/orbitofrontal measures include the Executive Interview,²⁰⁸ Frontal Assessment Battery,²⁰⁹ and Addenbrooke's Cognitive Examination.²¹⁰ More selective tasks such as Wisconsin Card Sorting Test and clock drawing should also be considered.^{211,212}

Other potential primary outcome measures for symptomatic RCTs in FTD could include NPS evaluated with the NPI,¹⁰⁵ Frontal Behavioral Inventory,²¹³⁻²¹⁵ and Frontal Systems

Behavior Scale (FrSBe) as well as global assessments.^{216,217} Measures of functional assessment, caregiver stress, and QOL should also be considered as secondary outcomes. Study groups should span the full range of severity in FTD, with outcome measure selected that are stage sensitive. Whereas the MMSE is standard for staging clinical severity in AD, it is relatively insensitive to early FTD. Severity measures to consider include the NPI, FBI, and FrSBe.^{105,213-217}

Management of PPA and SD focuses on speech-language treatments rather than pharmacological approaches. Future developments could lead to drug trials in these conditions, and, the general principles outlined for FTD apply to PPA and SD.

Recommendations on Therapeutic Approaches to FTLD

The currently available treatments for FTD/FTLD are limited with a large unmet need for therapy that can treat both the symptoms and the disease process across these dementia subtypes. There are currently no formal standards for therapeutic trials in FTD/FTLD, underscoring the need to define consensus standards for clinical trials. The outcome measures for FTD/FTLD will not be interchangeable with AD and they will have to address the different cognitive and neuropsychiatric impairments that are present in these conditions. Consensus working groups may be necessary to advance clinical trial designs and methods for this spectrum of dementia.

FUTURE DEVELOPMENTS

The search for effective medicines has benefited enormously from the unprecedented growth in our understanding of mechanisms of neurodegenerative disease and the elaboration of the pathological bases of the dementias. This new knowledge is allowing a more focussed approach to treatments based on pathogenic targets. Of course, this will be only the first step as the ultimate approach will be to prevent the changes that underline the functional decline. The development pipeline includes approaches that aim to protect the brain from damage by reactive oxygen species or inflammation,²¹⁸⁻²²⁰ that can stimulate nerve regeneration and can either prevent or enable the removal of the protein aggregates that form the neuropathological tombstones of neurodegeneration.²²¹ There are now strong grounds for believing that compounds that act to prevent or reverse amyloid plaque formation will modify the progression of AD and possibly related forms of dementia.²²²⁻²²⁸ In the next few years, many medicines directed at these targets will enter Phase II and Phase III clinical trials. Anti-amyloid therapies, antioxidants, stem cells, nerve growth factors, insulin modulating approaches and neurotransmitter based therapies are all on the visible horizon of clinical trials.²¹⁸⁻²²⁹

SUMMARY

These Canadian Guidelines have evolved through a broad collaboration of the 2nd Canadian Conference on the Development of Antidementia Therapies among academic and clinical experts, representatives of the regulatory authorities of Health Canada and the Alzheimer Society of Canada. They serve to update the initial set of 1995 Canadian Guidelines for the Development of Antidementia Therapies. A set of Guidelines, developed through the process undertaken for this Conference,

provides a point of common reference to clinical researchers, government agencies and the pharmaceutical/biotechnology industries engaged in the therapeutic development in this field.

The approach taken by the conference was "oracle-based" with topic review and presentation by recognized experts who were asked to reference evidence-based data where it existed, and to craft recommendations within each topic area. They were also asked to provide working recommendations and expert opinion where there was no substantive evidence base or where opinions were disparate but where some guidance was still desirable. The Conference did not adhere to a consensus-based approach with voting and with levels of evidence, rather the authorship of this paper was charged with providing a unifying synthesis of the presentations and discussions at the meeting, and the written submissions of the presenters.

These Canadian Guidelines are unique for having been peer-reviewed and then published within a peer-reviewed journal. This has allowed for significant feedback prior to publication, as well as for the anticipated discussion in the broader community that will follow their publication. They stand apart from the more usual process where draft guidelines are developed by the Regulatory agencies with some consultation from the expert community. At the same time, there are clearly significant limitations to Guidelines that are developed in this way. In some topic areas, generalizations may have been made that over-represent the opinions of the community of experts that convened for the meeting. The response of the community-at-large to this publication may help address this deficiency and is encouraged. In the development of the Guidelines, outside of the conference, there was no formal process for presenting dissenting opinions and these may not have been fully represented in the final Guidelines. Though there was participation and input received from the representatives of the Regulatory agency through discussion at the Conference, to date these published Guidelines have not been accorded any formal standing as an official government-endorsed Guidelines and should not be construed as having such standing.

A reflection of the progress in this field of dementia can be appreciated in comparing the current Guidelines with those of 1995. Our updated list of topic areas, covered in detail in the current Guidelines, in many instances were only alluded to in the 1995 version of the Guidelines. At the same time, there are significant uncertainties that are apparent within a variety of these topic areas. Mild Cognitive Impairment (MCI) was one such area, and was the topic that led to the most contentious discussion. Whereas there was general agreement that it represents a state of cognitive function that falls outside of normal for age and short of dementia by formal criteria, it was unclear whether the amnesic form MCIa will survive as a meaningful diagnostic construct or defining characteristic suitable for clinical trials. The heterogeneity of populations enrolled and outcomes of RCTs that have used this MCIa is apparent and not fully resolved. In the area of VaD RCTs the adoption of AD clinical trials methodology and outcomes has likely hampered the ability to evaluate emerging therapies. The necessity for standardization of the neuroimaging criteria for RCTs is now recognized for VCI/VaD as is the need for longer study durations to address some of the more important clinical outcomes and changes that occur in this condition. For PDD and

DLB, there is a fundamental uncertainty over whether these are discrete clinical disorders that should be evaluated separately in RCTs or whether they are part of a continuum with pathological overlap that should allow them to be studied together in larger scale RCTs. In FTD there is a large unmet need for treatment and there are no formal standards yet for therapeutic trials.

This Conference concludes that there is room to define consensus standards for clinical trials outside of AD and that this might well be undertaken even in advance of promising candidate therapeutic interventions. Finally, among the new topics is the area of mixed dementia, where there has been a growing recognition that a significant proportion of dementia cases do have multiple overlapping neuropathological processes. The regulatory input is that some definition of mixed dementia will be needed, with data presented to receive therapeutic labeling for such conditions whose inclusion in RCTs is recommended.

It is clear, from the reflections of the progress of the past ten years and the challenges outlined, that the development of Guidelines will not be a static process. There will be a foreseeable future need to update these 2004 Guidelines. The Conference is optimistic that this future challenge will be met in time and that the current set will serve us well.

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