

REVIEW

Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012

Nathan Herrmann^{*1,2}, Krista L Lanctôt^{1,2} and David B Hogan³

Abstract

Background While there have been no new medications approved for the treatment of Alzheimer's disease (AD) or other dementias in Canada since 2004, the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD) reviewed and updated the clinical practice guidelines on the pharmacological management of dementia that were published previously.

Methods This review focused on the literature for the pharmacological treatment of dementia based on studies published since the third CCCDTD in 2006. A literature search of English-language medical databases was performed for studies pertaining to the pharmacological treatment of AD and other dementias that examined the management of cognitive and functional impairment, as well as neuropsychiatric symptoms. All previous recommendations were reviewed, and only those that required updating based on new published studies were revised. Several new recommendations were also added. Recommendations were rated for quality of evidence and were approved by consensus.

Results There were 15 revised or new recommendations approved by consensus. The revised recommendations included acknowledging that cholinesterase inhibitors (ChEIs) possess a class effect and any of the agents can be used for AD across the spectrum of severity and with co-existing cerebrovascular disease. There was insufficient evidence to recommend for or against the use of ChEIs in combination with memantine for the primary indication of treating neuropsychiatric symptoms, or for the treatment of vascular dementia. Recommendations for the discontinuation of cognitive enhancers were revised and clarified, as well as the risks associated with discontinuing these drugs. ChEIs were recommended as a treatment option for dementia with Parkinson's disease. Risks associated with use of antipsychotics for neuropsychiatric symptoms were strengthened, and guidelines regarding the use of antidepressants for affective disturbances in dementia were weakened, and are now considered an option but not a firm recommendation. Valproate was recommended not to be used, and there was insufficient evidence to recommend for or against the use of selective serotonin reuptake inhibitors or trazodone for the treatment of agitation and aggression.

Conclusion In spite of the lack of new therapeutic agents for the treatment of dementia, recent studies have helped to clarify and strengthen recommendations to optimize the pharmacological management of these illnesses.

Background

Alzheimer's disease (AD) and other dementias are prevalent illnesses that represent a dramatic burden to individuals, their families and society. Worldwide there are

currently 25 to 35 million individuals with these illnesses, with 5 to 7 million new cases diagnosed each year, or one new case every 7 seconds [1,2]. In Canada the estimated 500,000 individuals with dementia require about 231 million informal caregiver hours/year and cost \$15 billion/year [3]. To help patients, families and their physicians cope with these illnesses, numerous clinical practice guidelines have been developed [4-6].

The third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD) met in 2006 and published guidelines in 2007 and 2008. The

*Correspondence: nathan.herrmann@sunnybrook.ca

¹Department of Psychiatry and the Brain Sciences Research Program, Sunnybrook Health Sciences Centre, Suite FG08, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada

Full list of author information is available at the end of the article

fourth CCCDTD convened in spring 2012 and focused on proposed changes in diagnosis and nomenclature, as well as emerging data on biomarkers. Since no new medications had been approved in Canada since the last CCCDTD, a working group was formed to review the previous pharmacological recommendations and revise where necessary, given new data from randomized controlled trials (RCTs). Particular attention was paid to recommendations pertaining to combination treatment with cognitive enhancers and to recommendations related to discontinuing cognitive enhancers. The background for the revised recommendations that were proposed, and the final recommendations, approved by the CCCDTD in May 2012, are presented.

Methods

Details describing the guideline-creation process of the CCCDTD have been published previously [7,8]. Briefly, the consensus conference adhered to the methods of the AGREE collaboration [9]. For this update, the working group reviewed the previous pharmacological recommendations from each working group of CCCDTD3 [10-14]. A literature search was conducted with PubMed and Embase, examining articles published from January 2006 until April 2012. Major search terms included 'dementia' OR 'Alzheimer's disease' AND 'therapy' OR 'treatment' with secondary terms, which included cognitive enhancers, cholinesterase inhibitors (ChEIs), donepezil, galantamine, rivastigmine, memantine, agitation, aggression, anxiety, apathy, depression, psychosis, delusions, hallucinations, sleep, appetite, antidepressants, antipsychotics, anxiolytics, sedatives, hypnotics, anticonvulsants.

The completed background papers were provided to all consensus conference delegates for comment and to suggest revisions and then recommendations were presented at the consensus conference. Final recommendations required 80% or more of the delegates voting for the recommendation to be approved. The evidence was graded both numerically by strength of recommendation (1 = strong, recommended; 2 = weak, suggested) and then alphabetically by quality of evidence (A = high, B = moderate, C = low) – such that 1A suggests the recommendations would apply to most patients with no further research needed, whereas 2C implies that other alternatives are reasonable and higher quality research may impact the recommendation, as suggested by Guyatt and colleagues [15].

Results

All 14 recommendations proposed by the workgroup were approved by consensus. There were 11 recommendations from the previously published guidelines that were revised and three new recommendations. Nine of the recommendations underwent minor wording

changes. Additionally, Consensus Conference delegates approved an extra recommendation related to the use of quetiapine for agitation and aggression. The final CCCDTD 2012 recommendations are presented in Table 1.

New recommendation for the management of Alzheimer's disease

- *New recommendation* Many cases of dementia have more than one condition contributing to causation. Most commonly this will be a combination of AD with other brain pathology. The recommendation is that management be based on what is (are) felt to be the predominant contributing cause(s). (Grade 1B)

Rationale

Dementia frequently arises from more than one condition [16-19]. For example, in the Rush Memory and Aging Study, 38% of patients had AD and infarcts, 30% had pure AD, 12% had vascular dementia (VaD) and 12% had AD with either Parkinson's disease (PD) or Lewy body dementia at autopsy [20]. In the BrainNet Europe Consortium, 53.3% of patients had mixed diagnoses among all cases of dementia [21]. The presence of multiple brain pathologies markedly increases the odds of cognitive impairment becoming evident [20,22].

In their clinical practice guideline for dementia, the National Institute for Health and Clinical Excellence noted the high prevalence of mixed pathology and suggested management according to the predominant cause [23]. This recommendation recognizes how commonly mixed pathologies underlie dementia and gives management advice to practicing physicians.

Revised recommendation for management of Alzheimer's disease and cerebrovascular disease

- *Previous recommendation* There is fair evidence for benefits of small magnitude for galantamine in cognitive, functional, behavioral, and global measures in AD with cerebrovascular disease. Galantamine can be considered a treatment option for mixed AD with cerebrovascular disease [14].
- *Revised recommendation* ChEIs are recommended as a treatment option for AD disease with cerebrovascular disease. (Grade 1B)

Rationale

AD and cerebrovascular lesions are frequently co-identified; for example, 37.5% (30/80) of those with intermediate or high likelihood of AD in a community-based clinical-pathologic cohort study [20]. In accord with the preceding new recommendation, ChEIs and/or memantine to deal with the AD component would be treatment considerations for these cases. The prior recommendation that singled out galantamine was based

Table 1. Summary of approved recommendations

- Many cases of dementia have more than one condition contributing to causation. Most commonly this will be a combination of AD with other brain pathology. We recommend management be based on those diagnoses that are believed to be the predominant contributing cause(s). (Grade 1B)
- We recommend ChEIs as a treatment option for AD with cerebrovascular disease. (Grade 1B)
- We recommend ChEIs as a treatment option for dementia associated with Parkinson's disease. (Grade 1A)
- There is insufficient and inconsistent evidence on which to make a recommendation either for or against the use of the currently available ChEIs for the treatment of vascular dementia. (Grade 2B)
- All three ChEIs have demonstrated efficacy for mild to severe AD. We recommend a trial of a ChEIs for most patients with AD. (Grade 1A)
- Direct comparisons do not suggest differences between ChEIs (Grade 2B). Selection of which agent to be used will be based on the adverse effect profile, ease of use, familiarity, and differences between the agents in their pharmacokinetics and other mechanisms of action.
- There is insufficient evidence to recommend for or against the combination of a ChEI and memantine. (Grade 2B)
- Discontinuing ChEIs in patients with moderate to severe AD may lead to worsening of cognitive function and greater functional impairment as compared with continued therapy (Grade 2B). This risk must be balanced with the risk for known side-effects and drug costs if therapy continues. It is suggested that ChEIs be discontinued when:
 - (i) the patient and/or their proxy decision-maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation;
 - (ii) the patient is sufficiently nonadherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem;
 - (iii) the patient's rate of cognitive, functional, and/or behavioral decline is greater on treatment compared with that prior to being treated;
 - (iv) the patient experiences intolerable side effects that are definitely or probably related to the ChEI;
 - (v) the comorbidities of the patient make continued use of the agent either unacceptably risky or futile (for example, terminally ill); or
 - (vi) the patient's dementia progresses to a stage (for example, Global Deterioration Scale stage 7) where there would be no clinically meaningful benefit from continued therapy.
- When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, the suggestion is that the dose be tapered before stopping the agent and that the patient be monitored over the next 1 to 3 months for evidence of an observable decline. If this decline occurs, it is suggested that consideration be given to reinstating therapy. (Grade 2C)
- If the patient had an inadequate response to the nonpharmacological interventions or has a major depressive disorder, severe dysthymia or severe emotional lability, we recommend that a trial of an antidepressant could be considered. (Grade 2A)
- Based on good evidence we recommend that valproate should not be used for agitation and aggression in AD. (Grade 1A)
- There is insufficient evidence to recommend for or against the use of ChEIs and/or memantine for the treatment of neuropsychiatric symptoms as a primary indication. (Grade 2B)
- We recommend that risperidone, olanzapine and aripiprazole be used for severe agitation, aggression and psychosis associated with dementia where there is risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks, such as cerebrovascular adverse events and mortality. (Grade 2A)
- There is insufficient evidence to recommend for or against the use of quetiapine in the management of severe agitation, aggression and psychosis associated with dementia. (Grade 2B)
- There is insufficient evidence to recommend for or against the use of selective serotonin reuptake inhibitors or trazodone in the management of agitated patients. (Grade 2B)

AD, Alzheimer's disease; ChEI, cholinesterase inhibitor.

on a subgroup analysis from a RCT in those with AD and cerebrovascular disease that was not replicated [24]. The Cochrane Review on the use of galantamine for vascular cognitive impairment concluded that 'More studies are needed before firm conclusions can be drawn' about its use [25].

There is evidence that other ChEIs can be beneficial in this form of mixed dementia. Subgroup analyses of the AD2000 study showed greater cognitive response in patients with AD and a vascular component than without ($P = 0.02$) [26]. A RCT of rivastigmine in patients with AD showed generally larger treatment effects in those with Modified Hachinski Ischemia Scores ≥ 1 [27]. An open-label study of rivastigmine in patients with mixed dementia also showed benefit. In the VantagE study, older patients with a higher likelihood of concurrent AD demonstrated a significant cognitive response while younger patients showed none [28,29].

The benefits seen with ChEIs in the treatment of dementia where both cerebrovascular disease and AD are felt to be significant contributing factors could result from treating the AD component. If this is the case, there is no reason to single out galantamine as the ChEI of choice because benefits are most probably a class effect. Although no ChEI in Canada has been specifically approved for the treatment of mixed dementia, in situations where both AD and cerebrovascular disease are felt to be making significant contributions to the dementia then a ChEI to deal with the AD contribution would be a treatment consideration.

New recommendation for dementia associated with Parkinson's disease

- *New recommendation* ChEIs are recommended as a treatment option for dementia associated with PD. (Grade 1A)

Rationale

In a placebo-controlled study, treatment with rivastigmine was associated with moderate improvements in dementia associated with PD [30]. Two small randomized studies of subjects with PD and dementia showed that donepezil was well tolerated, did not worsen PD and was associated with modest benefits in cognition and global functioning [31,32].

The American Academy of Neurology Practice Parameter dealing with the treatment of dementia in PD concluded that donepezil and rivastigmine should be considered for the treatment of dementia in PD. Those recommendations are currently being updated [33]. The conclusion of a Cochrane Systematic Review was that 'The currently available evidence supports the use of ChEIs inhibitors in patients with PD dementia, with a positive impact on global assessment, cognitive function, behavioural disturbance and activities of daily living rating scales' [34].

Symptomatic treatment of patients with idiopathic PD and mild to moderate dementia is included as an indication in the revised 2011 Canadian drug monograph for rivastigmine, and can be found in the 2011 and 2012 editions of the *Compendium of Pharmaceuticals and Specialties* [35,36]. The working group's opinion was that the benefits seen are from a class effect of ChEIs.

Revised recommendation for management of vascular dementia

- *Previous recommendation* Use of ChEIs in probable/possible VaD using the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences diagnostic criteria: (a) there is insufficient evidence for or against the use of galantamine; and (b) there is fair evidence of benefits of small magnitude for donepezil in cognitive and global outcomes, with less robust benefits on functional measures. Donepezil can be considered a treatment option for VaD [14].
- *Revised recommendation* There is insufficient and inconsistent evidence on which to make a recommendation either for or against the use of the currently available ChEIs for the treatment of probable or possible VaD. (Grade 2B)

Rationale

In a randomized, double-blind, placebo-controlled, parallel-group clinical trial of 788 patients with probable VaD, galantamine did not lead to a statistically significant benefit on both co-primary endpoints; that is, the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog), and the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory

total score. After 26 weeks, those patients treated with galantamine had a small but greater improvement in ADAS-cog/11 but not on the Alzheimer's Disease Cooperative Study – Activities of Daily Living score. Safety data revealed that 13% of galantamine patients and 6% of placebo patients discontinued treatment because of adverse events [37]. Erkinjuntti and colleagues randomly allocated patients with either probable VaD or AD and cerebrovascular disease to galantamine or placebo. In those patients with probable VaD, no statistically significant benefit was seen on either of the two primary outcome measures (ADAS-cog and Clinician's Interview Based Impression of Change plus caregiver input) [24].

There are three published clinical trials of donepezil for probable or possible VaD [38-40]. Donepezil was not shown to be an effective agent in two of these studies. In two of the three studies reviewed in the Canadian product monograph for donepezil, numerically higher mortality was found among patients treated with donepezil (statistically significant in one study). For the three trials combined, the mortality rate during double-blind treatment was numerically but not significantly higher in the donepezil group [41].

A 24-week, multicenter, double-blind study of patients with probable VaD demonstrated superiority of rivastigmine over placebo on cognition (Vascular Dementia Assessment Scale, ADAS-Cog, and Mini-Mental State Examination (MMSE)) but not on activities of daily living or neuropsychiatric symptoms. The efficacy apparent on the cognitive outcomes was seen only in older patients who were more likely to have concomitant AD pathology, supporting the argument that the putative cholinergic deficit seen in VaD reflects the presence of concomitant AD pathology [28].

These studies do not show statistically significant benefits in function, neuropsychiatric symptoms or global status on a consistent basis. There were consistent but modest cognitive benefits (about 1.5 to 2 points on the ADAS-Cog) of uncertain clinical significance. No ChEI in Canada has been specifically approved for VaD. A methodological issue in the trials reviewed has been the difficulty in diagnosing 'pure' VaD as the criteria used are relatively insensitive (that is, will miss a proportion of those with significant cerebrovascular disease) and many of those fulfilling probable VaD criteria have mixed pathologies (typically AD and cerebrovascular disease) [42].

Revised recommendations for the management of mild to severe Alzheimer's disease

- *Previous recommendation* All three ChEIs available in Canada are modestly efficacious for mild to moderate AD. These ChEIs are all viable treatment options for most patients with mild to moderate AD [12].

- *Revised recommendation* All three ChEIs have demonstrated efficacy for mild to severe AD. A trial of a ChEI is recommended for most patients with AD. (Grade 1A)

Rationale

As per the third CCCDTD, randomized placebo-controlled, double-blind trials supported the efficacy of all three ChEIs for mild to moderate dementia, with one additionally demonstrating efficacy for moderate to severe AD [43,44]. The patient numbers needed to treat and to harm are similar [45]. There is better awareness of syncope [46] and bradycardia [47] from cohort studies. The recommendation for a trial of ChEIs in mild to moderate AD remains unchanged.

Since the third CCCDTD, new information has emerged on the indication for severe AD (commonly considered MMSE <10). RCTs have demonstrated efficacy in severe AD for donepezil [48-52], rivastigmine (secondary analysis only) [53] and galantamine (MMSE 5 to 12) [54]. The DOMINO trial assigned 295 community-dwelling patients with moderate or severe AD (MMSE 5 to 13) stabilized on donepezil to continued donepezil monotherapy, combined donepezil and memantine therapy, memantine monotherapy, or no active therapy for 52 weeks. Those patients randomized to continue donepezil versus discontinue donepezil had higher scores on cognition and function after adjustment for center, duration of donepezil treatment before entry, baseline MMSE and age [55].

- *Previous recommendation* While all three ChEIs available in Canada have efficacy for mild to moderate AD, equivalency has not been established in direct comparisons. Selection of which agent to be used will be based on the adverse effect profile, ease of use, familiarity and beliefs about the importance of the differences between the agents in their pharmacokinetics and other mechanisms of action [12].
- *Revised recommendation* Direct comparisons do not suggest differences between ChEIs (Grade 2B). Selection of which agent to be used will be based on the adverse effect profile, ease of use, familiarity and beliefs about the importance of the differences between the agents in their pharmacokinetics and other mechanisms of action.

Rationale

Studies have presented four head-to-head comparisons of ChEI, with donepezil being compared with both rivastigmine [56,57] and galantamine [58,59]. These randomized open-label, rater-blinded trials show similar benefits, but they are methodologically limited. Criticisms included a lack of double-blinding, small sample sizes, suboptimal dosing regimens and short treatment durations [60]. These data were available for

the third CCCDTD except for Bullock and colleagues [56], which was a 24-month, larger ($n = 994$), double-blind, flexible-dose study in patients with moderate to severe AD (MMSE 10 to 20). Similar to the previous studies, the two ChEIs were similar on measures of cognition and behavior. While rivastigmine showed possible advantages on activities of daily living and global function, the results were not consistent. Adverse events were similar. The more recent trial supports the previous recommendation that there are no differences between ChEIs.

- *Previous recommendation for mild to moderate AD* Combination therapy of a ChEI and memantine is rational (as the medications have different mechanisms of action), appears to be safe, and may lead to additional benefits for patients with moderate to severe AD. This would be an option for patients with AD of a moderate severity [12].
- *Previous recommendation for severe AD* Patients with severe AD can be treated with ChEIs, memantine or the combination. Expected benefits would include modest improvements in cognition, function and behavior and/or slower decline [13].
- *Revised recommendation* There is insufficient evidence to recommend for or against the combination of a ChEI and memantine (Grade 2B)

Rationale

While the first published trial by Tariot and colleagues adding memantine or placebo to donepezil in moderate to severe AD ($n = 404$) was supportive [61], subsequent trials by Porsteinsson and colleagues in mild to moderate patients [62] and the DOMINO trial in moderate to severe patients [55] were not. Porsteinsson and colleagues studied 433 participants with mild to moderate AD (MMSE 10 to 22) who were stable on any of the three ChEIs and were randomized to receive placebo or memantine (20 mg once daily) for 24 weeks. They found no significant differences between the memantine and placebo groups on cognition, function or behavior, and tolerability was similar. The DOMINO trial ($n = 295$) found no benefits in cognition in those patients randomized to donepezil and memantine ($n = 72$, 38 completers) versus donepezil alone ($n = 73$, 34 completers), after adjustment for center, duration of donepezil treatment before entry, baseline MMSE and age [55]. There were no differences between groups in serious adverse events. Overall, while the combination appears safe, there is insufficient evidence of additional efficacy.

The recommendation for memantine monotherapy from the previous consensus conference is still considered valid: memantine is an option for patients with moderate to severe stages of AD. Use of memantine in mild stages of AD is not recommended [63].

- *Previous recommendations referring to discontinuation of therapy with ChEIs and memantine* Medications for the treatment of cognitive and functional manifestations of AD should be discontinued when: the patient and/or their proxy decision-maker decides to stop; the patient refuses to take the medication; the patient is sufficiently nonadherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem; there is no response to therapy after a reasonable trial; the patient experiences intolerable side effects; the comorbidities of the patient make continued use of the agent either unacceptably risky or futile (for example, terminally ill); or the patient's dementia progresses to a stage where there is no significant benefit from continued therapy [12].

After stopping therapy for AD, patients should be carefully monitored – if there is evidence of a significant decline in their cognitive status or functional abilities or the development/worsening of behavioral challenges, consideration should be given to reinstating the therapy [12].

Treatment with ChEIs and/or memantine should persist until clinical benefit can no longer be demonstrated. Treatment should not be discontinued simply because of institutionalization [13].

- *Revised recommendations* Discontinuing ChEIs in patients with moderate to severe AD may lead to worse cognitive function and greater functional impairment as compared with continued therapy (Grade 2B). This effect must be balanced with the risk for known side-effects and drug costs if therapy continues. ChEIs should be discontinued when:
 - (i) the patient and/or their proxy decision-maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation;
 - (ii) the patient refuses to take the medication;
 - (iii) the patient is sufficiently nonadherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem;
 - (iv) the patient's rate of cognitive, functional and/or behavioral decline is greater on treatment compared with that prior to being treated;
 - (v) the patient experiences intolerable side effects that are definitely or probably related to the ChEI;
 - (vi) the comorbidities of the patient make continued use of the agent either unacceptably risky or futile (for example, terminally ill); or
 - (vii) the patient's dementia progresses to a stage (for example, Global Deterioration Scale stage 7 [64]) where there would be no clinically meaningful benefit from continued therapy.

When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, the dose should be tapered before stopping the agent and the patient should be monitored over the next 1 to 3 months for evidence of significant decline. If decline occurs, it is suggested consideration be given to reinstating therapy. (Grade 2C)

Rationale

After treatment with a ChEI is started, the likelihood of stopping within a year is high [65]. When this cessation is done on the basis of patient/caregiver preference or adverse events, these decisions are in general not controversial. The one qualification to this statement relates to stopping because of adverse events. In many older patients, possible adverse events that emerge during therapy could be due to alternative causes. Before acting, an assessment of the probability that the adverse event is related to therapy should be made [66].

A persisting area of uncertainty is when to discontinue a ChEI because of a perceived lack of clinically relevant benefit. There is agreement that these decisions should be individualized and based on clinical judgment rather than arbitrarily stopping once a patient scores less than a predefined threshold on a brief cognitive measure such as the MMSE or is institutionalized [12,13]. An Internet-based survey of Canadian dementia experts (geriatric psychiatrists, geriatricians, neurologists) on when to discontinue ChEI therapy led to a number of recommendations where there was reasonable consensus among the respondents [67].

The DOMINO study provides RCT data on the consequences of discontinuing therapy with a ChEI (donepezil) in patients with moderate to severe AD [55]. After a year, those patients who continued therapy scored on average 1.9 points higher on a Standardized MMSE and 3 points better on the Bristol Activities of Daily Living Scale. Similar data exist for ChEIs in mild to moderate AD [68]. Some patients show withdrawal phenomena after stopping a ChEI [69]. Although there is no rigorous research data to support the suggestion, some recommend tapering before stopping [67]. Older studies suggested that interrupting therapy for prolonged periods of time (for example, 6 weeks) could result in the loss of treatment benefits that could not be recaptured [70]. This would suggest that if a decision is made to restart after stopping a ChEI, it would be better to do so earlier rather than later.

Revised recommendation for the management of mood disorders associated with Alzheimer's disease

- *Previous recommendation* If the patient had an inadequate response to the nonpharmacological interventions or has a major affective disorder, severe dysthymia or severe emotional lability, a trial of an antidepressant should be considered [13].

- *Revised recommendation* If the patient had an inadequate response to the nonpharmacological interventions or has a major affective disorder, severe dysthymia or severe emotional lability, a trial of an antidepressant *could* be considered. (Grade 2A)

Rationale

At the time of the third CCCDTD there was reasonable evidence to support this recommendation. For example, a meta-analysis of the RCTs of antidepressants for treatment of depression in AD concluded that treatment was efficacious with discontinuation rates that were equivalent to placebo [71]. Since then, two large RCTs on the treatment of depression in dementia have shown benefits equivalent to placebo. Using the provisional diagnostic criteria for depression in AD [72], the DIADS-2 study compared 131 patients randomized to sertraline or placebo for 12 weeks [73]. Both groups experienced significant and similar reductions in depressive symptoms, although the sertraline-treated group experienced more adverse events. Similarly, in the HTA-SADD study, 218 patients judged clinically to have depression requiring antidepressant treatment were randomized to treatment with mirtazapine, sertraline or placebo [74]. At both 13-week and 39-week follow-ups, all three groups experienced significant and similar declines in depression rating scores, although the patients treated with active drug experienced significantly more adverse events. While both studies appear to confirm that depression in AD responds to treatment, it is unclear whether treatment with antidepressants is better than psychosocial interventions and whether treatment with active drug is clearly associated with adverse effects. Finally, while there is evidence that depression and depressive symptoms are persistent in many patients, the significant variability supports spontaneous remission of symptoms in some individuals [75,76].

Given data from newer studies, the working group suggested the recommendation should be modified. The original recommendations were wisely worded to indicate that nonpharmacological interventions should precede medications, however, and antidepressants could still be considered an option in cases where nonpharmacological interventions have failed. As noted in the previous guidelines, preference should be given to the selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants should be avoided because of their anticholinergic effects and resultant concerns about worsening cognition.[77]

New recommendation for the management of agitation and aggression in Alzheimer's disease

- *New recommendation* There is good evidence that valproate should not be used for agitation and aggression in AD. (Grade 1A)

Rationale

At the time of publication of the third CCCDTD, five RCTs had examined the efficacy of valproate preparations for agitation and aggression in patients with dementia [78], with none showing efficacy on any of the primary outcome measures although some of the secondary outcome measures were positive. Valproate was associated with significant adverse events and dropouts. More recently, the Alzheimer's Disease Cooperative Study published results of a large RCT of divalproex sodium for prevention of the emergence of agitation or psychosis in mild to moderate AD [79]. This 24-month randomized placebo-controlled study of 313 patients showed no differences in the emergence of neuropsychiatric symptoms, and divalproex sodium was poorly tolerated with significant toxicity. Even more worrisome, patients treated with divalproex in a substudy were found to experience accelerated brain volume loss and greater cognitive impairment compared with placebo-treated patients [80]. Finally, in a recently published administrative health database study, valproate appeared to have a similar risk of mortality in dementia patients compared with haloperidol, risperidone and olanzapine [81].

Revised recommendations for management of neuropsychiatric symptoms

- *Previous recommendation* Patients who have mild to moderate AD and neuropsychiatric symptoms can be considered for a trial of a ChEI and/or memantine for these symptoms [12].
- *Revised recommendation* There is insufficient evidence to recommend for or against the use of ChEIs and/or memantine for the treatment of neuropsychiatric symptoms as a primary indication. (Grade 2B)

Rationale

At the time of the third CCCDTD this recommendation was supported by secondary outcome measures reported from pivotal trials of cognitive enhancers in patients with low levels of neuropsychiatric symptoms at baseline. There was also one randomized placebo-controlled withdrawal study of donepezil, which demonstrated efficacy for the treatment of neuropsychiatric symptoms in mild to moderate AD patients with moderate levels of neuropsychiatric symptoms at baseline [82]. Subsequently, a large well-designed RCT of donepezil was conducted in patients with significant agitation at baseline that demonstrated no significant benefit compared with placebo [83]. This study, however, provided a powerful psychosocial intervention to both groups that may have contributed to the lack of demonstrable drug-placebo differences. With respect to memantine, the results of a large Canadian RCT were recently presented [84]. In this study of over 300 AD patients with significant agitation at

baseline, there were no differences on any of the neuro-psychiatric outcome measures compared with placebo.

- *Previous recommendation* Risperidone and olanzapine can be used for severe agitation, aggression and psychosis. The potential benefit of all antipsychotics must be weighed against the potential risks such as cerebrovascular adverse events and mortality [13].
- *Revised recommendation* Risperidone, olanzapine and aripiprazole can be used for severe agitation, aggression and psychosis where there is risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks such as cerebrovascular adverse events and mortality. (Grade 2A)

Rationale

At the time of publication of the third CCCDTD, aripiprazole was not approved for use in Canada, although it subsequently became available in 2009. Three RCTs comparing aripiprazole with placebo in AD patients for treatment of agitation and psychosis demonstrated reasonable tolerability and benefits significantly greater than placebo [85-87]. In a meta-analysis of these trials, the pooled estimate of effect sizes was small but statistically significant and similar to benefits found with risperidone and olanzapine [88].

While Health Canada warnings for increased rates of cerebrovascular adverse events and mortality based on the RCTs of the atypical antipsychotics had already been published at the time of the third CCCDTD and were carefully considered, subsequent RCTs and data from large administrative health databases raise further concerns about the safety of the antipsychotics in older dementia patients. These concerns include cognitive decline [89], adverse metabolic effects [90,91], and extrapyramidal symptoms [92]. Similarly, newer studies appear to confirm the risk of excess mortality in antipsychotic-treated patients with dementia, although different antipsychotics may have relatively different risks and some other nonantipsychotic drugs may carry similar risks [93-96].

- *Previous recommendation* There is insufficient evidence to recommend for or against the use of trazodone in the management of nonpsychotic, agitated patients [13].
- *Revised recommendation* There is insufficient evidence to recommend for or against the use of SSRIs or trazodone in the management of agitated patients. (Grade 2B)

Rationale

There have been two recent double-blind RCTs that compared citalopram [97] and escitalopram [98] with

risperidone in moderate to severe AD patients with significant behavioral and psychological symptoms of dementia. Both SSRIs demonstrated efficacy that was similar to risperidone, but with better tolerability. In a randomized placebo-controlled trial of SSRI antidepressant discontinuation in nondepressed nursing home residents with dementia, discontinuation was associated with significant increases in depression rating scale scores although scores for agitation and psychosis were similar [99]. A recent Cochrane Review concluded that while larger randomized placebo-controlled studies are needed, the SSRIs and trazodone appear to be reasonably well tolerated when compared with placebo and typical and atypical antipsychotics [100].

Discussion

All of the recommendations from the working group on the updated pharmacological treatment of dementia were approved by consensus. Some recommendations underwent minor wording changes for consistency or in response to input from other working groups.

As noted in Table 1, at CCCDTD 2012 another recommendation was added, which suggested that there was insufficient evidence for or against the use of quetiapine for severe agitation, aggression or psychosis associated with dementia. Participants argued for inclusion of this guideline recognizing the significant increase in frequency of use of quetiapine for these indications in the past few years. Whether this increase was due to the fact that, unlike risperidone and olanzapine, there were no Health Canada warnings about increased cerebrovascular adverse events in dementia trials with quetiapine or whether it was because of perceived advantages with respect to the development of extrapyramidal effects is unclear [101]. While previous reviews and meta-analyses concluded there was no evidence of efficacy for quetiapine for behavioral and psychological symptoms of dementia in AD [75,102], a recent meta-analysis suggested somewhat different results [103]. In that meta-analysis of six RCTs, quetiapine was found to have statistically significant greater benefit than placebo on behavioral measures and clinical global impression. Interestingly, in spite of these findings, those authors concluded that the current literature does *not* support the use of quetiapine for behavioral and psychological symptoms of dementia. One should also note that, unlike the positive trials of clozapine for the treatment of psychosis in dementia with PD, RCTs of quetiapine for PD have demonstrated mixed (mostly negative) results, and recent evidence-based clinical practice guidelines from the Movement Disorders Society consider the use of quetiapine only 'investigational' at the present time [104].

One potential advantage for the use of quetiapine relates to greater dose flexibility, which might be

particularly helpful for very old and frail individuals. For example, while use of the other recommended atypical antipsychotics falls within tight dose ranges related to their high potency (for example, risperidone 0.5 to 2.0 mg, olanzapine 5 to 10 mg, aripiprazole 5 to 15 mg), quetiapine, a low potency drug, can be titrated by 25 mg increments from 25 to 300 mg/day [6].

While beyond the mandate of the workgroup, a potential limitation of the guidelines was a lack of recommendations for the pharmacological management of other dementias, such as frontotemporal dementias. There are no approved therapies for frontotemporal dementias in Canada, and recent reviews have emphasized that the limited and conflicting nature of the available data makes the role of pharmacological management uncertain [105]. The workgroup identified seven trials of cognitive enhancers in frontotemporal dementia patients, including four open-label or nonrandomized studies with ChEIs [106-109], one small, negative double-blind placebo-controlled withdrawal study with galantamine [110], an open-label study with memantine [109], and a small negative randomized placebo-controlled trial with memantine [111]. There are also several open-label studies examining the use of antidepressants, psychostimulants and antipsychotics for neuropsychiatric symptoms [112-114], as well as three RCTs including a positive study with trazodone [115] and two small studies with contrasting results using paroxetine [116,117].

Another potential limitation is that these guidelines do not mention specific doses or formulations for the ChEIs. As noted above, ChEIs are considered of equivalent efficacy, with tolerability considerations guiding clinicians in their choice. These recommendations would therefore extend to the transdermal patch formulation of rivastigmine [118]. The 23 mg formulation of donepezil is not available in Canada and recommendations for its use were therefore not considered. One should, however, note that evidence for the tolerability and effectiveness of this dose has been controversial [119].

Conclusion

Since the third CCCDTD in 2006, the literature on new agents for the pharmacological management of AD and other dementias has been characterized by disappointing failures. Numerous therapeutic agents with rational mechanisms of action and positive findings in preclinical and even early phase II studies have shown disappointing results and have been abandoned [120]. These agents include drugs such as tramiprosate, flurbiprofen, glitazones, statins, dimebon, semagacestat and, most recently, bapineuzumab. These failures have left clinicians with therapies that have been generally available for over a decade, and provide modest benefits at best. In spite of this, we believe attempts to update treatment guidelines

such as those presented are the best way to optimize therapy and provide patients, families and their physicians with the best and safest interventions available at the present time. Our hope is that, at the time of the next CCCDTD, more effective interventions including disease-modifying therapies will be available.

Abbreviations

AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale – cognitive subscale; CCCDTD, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; ChEI, cholinesterase inhibitor; MMSE, Mini Mental State Examination; PD, Parkinson's disease; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor; VaD, vascular dementia.

Competing interests

NH has received research grants from Lundbeck, Sanofi-Aventis and Sonexa, and has also received honoraria from Lundbeck, Pfizer, Novartis and Janssen-Ortho Inc. He was a consultant for Lundbeck, and also participated in a speaker forum for Lundbeck and Pfizer. He is a Board Member for Pfizer and Lundbeck. KLL has received grants/funds from Abbot Laboratories, Lundbeck, Pfizer, Janssen-Ortho Inc., Roche and Wyeth, and has also received honoraria from Abbot Laboratories, Lundbeck, Pfizer, Janssen-Ortho Inc., MedImmune and Wyeth. She was also a consultant for Abbot Laboratories, Pfizer, Janssen-Ortho Inc., MedImmune and Wyeth. DBH holds and receives financial support from the Brenda Strafford Foundation Chair in Geriatric Medicine at the University of Calgary. He has no competing interests to declare.

Declarations

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Author's contributions

NH conceived of the design. All authors conducted the review, drafted the updated recommendations, and read and approved the final manuscript.

Author details

¹Department of Psychiatry and the Brain Sciences Research Program, Sunnybrook Health Sciences Centre, Suite FG08, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada. ²Department of Psychiatry, University of Toronto, Suite FG08, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada. ³Department of Medicine and The Hotchkiss Brain Institute, University of Calgary, HSC-3330 Hospital Dr. NW, Calgary, Alberta T2N 4N1, Canada.

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