Update of Pharmacological Intervention Recommendations for the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012

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 Alzheimer's disease with other brain pathology. It is recommended that management be based on what is (are) felt to be the predominant contributing cause(s). (Grade 1B)

Rationale: In late-life, dementia frequently arises from more than one condition. (1) For example, in the Rush Memory and Aging Study mixed brain pathologies were commonly found among persons dying with a dementia. At autopsy 38% had Alzheimer's disease (AD) and infarcts, 30% pure AD, 12% vascular dementia, and 12% AD with either Parkinson's disease or Lewy body dementia. (2) In the BrainNet Europe Consortium the proportion of patients with mixed diagnoses among all cases of dementia was 53.3%. (3) This observation has been reported in a number of other studies. (4-6) The presence of multiple brain pathologies markedly increases the odds of cognitive impairment becoming evident. (2,7)

In their clinical practice guideline for dementia, the National Institute for Health and Clinical Excellence note that many cases of dementia may have mixed pathology and unless stated otherwise should be managed according to the condition that is thought to be the predominant cause. (8)

This recommendation recognizes how commonly mixed pathologies underlies dementia and gives management advice to practicing physicians. It aligns with the practice of many if not most dementia specialists and is in accord with drug benefit coverage criteria in a number of Canadian provinces (see appendix).

2) Modified recommendation for management of Alzheimer's disease and cerebrovascular disease

Previous recommendation (7.7): Use of cholinesterase inhibitors in dementia due to combined Alzheimer's and Cerebrovascular disease: There is fair evidence of benefits of small magnitude for galantamine in cognitive, functional, behavioral, and global measures in AD with CVD. Galantamine can be considered a treatment option for mixed Alzheimer's with Cerebrovascular disease. (Grade B, Level 1).

Modified recommendation: Cholinesterase inhibitors are recommended as a treatment option for Alzheimer's disease with cerebrovascular disease. (Grade 1B)

Rationale: Alzheimer's disease and cerebrovascular lesions are frequently identified at autopsy in older persons. Vascular lesions (i.e., infarcts, amyloid angiopathy) were found in 37.5% (30/80) of cases fulfilling neuropathologic criteria for intermediate or high likelihood of Alzheimer's disease in a community-based clinical-pathologic cohort study. (2)

In accord with the preceding new recommendation, cholinesterase inhibitors and/or memantine to deal with the Alzheimer component would be treatment considerations for these cases. The prior recommendation that signaled out galantamine was based on a sub-group analysis from a randomized controlled trial that was not replicated. Subjects in this study with Alzheimer's disease and cerebrovascular disease assigned to receive galantamine showed statistically significant benefits compared to the placebo arm on the primary efficacy outcome measures used, the ADAS-Cog (treatment difference 2.7 points, $p = 0.0005$) and the CIBIC plus (32% improved compared to 19%, $p = 0.019$), at 6 months.(9) 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]. (10)

There is evidence that other cholinesterase inhibitors can be beneficial in this form of mixed dementia. Subgroup analyses of the AD2000 study showed greater cognitive response in patients with Alzheimer's disease and a vascular component than without ($p = 0.02$). (11) A randomized controlled trial of rivastigmine in patients with Alzheimer's disease showed generally larger treatment effects in those with Modified Hachinski Ischemia Scores of 1+. (12) An open-label study of rivastigmine in patients with a mixed dementia also showed benefit. In the VantagE study older patients with a higher likelihood of concurrent Alzheimer had a significant cognitive response while younger patients showed none. (13,14)

As previously noted, benefits seen in treating Alzheimer's disease with cerebrovascular disease could be from treating the Alzheimer component. If that is the case, there is no reason to signal out galantamine as the cholinesterase inhibitor of choice. We believe any benefits seen are most likely from a class effect and not limited to a particular cholinesterase inhibitor. No cholinesterase inhibitor in Canada has been specifically approved for the treatment of "mixed" dementia or vascular dementia. The revised recommendation is in line with current clinical practice and would allow clinicians to select which cholinesterase inhibitor they wish to use.

3) New recommandation for dementia associated with Parkinson's disease

New Recommendation: Cholinesterase inhibitors are recommended as a treatment option for dementia associated with Parkinson's disease. (Grade 1A)

Rationale: In a placebo-controlled study, treatment with rivastigmine was associated with moderate improvements in dementia associated with Parkinson's disease. (15) Two small randomized studies of subjects with Parkinson's disease (PD) and dementia showed that donepezil was well tolerated, did not worsen PD, and was associated with modest benefits in cognition and global functioning. (16,17)

The AAN Practice Parameter dealing with the treatment of dementia in Parkinson's disease (PD) concluded that donepezil and rivastigmine should be considered for the treatment of dementia in PD (Level B). These recommendations are currently being updated. (18) The conclusion of a Cochrane Systematic Review was that "The currently available evidence supports the use of cholinesterase inhibitors in patients with PDD, with a positive impact on global assessment, cognitive function, behavioural disturbance and activities of daily living rating scales." (19)

Symptomatic treatment of patients with idiopathic Parkinson's disease 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 CPS. (20,21) We believe the benefits seen are from a class effect to cholinesterase inhibitors and are not unique to rivastigmine.

4) Modified recommendation for management of vascular dementia

Previous recommendation (7.8): Use of cholinesterase inhibitors in probable/ possible vascular dementia using NINDS-AIREN diagnostic criteria: a. There is insufficient evidence for or against the use of galantamine (Grade C, Level 1). 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 Vascular Dementia (Grade B, Level 1)

Modified recommendation: There is insufficient and inconsistent evidence on which to make a recommendation either for or against the use of the currently available cholinesterase inhibitors for the treatment of probable or possible vascular dementia. (Grade 2B)

Rationale: In a multinational, randomized, double-blind, placebo-controlled, parallel-group clinical trial of 788 patients with probable VaD, treatment with galantamine did not lead to a statistically significant benefit on both co-primary endpoints (i.e., Alzheimer's Disease Assessment Scale-Cognitive subscale and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory total score). Patients treated with galantamine had a greater improvement in ADAS-cog/11 after 26 weeks compared with placebo (-1.8 vs -0.3; $p < 0.001$), but there was no difference between galantamine and placebo at week 26 on the ADCS-ADL score (0.7 vs 1.3; $p = 0.783$). Safety data revealed that 13% of galantamine and 6% of placebo patients discontinued treatment because of adverse events. (22) Erkinjuntti et al enrolled patients with either probable vascular dementia or Alzheimer's disease and cerebrovascular disease. They were randomly allocated to galantamine or placebo. Subgroup analyses were done though the study was not designed to be sufficiently powered to show significant differences in them. Notwithstanding this, in the subgroup of patients with probable vascular dementia no statistically significant benefit was seen on either of the two primary outcome measures (Alzheimer's disease assessment scale, cognitive subscale [ADAS-cog]) and global functioning (clinician's interview-based impression of change plus caregiver input [CIBIC-plus]). The treatment difference on the ADAS-cog scores was nearly but not quite statistically significant (treatment difference 1.9 points, $p = 0.06$). The proportion with improved CIBIC-plus scores at 6 months was higher with galantamine but this was not statistically significant (31% vs 23%; $p = 0.238$). (9)

There are three published clinical trials of donepezil for probable or possible vascular dementia. Donepezil was not shown to be an effective agent in two of these studies. In the Wilkinson et al study those on donepezil showed significant improvements versus placebo in cognition (mean endpoint treatment difference as measured by the change from baseline score of approximately 2 points on ADAS-Cog), and global function (32-39% showed improvement on CIBIC+ compared to 25% in the placebo group). (23) Black et al reported a significant benefit with treatment in cognition (again of about 2 points on the ADAS-Cog) but inconsistent results on the global measures used (CIBIC+ and sum of boxes of the CDR). (24) In the third trial of Román et al, patients treated with donepezil 5 mg/d did significantly better in cognition (about a point on the ADAS-Cog) compared to subjects allocated to the placebo arm but not on the global outcome. (25) In two of the three studies reviewed in the Canadian product monograph for

donepezil, a higher mortality was found among patients treated with donepezil. This was statistically significant in one of the studies ($p = 0.02$). For the three trials combined the mortality rate during double-blind treatment with donepezil was higher than seen in the placebo group (1.7% versus 1.1%), but this was not statistically significant ($p = 0.35$). (26)

A 24-week, multicentre, double-blind study of patients with probable vascular dementia of rivastigmine demonstrated superiority of rivastigmine over placebo on three measures of cognitive performance (Vascular Dementia Assessment Scale, Alzheimer's Disease Assessment Scale cognitive subscale, Mini-Mental State Examination; all $p <$ or $= 0.05$, intent-to-treat population [ITT]) but no other outcomes (e.g., activities of daily living, neuropsychiatric symptoms). The efficacy apparent on the cognitive outcomes was seen only in older patients who were more likely to have concomitant Alzheimer pathology, supporting the argument that the putative cholinergic deficit seen in vascular dementia reflects the presence of concomitant Alzheimer pathology. (13)

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) seen. The clinical significance of the cognitive benefits is uncertain. No cholinesterase inhibitor in Canada has been specifically approved for the treatment of vascular dementia. A methodological issue in the trials reviewed has been the difficulty in diagnosing “pure” vascular dementia as the criteria used, while specific, are relatively insensitive (i.e., will miss a proportion of those with significant cerebrovascular disease) and have poor positive predictive values because of the relatively low prevalence of “pure” vascular dementia among all those presenting with a dementia (i.e., many of those individuals meeting criteria for probable or possible vascular dementia have mixed pathologies). (27)

5) Modified recommendations for the management of mild to severe Alzheimer's disease

Previous recommendation (5.14a): All three cholinesterase inhibitors available in Canada are modestly efficacious for mild to moderate AD. They are all viable treatment option for most patients with mild to moderate AD. (Grade A, Level 1)

a) Modified recommendation: All three cholinesterase inhibitors have demonstrated efficacy for mild to severe AD. A trial of a ChEI is recommended for most patients with AD. (Level 1A).

Rationale: As per CCCDTD3, randomized placebo controlled double-blind trials supported the efficacy of all 3 ChEIs for mild to moderate dementia, with one additionally demonstrating efficacy for moderate to severe AD[1, 2]. The numbers needed to treat and to harm are similar [3]. This applies to most patients in most situations. There is better awareness of syncope[4] and bradycardia[5] from cohort studies. We continue to suggest a trial of cholinesterase inhibitors in mild to moderate AD.

Since the last consensus, new information has emerged on the severe indication (commonly MMSE <10). RCTs have demonstrated efficacy in severe AD for donepezil[6-10], rivastigmine (secondary analysis only)[11] and galantamine (MMSE 5-12)[12]. The DOMINO trial, assigned 295 community-dwelling patients with moderate or severe AD (MMSE 5-13) stabilized on donepezil to continue donepezil (+placebo memantine), continue donepezil plus memantine, discontinue donepezil (+placebo memantine),

discontinue donepezil + memantine, or groups for 52 weeks. Those randomized to continue donepezil (donepezil groups combined irrespective of whether on memantine or not) versus discontinue (2 groups who did not receive donepezil combined, irrespective of whether on memantine or not) had higher scores on cognition and function after adjustment for centre, duration of donepezil treatment before entry, baseline MMSE and age[13].

Previous recommendation (5.14b): While all three cholinesterase inhibitors 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 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. (Grade B, Level 1)

b) Modified recommendation: Direct comparisons do not suggest differences between cholinesterase inhibitors (Grade 2B). Selection of which agent to be used will be based on 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: There are 4 head to head comparisons of ChEI, with donepezil being compared to both rivastigmine [14, 15] and galantamine [16, 17]. These randomized open label, rater blinded trials show similar benefits, but they are not well-designed. Criticisms included lack of double-blinding, small sample sizes, suboptimal dosing regimens and short treatment durations[18]. These data were available for CCCDTD 2004 except for Bullock et al 2005 [15], which was a 24 month, larger (n=994), double-blind, flexible dose study in patients with moderate to severe AD (MMSE 10-20). Similar to the previous studies, the 2 ChEI 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 (ITT-LOCF, but not ITT-LOCF analysis). Adverse events were similar. Thus, the more recent trial supports the previous recommendation that there are no differences between ChEI.

Previous recommendation for mild to moderate AD (5.15b): Combination therapy of a cholinesterase inhibitor 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. (Grade B, Level 1)

Previous recommendation for severe AD (6.6): 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. (Grade A, Level 1)

c) Modified Recommendation: Combination therapy of a cholinesterase inhibitor and memantine is rational (as the medications have different mechanisms of action) and appears to be safe, but there is insufficient evidence to recommend for or against this combination (Grade 2B)

Rationale: While the first published trial by Tariot et al 2004[19] adding memantine or placebo to donepezil in moderate to severe AD (n=404) was supportive, subsequent trials by Porsteinsson in mild to moderate patients (all ChEI)[20] and the DOMINO trial in moderate to severe [13] were not. Porsteinsson studied 433 participants with mild to moderate AD (MMSE10-22) who were stable on any of the 3 ChEI to placebo or memantine (20 mg once daily) for 24 weeks. They found no significant

differences between the memantine and placebo group on cognition, function or behaviour, and tolerability was similar. The DOMINO trial (n=295) found no benefits in cognition in those randomized to donepezil and memantine (n=72, 38 completers) versus donepezil alone (n=73, 34 completers), after adjustment for centre, duration of donepezil treatment before entry, baseline MMSE and age[13]. There were no differences between groups in serious adverse events.

Previous recommendations in Topics 5 and 6 referred to discontinuation of therapy with ChEIs and memantine. 5.16: 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 non-adherent 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 (e.g., terminally ill); or, The patient's dementia progresses to a stage where there is no significant benefit from continued therapy. (Grade B, Level 3). 5.17: After stopping therapy for AD, patients should be carefully monitored and if there is evidence of a significant decline in their cognitive status, functional abilities, or the development/worsening of behavioural challenges, consideration should be given to re-instating the therapy. (Grade B, Level 3). 6.7: 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. (Grade C, Level 3)

d) Modified Recommendations: Discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer's disease may lead to worse cognitive function and greater functional impairment as compared to continued therapy (Level 2B). This must be balanced with the risk for known side-effects and drug costs if therapy continues. It is suggested that cholinesterase inhibitors be discontinued when:
   a) The patient and/or their proxy decision maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation;
   b) The patient refuses to take the medication;
   c) The patient is sufficiently non-adherent 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;
   d) The patient's rate of cognitive, functional, and/or behavioural decline is greater on treatment compared to that prior to being treated;
   e) The patient experiences intolerable side effects that are definitely or probably related to the cholinesterase inhibitor;
   f) The comorbidities of the patient make continued use of the agent either unacceptably risky or futile (e.g., terminally ill); or,
   g) The patient's dementia progresses to a stage (e.g., Global Deterioration Scale stage 7 [1]) 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, it is suggested that the dose be tapered before stopping the agent and that the patient be monitored over the next 1-3 months for evidence of significant decline. If this occurs, it is suggested that consideration be given to reinstating therapy. (Level 2C)

Rationale: After treatment is started with a cholinesterase inhibitor the likelihood of stopping within a year is high. (1) When this 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 done. (2)

A persisting area of uncertainty is when to discontinue a cholinesterase inhibitor 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 pre-defined threshold on a brief cognitive measure like the Mini-Mental State Examination or is institutionalized. (3,4) An internet-based survey of Canadian dementia experts (geriatric psychiatrists, geriatricians, neurologists) on when to discontinue cholinesterase inhibitor therapy led to a number of recommendations where there was reasonable consensus among the respondents. (5)

The DOMINO study does provide RCT data on the consequences of discontinuing therapy with a cholinesterase inhibitor (donepezil) in patients with moderate to severe Alzheimer's disease. (6) After a year, those who carried on with therapy scored on average 1.9 points higher on a Standardized Mini-Mental State Examination and 3 points better on the Bristol Activities of Daily Living Scale. Some patients after stopping a cholinesterase inhibitor have shown abrupt withdrawal phenomena. (7) Though there is no rigorous research data to support the suggestion, some recommend tapering before stopping. (5) Older studies suggested that interrupting therapy for prolonged periods of time (e.g., 6 weeks) could result in the loss of treatment benefits that could not be recaptured. (8) This would suggest that if a decision is made to re-start after stopping a cholinesterase inhibitor, it would be better to do so earlier than later.

6) Modified recommendation for the management of mood disorders associated with AD

Previous recommendation: (5.21c) If the patient had an inadequate response to the non-pharmacological interventions or has a major affective disorder, severe dysthymia, or severe emotional lability, a trial of an antidepressant should be considered.

Modified Recommendation: If the patient had an inadequate response to the non-pharmacological 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 CCCDTD3 there was reasonable evidence to support this recommendation. In fact, shortly after publication, a meta-analysis of the RCTs of antidepressants for treatment of depression in AD concluded that treatment was efficacious with an NNT of 5 and discontinuation rates that were equivalent to placebo (Thompson et al CJP 2007). Since then however, 2 of the largest RCTs on the treatment of depression in dementia have been published, that show benefits equivalent to placebo. Using the provisional diagnostic criteria for depression in AD (Olin et al AJGP 2002 Pgs 125-128), the DIADS-2 study (Rosenberg et al AJGP 2010) compared 131 patients randomized to sertraline or placebo for 12 weeks. Both groups experienced significant and similar reductions in depressive symptoms, though the sertraline-treated group experienced more adverse events. Similarly, in the HAT-SADD study (Banerji et al Lancet 2011), 218 patients judged clinically to have depression requiring antidepressant treatment, were randomized to treatment with mirtazapine, sertraline or placebo. At both 13 and 39 week

follow-ups, all 3 groups experienced significant and similar declines in depression rating scores though the patients treated with active drug experienced significantly more adverse events (sertraline – gastrointestinal; mirtazapine – sedation). While both studies appear to confirm that depression in AD responds to treatment, it is unclear whether treatment with antidepressants are better than psychosocial interventions, and 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, there is significant variability, and therefore spontaneous remission of symptoms might be part of the natural illness course for some individuals (Olin et al AJGP 2002 Pgs 129-141; Eustace et al Int J Geriatr Psych 2002).

Given data from newer studies, we suggest the recommendation be modified. It is noted however, that the original recommendations were wisely worded to indicate that non-pharmacological interventions should precede medications, and therefore, in cases where non-pharmacological interventions have failed, antidepressants could still be considered an option.

7) New recommendation for the management of agitation and aggression in AD:

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 CCCDTD3, there were already 5 RCTs that examined the efficacy of valproate preparations for agitation and aggression in patients with dementia (Herrmann and Lanctot CJP 2007). In none of these studies was valproate better than placebo on any of the primary outcome measures, though in some studies, 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 (Tariot et al Arch Gen Psych 2011). In this 24 month randomized placebo controlled study of 313 patients, there were no differences in the emergence of neuropsychiatric symptoms and divalproex sodium was poorly tolerated with significant toxicity. Even more worrisome, in a sub-study, patients treated with divalproex were found to experience accelerated brain volume loss and greater cognitive impairment compared with placebo-treated patients (Fleisher et al Neurology 2011). 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 (Kales et al AJP 2012). We have therefore decided to include a recommendation specifically against the use of this agent for BPSD in patients with AD.

8) Modified recommendations for management of neuropsychiatric symptoms

Previous Recommendation (23.g) Patients who have mild to moderate AD and neuropsychiatric symptoms can be considered for a trial of a cholinesterase inhibitor and/or memantine for these symptoms.

a) Modified Recommendation: There is no good evidence to recommend for or against the use of cholinesterase inhibitors and/or memantine for the treatment of neuropsychiatric symptoms as a primary indication (Grade 2B).

Rationale: At the time of the CCCDTD3 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-moderate AD patients with moderate levels of neuropsychiatric symptoms at baseline (Holmes et al 2004). 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 (Howard et al 2007). It should be noted however, that this study 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 (Gauthier et al, 2011 Results of the Lundbeck 10158 presented at the Canadian Conference on Dementia). In this study of over 300 AD patients with significant agitation at baseline, there were no differences on any of the neuropsychiatric outcome measures compared with placebo.

Previous Recommendation (6.13): 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.

b) Modified 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 CCCDTD3, aripiprazole was not approved for use in Canada, though it subsequently became available in 2009. There have been 3 RCTs comparing aripiprazole to placebo in AD patients for treatment of agitation and psychosis (De Deyn et al J Clin Psychopharm 2005, Mintzer et al AJGP 2007, Streim et al AJGP 2008) which demonstrated reasonable tolerability and benefits significantly greater than placebo. 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 (Maher et al JAMA 2011).

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 CCCDTD3 and were considered carefully in the recommendations, subsequent studies, including both RCTs and data from large administrative health databases raise further concerns about the safety of the antipsychotics in elderly dementia patients. These concerns include cognitive decline (Vigen et al AJP 2011), adverse metabolic effects (Zheng et al AJP 2009, Lipscombe et al Arch Int Med 2009), and extrapyramidal symptoms (Rochon et al Arch Int Med 2005). Similarly, newer studies appear to confirm the risk of excess mortality in antipsychotic treated patients treated with dementia, though different antipsychotics may have relatively different risks, and some other non-antipsychotic drugs may carry similar risks (Ballard et al DART-AD Lancet 2008, Huybrechts et al CMAJ 2011, Kales et al AJP 2012, Huybrechts et al BMJ 2012).

Previous Recommendation: (6.14): There is insufficient evidence to recommend for or against the use of trazodone in the management of non-psychotic, agitated patients.

c) Modified 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: Prompted in part by concerns about the safety of antipsychotics, since the publication of the CCCDTD3 there has been increased interest in the use of antidepressants to treat agitation in AD. There have been 2 recent double-blind RCTs which compared citalopram (Pollock et al AJGP 2007) and escitalopram (Barak et al Int Psychogeriatr 2011) to risperidone in moderate to severe AD patients with significant BPSD. Both SSRIs demonstrated efficacy that was similar to risperidone, but with better tolerability. In a randomized placebo-controlled trial of SSRI antidepressant discontinuation in non-depressed nursing home residents with dementia, discontinuation was associated with significant increases in depression rating scale scores, though scores for agitation and psychosis were similar (Bergh S et al, BMJ 2012). 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 to placebo, typical and atypical antipsychotics (Seitz et al 2011 Cochrane Collaboration).