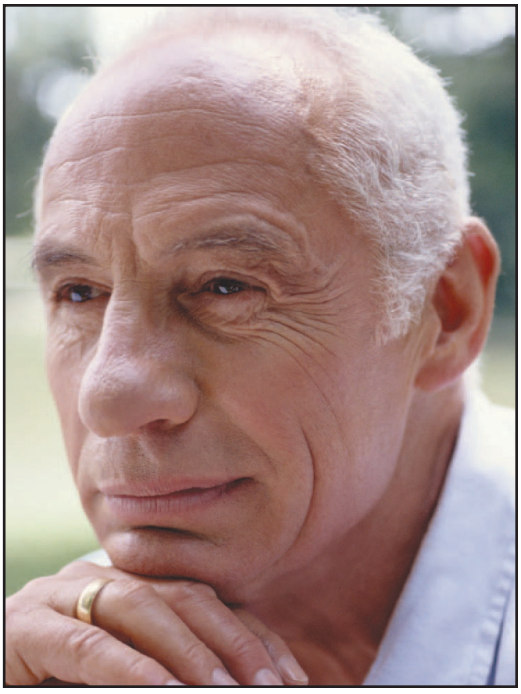
Alzheimer's:

What More Can We Do?



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In this article:

1. How do I manage a patient with Alzheimer's disease?
2. What is an acceptable trial period for medications?
3. What is the correlation between delirium and late-stage dementia?
4. How are depression and dementia linked?

Despite sizable progress made in the diagnosis and management of dementiform conditions over the past decade, the further evaluation and management of patients in middle and more advanced stages of dementia still constitutes an enormous challenge to both primary care physicians and specialists.

A few comments on diagnosis formulation should suffice. There is an enormous added value with early diagnosis. It allows the physician to identify candidates for treatment intervention prior to extensive neuronal loss, as well as having an early (albeit mild) therapeutic effect on cognitive and functional abilities. As well, it sets the stage for potential cost savings by avoiding years of multiple diagnostic evaluations, as well as giving patients and caregivers an opportunity to plan before the loss of mental capacity leads to personal incompetence.[1]

How do I manage my patient?

The treatment and management of early Alzheimer's disease (AD) include significant caregiver support, education from the Alzheimer's Society about the nature of the disorder, as well as timely and practical interventions, and, when necessary, environmental modifications. From a pharmacologic point of view, it can now be stated that all patients diagnosed with AD, vascular dementia, mixed dementia, or Lewy body dementia should receive exposure to a cholinesterase inhibitor. Difficulties arise in those provinces which do not include these compounds within their formulary, or in vascular dementia, which is

not yet covered. Numerous trials have been conducted that have issued Level 1 evidence of a significant symptomatic effect on cognition, function, and behaviour in these disorders.[2,3,4] Notwithstanding that, probably less than 50% of individuals with these diagnoses have been offered such treatment. Even though the results of treatment are best described by the term "modest but significant," many knowledgeable experts feel these agents do alter the course of the progression of these diseases. Furthermore, results now indicate that even when a physician inherits a patient with a moderately advanced stage of AD, benefits will still accrue in the majority of patients using such drugs. In a largely Canadian trial, studying the effect of donepezil on patients with moderately advanced to severe dementia, the results indicated clearly those with Folstein Mini Mental Status Examination (MMSE) scores between five and 11 benefited substantially from exposure to this drug, even though their condition had evolved to the later stages.[5]

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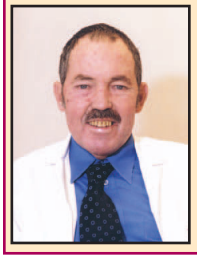

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How do I rotate my patient's medication?

As dementia progresses, there are a number of scenarios for the treating physician to keep in mind. Over the past two years, it has become fashionable for cognitive neurologists or geriatricians to consider switching individual patients from one cholinesterase inhibitor to another. The concept of switching is hardly new. For decades, this tactic has been employed for patients with refractory infections, with a change in the choice of antibiotics. Within these considerations, the purpose of changing drugs is always to maximize the benefits of treatment. However, in the case of cholinesterase inhibitors, few physicians are accustomed to using this strategy. Practitioners should discard the illusion that all cholinesterase inhibitors are the same. The lack of response or intolerability to one agent does not mean the same will transpire when another is substituted. A further problem for physicians is the lack of practical knowledge on how to make the switch.

A further problem for physicians is the lack of practical knowledge on how to switch from one agent to another.

Perhaps the first task should be to emphasize the difference between these three agents now in use:

1. Donepezil is a piperidine type medication that is rapidly reversible, and that selectively inhibits acetyl cholinesterase.[2] It has a long half-life.
2. Rivastigmine is a phenylcarbonate, a slowly reversible inhibitor of both acetyl cholinesterase and butyryl cholinesterase.[3]
3. Galantamine is a tertiary alkaloid, rapidly reversible, that selectively inhibits acetyl cholinesterase, but not butyryl cholinesterase.[3]

With respect to metabolism, both donepezil and galantamine utilize the cytochrome P450 system, while rivastigmine does not.[4] Furthermore, it has been shown that donepezil and galantamine up-regulate acetyl cholinesterase within the cerebral spinal fluid, whereas this effect is not seen with the use of rivastigmine.[6] This up-regulation is not an issue as long as that same drug is provided, but when sudden cessation occurs, the over availability of acetyl cholinesterase can, in theory, lead to a significant "crash" on the part of the patient.[7]

Not unlike other medications, there are four basic outcomes that can result from an AD patient's exposure to an acetyl cholinesterase inhibitor:

1. A lack of response.
2. Intolerability to the cholinomimetic effects of the medication.
3. A response (which at times can be subclinical or unrecognized).
4. An initial response with decline (subsequently there can be initial response with a loss of effect later downstream).

What is an acceptable trial period for medications?

Physicians prescribing these compounds should continue them for at least six months before deciding on their ineffectiveness. Again, a large proportion of responders can be subclinical in nature (*i.e.,* not showing robust improvement but holding steady from the point when the drug was started). Not uncommonly, the cessation of donepezil in a patient, who presumably was not benefiting from the drug, is followed by a steep decline in patient function, suggesting a therapeutic benefit went unrecognized.

The apo E genotype, particularly the E4 variant, had been shown to be a risk factor for AD. It does appear that some cholinesterase inhibitors are significantly more effective in E4 positive patients than in those individuals who are E4 negative. Some evidence demonstrates rivastig-

Table 1

Suggestions for the patient with poor tolerability to a cholinesterase inhibitor

- Take the drug with meals
- Reduce the dose
- Plan skipped doses
- Go for a longer titration period
- Take antiemitics (occasionally)
- Switch medications

Table 2
The most common early changes in psychomotor behaviour

- Protracted drowziness
- Anxiety
- More difficulty with thinking clearly
- Insomnia
- Disturbing dreams and psychotic features.

Adapted from: McCracken PN: Delirium in Alzheimer's Disease. The Canadian Alzheimer Disease Review 2000; 3(3):11-4.

mine appears to have benefits in AD patients that are E4 positive and negative, although certainly therapeutic failures are seen with its use in clinical practice.[7]

For the individual with AD who initially responds to a cholinesterase inhibitor, but in whom the medication seems to lose its effectiveness two or three years later, the practicing physician should discipline himself to look for underlying pathology, such as:

- a subtle CVA,
- the new onset of delirium, and
- a depression that has entered the picture.

If no such evidence is found, increasing the dose of the cholinesterase inhibitor is another tactic. Another strategy is to add an additional drug, such as an antipsychotic agent or an antidepressant drug when the clinical situation calls for it. Finally, such patients who have "run out of gas" on a certain compound can be switched to another agent within this class.[8]

Certain suggestions should be made to patients who can't tolerate cholinesterase inhibitors (Table 1).

Different approaches or recipes exist when switching these drugs. Because of the up-regulation of acetyl cholinesterase alluded to before, it is often useful to continue the first drug in a lower dosage rather than stopping it abruptly. Many clinicians use this tactic until the second drug can be titrated up to at least a minimum effective dosage, after which the first agent usually can be weaned off. When intolerability is the reason for switching drugs, it is advisable to stop all cholinesterase inhibitors for seven to 14 days, after which the second drug should be titrated upward gradually. However, when switching cholinesterase inhibitors for other reasons, some studies have featured a rapid titration upward of the second drug and a much faster rate than those in the original protocols for these drugs.

What material has been published concerning medication switches?

Published editing for these strategies is meagre. What is recorded often has appeared in non peer-reviewed journals. Switching from other therapies (such as piracetam, memantine or gingko-biloba) to donepezil revealed a significant response within three months in both the MMSE scores and a quality of life instrument.[9] As donepezil was the first such drug available, most of the published descriptions entail a switch from it to another agent within the class. The switch to rivastigmine has already been documented.[6,10] Such reports reveal that even patients (80%) intolerable to the cholinolmimetics effects of donepezil can often be switched quite comfortably to rivastigmine. Accounts also have been

Delirium is the most common cognitive problem in hospitalized elderly patients.

Table 3

Dementia and depression: Patient categories

- Major depression with secondary cognitive impairment as part of the depressive illness.
- Pseudo-dementia, in which the patient presents with symptoms and signs of dementia but in reality has an underlying depression.
- Depression occurring in patients with an established clinical diagnosis of dementia, most commonly probable Alzheimer's disease.

Adapted from: Devanard D: Depression in Dementia. Alzheimer Disease and Related Disorders 2001; 6:97-122.

described, and are in progress, about the switch from donepezil to galantamine.[11,12]

What is the correlation between delirium and late-stage dementia?

Another practical problem in the later stages of dementia is the arrival of delirium into the picture. Space does not permit for the detailed view of this particular issue, but some basic features are worthy of mention. It is well recognized that delirium is the most common cognitive problem in hospitalized elderly patients.[13] Given the prevalence of dementia in the older age groups, it is hardly surprising the two disorders are frequently associated with each other. Dementia and advanced age are risk factors for delirium. The differentiation of delirium from dementia is not difficult for the experienced physician, but combinations of the two in one patient can pose a perplexing challenge for the health-care team. Delirium in the demented patient can be difficult to determine. Its onset may well appear to be more incidious, and can take several days to develop. Psychomotor behaviour is affected by the most common early change (Table 2).

In particular, hypoactive delirium tends to go unrecognized, and there is a lack of general appreciation of this potential medical emergency. An abrupt change in the extent of psychotic features is another common manifestation. Delusions, commonly influenced by surrounding environmental stimuli, may surface or worsen. Hallucinations and sensory illusions, usually visual and very intense, are particularly common. Even with dementia, delirious patients will fluctuate and often appear to be most lucid in the morning and at their worst at night. The sleep/wake cycle becomes completely disorganized.

How do I treat my delirious patient?

A delirious patient with severe agitation will usually require neuroleptic medication to reduce the threat of injuring themselves or others. Careful consideration of the patient's premorbid status should proceed decision-making on which agent to use. Traditionally, clinicians have used the high potency neuroleptics, such as haloperadol, in this situation. The potential advantages of this compound are that it is non-sedating, does not have serious cardiorespiratory effects, can be given intravenously, and is easy to administer. The extrapyramidal side-effects of this agent are a distinct downside to their use for any significant length of time. In recent years, the medical community has moved to the atypical neuroleptic agents for these clinical situations, but, by now, physicians are well aware that even these drugs can be associated with significant extrapyramidal toxicity. The failure to anticipate delirium is not uncommon, and the treating physician must remain alert to this eventuality.

How do I treat my depressed patient?

Perhaps even more problematic for the treating physician is the arrival of major depression in the patient with advancing dementia. Recent consensus-based data from clinical settings could suggest that psychiatric disturbances effect approximately 90% of AD patients over the course of their illness.[14-18] They take on different forms, including agitation, delusions, hallucinations, depression, sleep disturbance, and problem behaviours. The natural history of depression in AD is poorly known. Depression is often one of the first symptoms of AD, and can herald its appearance. Epidemiologic studies indicate mood symptoms are common in mild to moderate dementia, and less prevalent in severe dementia. The decline in advanced dementia may be related to the difficulty in assessing depression in severe AD.

The importance of depression in AD is underscored by its consequences. Several categories of patients lie at the interface of depression and dementia (Table 3).

Another issue is that the Diagnostic and Statistic Manual 4 criteria for major depression can be met in the absence of depressed mood if the symptoms of lack of interest are present, accompanied by at least five other depressive symptoms. Symptoms of apathy, anhedonia, insomnia, and agitation commonly occur in both depression and dementia, increasing the likelihood of a diagnosis of major depression in a patient with symptomatic dementia. Suicidal ideation is uncommon in the more advanced patients, but tends to occur in mild stages of dementia when insight is preserved; as well, the risk of completed suicide in moderate to advanced dementia is low.[19]

Clinical assessment of depression in a patient with dementia also needs to focus on distinguishing apathy and lack of interest from depressive symp-

Take-home message

Strategies *do* exist for advanced dementia:

- There is uncertainty about the natural history of depression in Alzheimer's disease and at different stages of dementia.
- In general, good clinical practice and common sense indicate that behavioural intervention should be maintained for the long term.
- Antidepressants should also be continued for at least several months after remission of depression, if not for much longer.
- In terms of safety issues, patients with dementia and depression treated with antidepressants should be monitored closely for treatment side-effects.

toms with prominent mood features. The former patient with apathy and lack of interest may be less likely to respond to antidepressant medications. This clinical dictum, however, has not been tested in properly designed research trials.[20]

Despite its importance, little research has been conducted on the treatment of depression in AD. Several treatment options exist, including pharmacologic treatment, behavioural modality focused on the patient, caregiver intervention, or electroconvulsive therapy (ECT). Unfortunately, there are few hard scientific data in the form of systematic control trials to support most of these approaches. The sparse data available support the notion that pharmacologic treatments are safer for elderly patients with dementia when used with appropriate dose adjustments and titration. No single class of antidepressant is clearly safer or more effective than another. Adverse effects of selective serotonin reuptake inhibitors (SSRIs) are less serious than those with tricyclic antidepressants.

The safety of ECT for depression in AD has not been adequately assessed. In general, it is believed by clinicians to be of acceptable safety if used cautiously.[18] High rates of delirium after ECT have been reported, as might be expected. Despite concerns it might worsen cognitive functioning in dementia patients, ECT has also been associated with improvement in cognition when used to treat depression in patients with degenerative dementia.

What attention should be paid to the caregiver?

Throughout these machinations, the treating physician must keep in mind the distress of the caregiver.

Caregiver burden is defined as the psychological, psychosocial, physical, and financial burden imposed by caring for a patient with AD. As this condition progresses, patient symptoms, such as behavioural disturbance, functional decline, and sleep disruption, begin to increase. These increasing patient symptoms have been identified as a major source of caregiver burden and distress. Studies focusing on the primary caregivers of patients with AD have found that over 75% will develop clinical depression, and 45% will suffer from sleep problems. The amount of time spent providing care ranges from 60 to 100 hours per week; the equivalent of two full-time jobs. Hence, the treating physician must use continually practical strategies to maintain caregiver stress and endurance. Periods of respite, or hiring sitters to stay with the patient, are useful strategies to allow the caregiver some freedom from the ongoing burden they carry.

Alzheimer's

What's the latest?

A number of clinical trials that use stabilization agents for AD are about to begin. Researchers will appreciate the fact that many of these will be "add on" studies, permitting the use of a cholinesterase inhibitor while the experimental drug will be tested against placebo. Hopes are increasing that some of these agents will significantly alter the progression of this very difficult disease. CME

References

1. Small GW, Robins PV, Bany PP, et al: Diagnosis and treatment of Alzheimer's disease and related disorders and consensus statement of the American Association for Geriatric Psychiatry, The Alzheimer Association and the American Geriatric Society. JAMA 1997; 278(16):1363-71.
2. Rogers SL, Farlow MR, Doody RS, et al: The Donepezil Study Group: A 24-Week Double-Blind Placebo-Controlled Trial of Donepezil in Patients with Alzheimer's Disease. Neurology 1998; 50(1):136-45.
3. Bullock R, Moulais R, Steinwads KC, et al: Effects of Rivastigmine on Behavioral Symptoms in Nursing Home Patients with Alzheimer's Disease. International Psychogeriatrics 2001; 13:242-45 (ABS P-248) EXL 296.
4. Carey-Bloom J, Anand R, Veach J: A randomized trial evaluating the safety and efficacy of EWA 713 (Rivastigmine Tartrate) a new acetyl cholinesterase inhibitor in patients with mild to moderately severe Alzheimer's Disease in the community setting. Inter J Geriatric Psychopharmacology 1998; 1:55-65.
5. Feldman H, Gauthier S, Hecker J, et al: Benefits of Donepezil on global function, behavior cognition and ADLs in patients with moderate to severe Alzheimer's Disease. Neurol 2000; 54 (Suppl 3):A469.
6. Auriacombe S, Pere J, Loria-Kanza Y, et al: Efficacy and safety of rivastigmine in patients with Alzheimer's disease who failed to benefit from treatment with donepezil. Cur Med Res Opin 2002; 18(3):129-38.
7. Davidson P, Biennow K, Andreasen N, et al: Differential increase in cerebrospinal fluid acetylcholinesterase after treatment with acetylcholinesterase inhibitors in Alzheimer's disease. Neuroscience Letters 2001; 300(3):157-60.
8. Poirier J: Evidence that the clinical effects of cholinesterase inhibitors are related to potency and targeting of action. Int J Clin Pract Suppl 2002; (127):6-19 Review.
9. Emre M: Switching cholinesterase inhibitors in patients with Alzheimer's disease. Int J Clin Pract Suppl 2002; (127):64-72 Review.
10. Bullock R, Connolly C: Switching cholinesterase inhibitor therapy in Alzheimer's disease-donepezil to rivastigmine, is it worth it? Int J Ger Psych. 2002; 17(3):288-89.
11. Ferris SH: Clinical therapeutics 2001; 29, Suppl A:A3-A7.
12. Rasmuten L, Berg et al. Study ongoing.
13. Gauthier S: The clinical diagnosis and management of Alzheimer's disease. Second edition. Dunitz, London, 1999, p. 28.
14. Drevets WC, Rubin EH: Psychotic Symptoms and the longitudinal course of Alzheimer disease. Biol Psychiatry 1989; 25(1):39-48.
15. Finkel S: Behavioral disturbance in dementia. Int Psychogeriatrics 1996; 8(suppl 3):215-551.
16. Mega MS, Cummings JL, Fiorello T, et al: The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996; 46(1):130-5.
17. Rao V, Lyketsos CG: The Benefits and risks of ECT for patients with degenerative dementia who also suffer from dementia. Int J Ger Psychiatry 2000; 15(8):729-35.
18. Tariot PN, Erb R, Podgorski CA, et al: Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry 1998; 155(1):54-61.
19. McCracken PN: Delirium in Alzheimer's disease. The Canadian Alzheimer disease review 2000; 3(3):11-4.
20. Devanard D: Depression in dementia. Alzheimer disease and related disorders 2001; 6:97-122.

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Net Readings

1. Alzheimer's Society of Canada: www.alzheimer.ca
2. Mental-Health-Matters.com: www.mental-health-matters.com