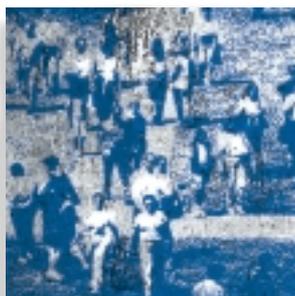


## *Regulatory aspects of mild cognitive impairment: toward a harmonized perspective*

Peter J. Whitehouse, MD, PhD



*The development of the concept of mild cognitive impairment (MCI) and its practical application have been intimately tied to attempts to produce therapeutic agents. Understanding the regulatory environment and determining the way in which it can be influenced are critical to the development of drugs and their eventual approval. In this article, we review some of the current challenges surrounding the concept of MCI relevant to drug development, summarize activities in various regions of the world, and conclude with some suggested next steps and an alternative framing for approving drugs for MCI and related conditions.*

© 2004, LLS SAS

*Dialogues Clin Neurosci.* 2004;6:409-414.

**Keywords:** *mild cognitive impairment; harmonization; drug regulation; Alzheimer's disease; ethics*

**Author affiliations:** Professor of Neurology, Case Western Reserve University, Cleveland, Ohio, USA

**Address for correspondence:** Case Western Reserve University, 12200 Fairhill Road, Suite C357, Cleveland, OH 44120-1013, USA  
(e-mail: peter.whitehouse@case.edu)

### Current challenges

**T**he most critical difficulty with the concept of MCI is that it is an arbitrary label on a continuum of cognitive changes that occur in people as they age.<sup>1</sup> As a result, there is considerable practice variation, even among experts who apply the label.<sup>2-4</sup> The arbitrary nature of the label can be seen most explicitly in the neuropsychological criteria, which may specify the threshold for applying the terms (one or one and a half standard deviations less than age-matched controls), the composition of the battery, and the norms.<sup>5,6</sup> The criteria concerning preserved or relatively preserved activities of daily living also permit considerable variability as to where the line is drawn by different clinicians. How complex must an impaired instrumental activity of daily living be before the label MCI is applied? For that matter, how simple should the task be before the affected person is said to convert to Alzheimer's disease (AD)?<sup>7,8</sup> Differences in an individual's performance of life's tasks create both patient and clinician variability in perceptions as well as cross-cultural challenges in multinational studies (Gaines A, Whitehouse PJ, unpublished data). The existence of a continuum of cognitive changes is illustrated by MCI being bounded on one side by AD and on the other by labels such as age-associated memory impairment (AAMI)<sup>9</sup> or age-related cognitive decline.<sup>10</sup> The emergence of AAMI was also closely linked to attempts to develop medicines to treat this condition. The criteria for applying this label included demonstrating test performance one standard deviation below younger-age controls, thus creating a large number of older individuals who could be labeled with AAMI. Yet this condition is generally considered to be

# Clinical research

---

“normal aging.” Whether MCI is normal or not is at the heart of the conceptual and practical ambiguities associated with this concept.

Clinicians know logically that there is a time in the life course of a patient, who will eventually be diagnosed as having AD, when the symptoms are present, but not sufficiently severe to warrant the label dementia. Any progressive medical condition must have a phase in which the symptoms are emerging, but not of sufficient intensity to warrant a disease label. In medicine, increasing attention is being paid to so-called preclinical states, such as in hypertension, depression, and Parkinson’s disease. Thus, it is not at all surprising that different variants of MCI have been identified, including amnesic MCI, MCI with symptoms in several different cognitive domains, and MCI with focal symptoms in an intellectual area other than memory.<sup>8,11</sup> The MCI associated with frontal lobe dementia and vascular dementia would more likely be predicted to be nonamnesic.

The symptoms in MCI are mild and perhaps more variable than in dementia; therefore, it is not surprising that the outcomes of longitudinal follow-up studies and drug studies might also be more variable. The logically complete set of outcomes for a patient with MCI includes no change over time, further deterioration or even improvement. All these outcomes can be demonstrated in epidemiological studies when patients are followed for several years.<sup>5</sup> Most experts suggest that the conversion rate to dementia is approximately 15% a year.<sup>6</sup> There are, however, some people who improve, at least for a period of time, suggesting either a benign course to their medical condition or a mislabeling of the individual in the first place, perhaps due to a bad testing day or mild depression. If one accepts the 15% annual conversion rate, one also has to ask what happens over a more extended period of time, such as that usually associated with epidemiological studies. At 15% a year, most people would have been expected to convert to AD within 10 years. This point returns us to the issue of MCI as an arbitrary label on the continuum of cognitive aging and raises the unresolved question of whether all human beings would develop AD if they lived long enough. Most studies of those in their 80s, 90s, and beyond suggest that the incidence of AD continues to increase with age.<sup>12</sup>

Thus, the major conceptual challenge to the further development of drugs to treat MCI is the ambiguity around definition and the relationship to normal aging.

Other challenges also exist in the development of trial designs to demonstrate the effectiveness and safety of drugs. One clear issue is what the therapeutic goal is. Most studies are classified as either trials to demonstrate symptomatic benefit or trials to demonstrate disease modification. Most of the interest in MCI surfaced because of the desire to develop medications to prevent AD. In order to conduct a primary prevention protocol, one needs to enter into the study individuals who do not currently suffer from dementia. One of the easiest ways to enrich the sample in a prevention study is to include people who already suffer from minor degrees of cognitive difficulties, as they are more likely to proceed to full dementia. Of course, this begs the question as to whether this is primary prevention, or really secondary prevention in which the enrolled individuals were already suffering from a dementia at an early stage and the observed deterioration was the further progression of the already existing disease condition.

The problem with conducting either primary or secondary prevention studies is that there are no agreed-upon designs.<sup>13</sup> Survival analysis as promoted by the National Institute of Aging’s Alzheimer’s Disease Cooperative Study in their studies of vitamin E, for example, cannot clearly differentiate a prolonged symptomatic benefit from a disease-modifying or neuroprotective effect.<sup>14,15</sup> The staggered-start, staggered-stop design, elaborated most clearly by Leber, has been used in a few studies.<sup>16</sup> However, it has been difficult for regulators to interpret the complex slope changes necessary to make the claim that a drug is disease-modifying.

Although considerable effort has been placed in developing biological markers, particularly neuroimaging, no test can currently replace a clinical diagnostic process for MCI.<sup>14</sup> Regulatory bodies will most likely not consider surrogate markers such as hippocampal atrophy unless they are clearly linked to clinical improvement. Thus, from a regulatory perspective, we are puzzled to know what designs to use to demonstrate a disease-modifying process that prevents the conversion of MCI to AD.

Attempts have also been made to demonstrate that medications provide symptomatic benefit for people with MCI. Such studies have been designed in a fashion parallel to those in AD, using outcome measures tailored to persons with less cognitive impairment. Here, the conceptual challenges are less evident in developing the trial designs, but the practical implications of such studies are perhaps less clear. Even if such studies show positive

effects, what are the functional benefits to individuals and the pharmacoeconomic impacts on societies?<sup>17</sup>

Another area of conceptual and practical confusion that permeates the study of people with mild degrees of cognitive impairment is the overlap with the emerging field of cognitive enhancement.<sup>18</sup> At what point on the continuum of cognitive aging is a drug not treating a disease, but rather enhancing a person's normal ability to function intellectually. Our pilot study of the use of donepezil in 53-year-old pilots flying in flight simulators suggests that cholinergic drugs may benefit individuals in their middle years who are performing complex cognitive tasks in society.<sup>19</sup> Studies of the biology of brain aging, particularly changes in neurotransmitter systems, support the idea that persons with AD and MCI lie on the continuum of neuronal alterations that begin perhaps quite early in life.<sup>20</sup>

A related conceptual and practical problem in developing drugs to treat MCI is the overlap between Western scientific allopathic medicine and so-called complementary and alternative medicine (Whitehouse PJ, Juengst E, unpublished data). Many individuals take herbal and nutraceutical products to try to improve their memories or slow the progression of age-related cognitive deterioration. Such therapies to treat brain aging overlap with those designed to slow the aging process itself. Practically, this means that decisions must be made about whether to enroll individuals in studies who are taking such products (and at what doses). Conceptually, and from a regulatory perspective, it raises issues of what products are to be regulated by the Food and Drug Administration (FDA) and other drug regulatory bodies or monitored through other means or by no means at all. In both the USA and Europe, there is increasing concern about the lack of oversight of such complementary and alternative medicines.<sup>21</sup> Yet, as we have seen, it is not often easy to place agents in one category or another. Vitamin E and ginkgo are examples of biological products that have been sold as essentially unregulated products, but that are also being studied scientifically.

A final major area of challenge to the development of more effective drugs from MCI is ethics.<sup>22</sup> MCI was developed as a concept to help develop medications to prevent AD. This is a laudable but very ambitious—and perhaps even overly ambiguous—goal. Given current science and resources, what would a drug profile look like that cured or prevented AD? How would this affect people with MCI and even completely normal individuals? How safe would such a product need to be?

The label MCI was developed in a research context. What are the implications of such a term for the individual labeled with it and for their partner and potential caregiver (Corner L, Bond J, unpublished data)?<sup>23</sup> The variable use of the concept of MCI creates considerable confusion. If I have a label of MCI, does that mean that I do not have AD, that I have a mild form of AD or another dementia, or that I may or will eventually get dementia? Moreover, we already noted that some persons with the label MCI improve. The implications of the term MCI for an individual patient and clinician are closely linked to the fear of AD itself. Perhaps in our enthusiasm for creating new medications, we have also intensified the terror that people feel about the possibility of suffering from dementia.<sup>24</sup>

Perhaps the greatest ethical issue facing the development of drugs for cognitive impairment has to do with conflict of interest between researchers, physicians, and the drug industry.<sup>25</sup> The acceptance of MCI as the therapeutic target would expand the markets enormously. One of the lessons of the introduction of drugs to treat erectile dysfunction is that the line between disease and normality is thin. Moreover, the ability to enhance cognition already motivates many people to take complementary and alternative medical products. The interest in the market is therefore profit—a strong motivator.

Recent publicity has focused on the relationship between physicians and industry. The concern about the use of serotonin reuptake blockers to treat depression in childhood is but one example.<sup>26</sup> A major challenge to biological psychiatry, but also to neurology, is maintaining the trust of our research participants and patients. One important issue that surfaced around the treatment of depression is the suppression of negative trials. We need to ensure that trials in dementia are entered into an international database and that the trial results made available to the scientific community or that research subjects are appropriately compensated.<sup>27</sup>

Fees paid to experts are a necessary part of doing business. What is appropriate commensuration? Academic experts for hire as authors of papers in which their contributions are limited is another example of a major problem. The pharmaceutical industry is amazingly effective at not only selling their drugs, but also at influencing the very way we think about health. The amount of money put into drug treatments limits our incentive to think about alternative ways of addressing social problems due to various age-related cognitive challenges.

# Clinical research

## Current regulatory perspectives

### United States of America

The FDA held a one-day hearing in March 2001 to address some of the conceptual issues surrounding the development of drugs for MCI. Although no official statement was made concerning the acceptability of MCI as a therapeutic target, many experts interpreted the FDA's position that MCI is very early dementia, most likely AD. Further elaboration of this issue will likely require submission by industry of drugs for MCI to the FDA for consideration for approval. The regulatory process in the USA is relatively open. Whether or not experts believe that a diagnostic entity is an appropriate target for drug development influences the regulators in the evaluation of protocols.

### Europe

The European Medicines Evaluation Agency (EMA) has not held open hearings about the concept of MCI. Individual members of their committees have spoken at scientific meetings. Such presentations suggest that the attitude in Europe is similar to that in the USA, ie, the regulators will wait for more development in the field and for the submission of actual trials.

### Canada

In the fall of 2004, a group of investigators in Canada will meet to examine the draft academic guidelines that were issued several years ago. Regulators will be involved in the meeting, and the topic of MCI and related conditions will be discussed. It is uncertain whether these guidelines will be considered official government position.

### Asia

No regulatory bodies in Asia have taken a stance on MCI as a target condition. Under the auspices of the International Working Group for the Harmonization of Dementia Drug Guidelines, organized for the first time 8 years ago by the author and currently by Jean-Marc Orgogozo, three Asian regional meetings have been held. From the first in Singapore in 2001, to the second in China, and now this year in Thailand, there has been

growing interest in the concept of MCI among academic opinion leaders in Asia.<sup>28,29</sup> Of course, this is largely influenced by the Western experts expressing their enthusiasm for the concept.

Attitudes toward the elderly and to age-related cognitive changes are different in Asia. The back-translation into English of the term, MCI, by a leading opinion leader in China is "loss of wisdom" (Prof Xu, personal communication). Labeling millions of Chinese with this term has some interesting social implications and potentially profound effects on attitudes toward the elderly in China.

### International issues

A variety of international professional organizations have organized meetings about MCI. The International Working Group for the Harmonization of Dementia Drug Guidelines has had regulatory issues at the heart of its mission to promote global discussion about designs to treat MCI, AD, and other conditions like vascular dementia. Currently under the direction of Lon Schneider with input from other experts, including the author, a manuscript addressing regulatory aspects of drug development for MCI is being prepared. The International Psychogeriatric Association is also planning a meeting for this winter (2004) on MCI, which will involve discussions about regulatory issues.

## Future directions

This author believes that a fundamental rethinking of MCI is necessary. He doubts that more conferences alone will lead to consensus, since there have been many such conferences and the differences of opinion remain. At the 9th Conference on Alzheimer's Disease and Related Disorders in Philadelphia, Pa, in July 2004, this author received the impression of a growing split between the USA and Europe. In fact, within the USA, the original Mayo Clinic concept of the MCI (perhaps to be renamed Petersen's syndrome) is still meeting resistance.

The main issue that remains is the need to address more seriously the continuum of aging. Of course, such a reconsideration of the categories of age-related cognitive impairment would have implications for AD as well.<sup>30</sup> Despite the work in genetics and neuroimaging, we are having a harder time differentiating the various types of dementia from each other.<sup>11</sup> This is most likely

explained by the fact that the process of brain aging affects individuals in many different ways and our attempts to assign dementias into discrete categories are failing because of the overlap in biologies at work in our brain.<sup>31</sup> Vascular and neurodegenerative processes interact. Neuronal loss occurs in multiple different systems to different degrees creating a wide spectrum of cognitive, affective, and motor symptoms.

Is there a regulatory implication for the development of medications to treat cognitive impairment? As I have suggested previously,<sup>1</sup> it may be possible to treat cognitive impairment as a nonspecific symptom rather than a feature of different discrete conditions. The biological substrate for such a claim is that overall loss occurs continuously in various brain nuclei as we age. For example, loss of cells in the cholinergic basal forebrain occurs in a variety of dementias and with normal aging. Cholinesterase inhibitors appear to work, albeit in modest ways, in a variety of dementias characterized by cholinergic pathology, including not only AD, but also Parkinson's disease, vascular dementia, and other overlapping conditions.

Could we consider cognitive impairment like pain? Perhaps an analogy closer to home is the treatment of agitation in dementia. Psychosis, which may be considered a discrete category, exists in a variety of conditions; agitation occurs on a continuum. Drugs to treat agitation are being developed and submitted for approval based on finding positive effects in three or more conditions, like dementia and mental retardation. Could we consider submitting a portfolio of results for a drug to treat cognitive impairment in several conditions and get a label for a general indication? Such an approach would not only avoid the problems of nosology in the field of

dementia, which are only increasing, but allow the use of these medications to treat mild degrees of symptoms as well as more profound cognitive deficits.

Such an approach would greatly expand the market for potential therapies. It might even allow normal individuals to take medications for cognitive enhancement. The boundaries between what is a disease and what is normality would grow even more unclear with an approach that labels cognitive impairment on a continuum. Physicians might be tempted to prescribe the medications for a larger number of individuals. The costs of drugs to our health care system would likely increase. As an advocate for the importance of pharmacoeconomic studies, especially studies of quality of life, I would urge that we stress the importance of such cost-utility approaches even in the current regulatory and reimbursement environment, and even if that would increase the size of the potential market.

A focus on drug treatment for cognitive impairment limits our thinking in several ways. First, we are constantly focusing on what is wrong with our cognition as we age. More emphasis on cognitive vitality and the potential for older people to further develop cognitively and gain wisdom would be helpful in society. Moreover, a focus on drugs makes us think that the only answers to the challenges of cognitive aging lie in medicine and biology. Clearly, there are many ways to prevent the deterioration that can occur in cognitive abilities as we age, besides waiting for a magic bullet. Developing a sense of purpose, engaging in civic activities, and taking responsibility for one's personal legacy are all activities that can contribute to a sense of cognitive vitality, even in persons who suffer from MCI and AD.<sup>32</sup> □

## REFERENCES

1. Whitehouse PJ. MCI and Alzheimer's disease: different conditions or diagnostic confusion? *Psychia Times*. 2004;(Feb):87-88.
2. Dubois B. "Prodromal Alzheimer's disease": a more useful concept than mild cognitive impairment? *Curr Opin Neurol*. 2000;13:367-369.
3. Maslow K, Whitehouse P. Mild cognitive impairment: should we be diagnosing it? What can we offer people who have it?" Paper presented at: 11th National Alzheimer's Disease Education Conference; July 20-23, 2003; Chicago, Ill.
4. Masounabe-Puyanne A, et al. *Issues in Diagnosis, Therapeutic Strategies and Management of MCI Disease in 2003: Results of an International Survey*. Paris, France: HELP Medical; 2003.
5. Ritchie K, Touchon J. Mild cognitive impairment: conceptual basis and current nosological status. *Lancet*. 2000;355:225-228.
6. Petersen R, Stevens J, Ganguli M, et al. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56:1133-1142.
7. Morris J, Storandt M, Miller P, et al. Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol*. 2001;58:397-405.
8. Whitehouse PJ. Guidelines abstracted from the American Academy of Neurology's Dementia Guidelines for Early Detection, Diagnosis, and Management of Dementia. *J Am Geriatr Soc*. 2003;51:869-873.
9. Crook T, Bartus R, Ferris S, Whitehouse P, Cohen G, Gershon S. Age-associated memory impairment: proposed diagnostic criteria and measures of clinical change. Report of a National Institute of Mental Health Work Group. *Dev Neuropsychol*. 1986;2:261-276.
10. Levy R, Whitehouse P, et al. Report of Working Party of International Psychogeriatric Association: Aging-Associated Cognitive Decline. *Int Psychogeriatr*. 1994;6:63-68.

# Clinical research

## Aspectos regulatorios del deterioro cognitivo leve: hacia una perspectiva armonizadora

El desarrollo del concepto de deterioro cognitivo leve (DCL) y su aplicación práctica han estado íntimamente vinculados con intentos por producir agentes terapéuticos. La comprensión del marco regulatorio y la determinación de la vía mediante la cual puede ser influenciado son críticos para el desarrollo de fármacos y su eventual aprobación. En este artículo se revisan algunos de los desafíos actuales alrededor del concepto de DCL que son relevantes para el desarrollo de fármacos, se resumen actividades en varias regiones del mundo y se concluye con algunas sugerencias de próximos pasos y una estructura alternativa para la aprobación de fármacos para el DCL y condiciones relacionadas.

## Aspects réglementaires du déficit cognitif léger : vers un avenir harmonisé

Le développement du concept de déficit cognitif léger (Mild Cognitive Impairment, MCI) et ses applications pratiques ont été intimement liés aux tentatives d'obtenir des agents thérapeutiques. La compréhension de l'environnement réglementaire et de la manière dont il peut être influencé est cruciale pour le développement des médicaments et leur agrément éventuel. Dans cet article, nous passons en revue certains défis actuels autour du concept de MCI et du développement de médicaments s'y rapportant, nous résumons les positions réglementaires adoptées dans diverses régions du monde et nous proposons en conclusion des orientations possibles dans l'avenir ainsi qu'un autre encadrement pour l'agrément des médicaments du MCI et des maladies qui y sont liées.

11. Ritchie K, Lovestone S. The dementias. *Lancet*. 2002;360:1759-1766.
12. Ritchie K. Mild cognitive impairment: an epidemiological perspective. *Dialogues Clin Neurosci*. 2004;6:401-408.
13. Bodick N, Forette F, Hadler D, et al. Protocols to demonstrate slowing of Alzheimer disease progression. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 3):S50-S53.
14. Gauthier S. Pharmacotherapy of mild cognitive impairment. *Dialogues Clin Neurosci*. 2004;6:391-395.
15. Sano M, Ernesto C, Thomas R. A controlled trial of selegiline, a-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med*. 1997;336:1216-1222.
16. Leber P. Slowing the progression of Alzheimer disease: methodologic issues. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 5):S10-S21.
17. Whitehouse P. Pharmacoeconomics. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 5):S22-S31.
18. Whitehouse P, Juengst E, Mehlman M, Murray T. Enhancing cognition in the intellectually intact: possibilities and pitfalls. *Hastings Center Report*. 1997;3:14-22.
19. Yesavage J, Mumenthaler M, Taylor J, et al. Donepezil and flight simulator performance: effects on retention of complex skills. *Neurology*. 2002;50:123-125.
20. Pepeu G. Mild cognitive impairment: animal models. *Dialogues Clin Neurosci*. 2004;6:369-377.
21. Mehlman M, Binstock R, Juengst E, Ponsaran R, Whitehouse P. Anti-aging medicine: can consumers be better protected? *Gerontol Soc Am*. 2004;44:304-310.
22. Whitehouse P, Moody H. Mild cognitive impairment: a hardening of the categories. *Dementia J*. 2005. In press.
23. Mittelman M. The psychological aspects of MCI. Paper presented at: Gerontological Society of America. Conference Proceedings; November 2003.
24. Whitehouse P. Losing My Mind: An Intimate Look at Life with Alzheimer's by Thomas DeBaggio [Book review]. *N Engl J Med*. 2002;347:861.
25. Whitehouse P, Karlawish J, Ballenger J. Conflict of interest in the development of drugs for dementia: a historical perspective. In: Tomosy W, Campbell, eds. *Symposium on Medicine and Industry*. Sydney, Australia: Kluwer Series; 2004.
26. Whittington C, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*. 2004;363:1341-1345.
27. Karlawish J, Schneider L, Hermans D, Whitehouse P. Silence science: the problem of not reporting negative trials. *Alzheimer Dis Assoc Disord*. 2005. In press.
28. Auchus A, Chen C, Orgogozo JM, Sawada T, Senanarong V, Whitehouse PJ. 2nd Asia Pacific Regional Meeting of the International Working Group on Harmonization of Dementia Drug Guidelines: Meeting Report. *Alzheimer Dis Assoc Disord*. 2003;17:129-131.
29. Auchus A, Chen C. Asia regional meeting of the International Working Group for the Harmonization of Dementia Drug Guidelines: Meeting Report. *Alzheimer Dis Assoc Disord*. 2001;15:66-68.
30. Whitehouse P, Maurer K, Ballenger J. *Concepts of Alzheimer Disease: Biological, Clinical, and Cultural perspectives*. Baltimore, Md: Johns Hopkins Press; 2000.
31. Whitehouse PJ. Classifications of the dementias. *Lancet*. 2003;361:1227.
32. Whitehouse P. Conclusion: the future of successful intergenerational health. In: *Successful Aging Through the Life Span: Intergenerational Issues in Health*. New York, NY: Springer Publishers; 2004.