



CALIFORNIA
HEALTH BENEFITS REVIEW PROGRAM

Analysis of Senate Bill 415
Prescription Drugs for
Alzheimer's Disease

A Report to the 2005-2006 California Legislature
April 16, 2005

CHBRP 05-05



Established in 2002 to implement the provisions of Assembly Bill 1996 (*California Health and Safety Code*, Section 127660, et seq.), the California Health Benefits Review Program (CHBRP) responds to requests from the State Legislature to provide independent analysis of the medical, financial, and public health impacts of proposed health insurance benefit mandates. The statute defines a health insurance benefit mandate as a requirement that a health insurer and/or managed care health plan (1) permit covered individuals to receive health care treatment or services from a particular type of health care provider; (2) offer or provide coverage for the screening, diagnosis, or treatment of a particular disease or condition; or (3) offer or provide coverage of a particular type of health care treatment or service, or of medical equipment, medical supplies, or drugs used in connection with a health care treatment or service.

A small analytic staff in the University of California's Office of the President supports a task force of faculty from several campuses of the University of California, as well as Loma Linda University, the University of Southern California, and Stanford University, to complete each analysis within a 60-day period, usually before the Legislature begins formal consideration of a mandate bill. A certified, independent actuary helps estimate the financial impacts, and a strict conflict-of-interest policy ensures that the analyses are undertaken without financial or other interests that could bias the results. A National Advisory Council, made up of experts from outside the state of California and designed to provide balanced representation among groups with an interest in health insurance benefit mandates, reviews draft studies to ensure their quality before they are transmitted to the Legislature. Each report summarizes sound scientific evidence relevant to the proposed mandate but does not make recommendations, deferring policy decision making to the Legislature. The State funds this work through a small annual assessment of health plans and insurers in California. All CHBRP reports and information about current requests from the California Legislature are available at CHBRP's Web site, www.chbrp.org.

A Report to the 2005-2006 California State Legislature

**Analysis of Senate Bill 415
Prescription Drugs for Alzheimer's Disease**

April 16, 2005

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Suggested Citation:

California Health Benefits Review Program (CHBRP). (2005). *Senate Bill 415: Prescription Drugs: Alzheimer's Disease*. Report to Calif. State Legislature. Oakland, CA: CHBRP. 05-05

PREFACE

This report provides an analysis of the medical, financial, and public health impacts of Senate Bill 415, a bill to mandate the coverage of cholinesterase inhibitors and other FDA-approved medications for the treatment of Alzheimer's Disease. In response to a request from the California Senate Banking, Finance and Insurance Committee on February 23, 2005, the California Health Benefits Review Program (CHBRP) undertook this analysis pursuant to the provisions of Assembly Bill 1996 (2002) as chaptered in Section 127600, et seq., of the California Health and Safety Code.

Edward Yelin, PhD, Laura Trupin, MPH, Wade Aubry, MD, and Patricia Franks, BA, all of the University of California, San Francisco (UCSF), prepared the medical effectiveness analysis. David J. Owen, MLS, PhD of UCSF conducted the literature search. Kenneth Covinsky, MD, MPH, provided technical assistance with the literature review and clinical expertise for the medical effectiveness analysis. Helen Halpin, PhD, Sara McMenamin, PhD, Nicole Bellows, MHSA, and Sangeeta Ahluwalia, MPH, all of the University of California, Berkeley, prepared the public health impact analysis. Gerald Kominski, PhD, Miriam Laugesen, PhD, and Nadereh Pourat, PhD, all of the University of California, Los Angeles, prepared the analysis of the cost impact. Robert Cosway, FSA, MAAA, and Chris Girod, FSA, MAAA, of Milliman, provided actuarial analysis. Michael E Gluck, PhD, Sachin Kumar, BA and Robert O'Reilly, BS, of CHBRP staff prepared the background section and integrated the individual sections into a single report. Other contributors include Susan Philip, MPP and Cynthia Robinson, MPP of CHBRP staff, and Cherie Wilkerson, who provided editing services. In addition, a subcommittee of CHBRP's National Advisory Council (see final pages of this report) reviewed the analysis for its accuracy, completeness, clarity, and responsiveness to the Legislature's request.

Jay Ripps, FSA, MAAA of Milliman recused himself from contributing to this and all other CHBRP analyses beginning March 1, 2005. His recusal is valid through his duration as acting chief actuary at Blue Shield of California.

CHBRP gratefully acknowledges all of these contributions but assumes full responsibility for all of the report and its contents. Please direct any questions concerning this report to CHBRP:

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EXECUTIVE SUMMARY

California Health Benefits Review Program Analysis of Senate Bill 415

The California Legislature has asked the California Health Benefits Review Program (CHBRP) to conduct an evidence-based assessment of the medical, financial, and public health impacts of Senate Bill 415.

Senate Bill (SB) 415 would mandate that health care service plans licensed under the Knox-Keene Act¹ and health insurance policies regulated under the California Insurance code include in their prescription drug “formularies,” or lists of allowed medications, drugs from the class of medications referred to as cholinesterase inhibitors as well as other U.S. Food and Drug Administration (FDA)-approved medications for the treatment of Alzheimer’s disease (AD).

Alzheimer’s disease is a progressive brain disorder that gradually destroys a person’s memory and ability to learn, make reasoned judgments, communicate and carry out daily activities. As Alzheimer’s progresses, individuals may also experience changes in personality and behavior, such as anxiety, suspiciousness or agitation, as well as delusions or hallucinations. There is no one diagnostic tool that can detect if a person has Alzheimer’s disease. The process involves several kinds of tests and may take more than one day. Diagnostic tools and criteria make it possible for physicians to make a diagnosis of Alzheimer’s with an accuracy of about 90 percent.

The FDA has approved five prescription drugs for the treatment of AD. These include four drugs in a class known as cholinesterase inhibitors: tacrine (tradename: Cognex), which is rarely used because of serious potential side effects, donepezil (tradename: Aricept), rivastigmine (tradename: Exelon), and galantamine (tradename: Reminyl). The fifth drug, memantine (tradename: Namenda), is the first approved medication in a class known as NMDA receptor antagonists and the first approved for the treatment of moderate to severe AD. All are tablets taken orally.

Under current law, any health care service plan and health insurer offering an outpatient prescription drug benefit must cover all FDA-approved prescription drugs that are medically necessary. Drugs that are not covered must be explicitly excluded in the plan’s Evidence of Coverage (EOC) document. Enrollee cost sharing obligations can vary regardless of whether the drugs are on the formulary or available only by prior authorization. Generic drugs usually require that enrollees pay the least out-of-pocket (Tier 1), followed by “preferred” brand name medication (Tier 2), and then all other brand name drugs that treat a condition in a similar way (Tier 3). Health plans can use a “preferred” designation to steer enrollees toward products they deem financially or clinically advantageous. Some health plans designate additional tiers for drugs whose use they monitor particularly closely. Plans may apply other pharmacy management requirements such as step therapy, in which the patient must try the preferred drug before the plan allows reimbursement for a non-preferred medication, and prior authorization in any pharmacy tier.

Based on the language of the legislation, CHBRP’s analysis assumes that the conditions of the bill are met if a health plan or insurer’s formulary contains at least one drug from each class of FDA-approved

¹ Health maintenance organizations in California are licensed under the Knox-Keene Health Care Services Plan Act, which is part of the California Health and Safety Code.



medications for AD. Given the current array of FDA-approved drugs, SB 415 would require that formularies include at least memantine (the only approved NMDA-receptor antagonist) plus one cholinesterase inhibitors.

I. Medical Effectiveness

A review of evidence concerning the medical effectiveness of FDA-approved medications for AD reveals that:

- All of the medications have some favorable effect on most of the outcomes analyzed. These outcomes include:
 - Cognitive function;
 - Clinician and/or caregiver global assessment of outcome;
 - Function in activities of daily living (ADL) and instrumental activities of daily living (IADL);
 - Behavioral and neuropsychological outcomes, e.g. agitation, sleeplessness, confusion;
 - Caregiver time devoted to the person with AD and caregiver stress;
 - Nursing home placement.
- Research and expert opinion indicate that the clinical benefit of the medications is modest. The medications allow patients to maintain a given level of functioning for several months, but no longer than a year. In addition, the only double-blinded randomized controlled trial that measured outcomes for longer than a year found at the end of the trial no differences between patients who received medications and those who received a placebo. This study suggests that the benefit is temporary.
- From studies comparing one FDA-approved medication for AD to another, there is no evidence that one agent achieves better outcomes than another.²
- Among the particular outcomes examined in clinical trials comparing FDA-medications to placebo:
 - Results were favorable for the medications with respect to cognitive outcomes, clinician/caregiver global assessment, daily functioning, and caregiver time spent on the person with AD, and caregiver distress;
 - There was a pattern suggesting favorable results for behavioral and neuropsychological outcomes;
 - There was ambiguous/mixed evidence with respect to the hazard of or relative risk of nursing home placement.

² As noted earlier, one of the cholinesterase inhibitors, tacrine (Cognex), has serious potential side effects and is not often prescribed, even though it appears similar to other drugs in terms of its effectiveness.



II. Utilization, Cost, and Coverage Impacts

- A total of 20,014,000 individuals, ages 0-64 years, are currently covered by public and private payers affected by SB 415. Of these, 18,987,000 individuals have prescription drug coverage.
- There are no data on the actual prevalence of AD in California among the under-65 population. An analysis of national claims data corrected for the characteristics of the California marketplace indicates that about 1,000 persons or about 1 out of every 18,519 Californians subject to the mandate currently receives an FDA-approved drug for the treatment of AD.
- Health plans and health insurers in California currently include at least one cholinesterase inhibitor as well as memantine (the other FDA-approved medication for AD) on their formularies.
- Given current coverage practices, SB 415 would not affect coverage, utilization, costs, or access to current FDA-approved medications for AD.

III. Public Health Impacts

- Although there are no direct data on the prevalence of AD among the under-65 population in California, community studies undertaken in other parts of the U.S. and in Europe have yielded prevalence estimates for this age group that range from 0.02% to 1.00% [from one out of every 5,000 children to one out of every 100 children] depending on the way the study defined early onset of the illness. Prevalence of AD among all ages in California was 440,000 in 2000.
- Because CHBRP estimates that SB 415 would have no effect on coverage, access, or utilization of current FDA-approved medications for the treatment of AD, the bill will have no impact on:
 - Community health.
 - Gender and racial disparities that exist in the prevalence of AD.
 - Economic loss from lost wages and productivity of AD patients and caregivers
 - Mortality associated with AD.
- Furthermore, although AD is associated with a high risk of death and medicines are effective in maintaining patient function only in the short-term, there is no evidence to indicate whether having *insurance coverage* for AD medications affects the longevity of persons with the disease.



INTRODUCTION

Senate Bill (SB 415) would mandate that health care service plans licensed under the by Knox-Keene Act³ and to health insurance policies regulated under the California Insurance code include in their prescription drug “formularies,” or lists of allowed medications, drugs from the class of medications referred to as cholinesterase inhibitors as well as other U.S. Food and Drug Administration (FDA)-approved medications for the treatment of Alzheimer’s disease (AD).

Alzheimer’s disease is a progressive brain disorder that gradually destroys a person’s memory and ability to learn, reason, make judgments, communicate and carry out daily activities. As Alzheimer’s progresses, individuals may also experience changes in personality and behavior, such as anxiety, suspiciousness or agitation, as well as delusions or hallucinations. There is no one diagnostic test that can detect if a person has Alzheimer’s disease. The process involves several kinds of tests and may take more than one day. Diagnostic tools and criteria make it possible for physicians to make a diagnosis of Alzheimer’s with an accuracy of about 90 percent. Diagnostic tools and criteria make it possible for physicians to make a diagnosis of Alzheimer’s with an accuracy of about 90 percent.

The FDA has approved five prescription drugs for the treatment of AD. These include four drugs in a class known as cholinesterase inhibitors: tacrine (tradename: Cognex), which is rarely used because of serious potential side effects, donepezil (tradename: Aricept), rivastigmine (tradename: Exelon), and galantimine (tradename: Reminyl). The fifth drug, memantine (tradename: Namenda), is the first approved medication in a class known as NMDA-receptor antagonists and the first approved for the treatment of moderate to severe AD. All are tablets taken orally.

Evaluations may include the following steps:

- consultation with a primary care physician and possibly a neurologist or other specialists
- a medical history, which collects information about current mental or physical conditions, prescription and nonprescription drug use, and family health history
- a mental status evaluation to assess sense of time and place; ability to remember, understand, and communicate; and ability to do simple math problems
- a series of evaluations that test memory, reasoning, vision-motor coordination, and language skills
- a physical examination, which includes the evaluation of the person's nutritional status, blood pressure, and pulse
- an examination that tests sensation, balance, and other functions of the nervous system
- a brain scan to detect other causes of dementia such as stroke
- laboratory tests, such as blood and urine tests, to provide additional information about problems other than Alzheimer’s that may be causing dementia
- psychiatric evaluation, which provides an assessment of mood and other emotional factors that could cause dementia-like symptoms or may accompany Alzheimer’s disease

³ Health maintenance organizations in California are licensed under the Knox-Keene Health Care Services Plan Act, which is part of the California Health and Safety Code.



Currently, no other states have an existing mandate specifically requiring health insurers to cover cholinesterase inhibitors and other medications approved by the FDA for the treatment of AD.

The population affected by this mandate includes insured individuals with prescription drug coverage enrolled in Knox-Keene and Department of Insurance healthcare service plans, as well as HMO enrollees covered by CalPERS, Medi-Cal and Healthy Families programs. Effective January 1, 2006, Medicare Part D will offer drug coverage for all Medicare enrollees, and Medicare supplement plans will no longer be able to offer prescription drug coverage. This analysis reflects the fact that SB 913 would not affect those who are eligible for drug coverage through Medicare Part D.

Under current law, any health care service plan and health insurer offering an outpatient prescription drug benefit must cover all FDA-approved prescription drugs that are medically necessary. Drug therapies that are not considered medically necessary are excluded from coverage. Such exclusions must be explicitly specified in the “evidence of coverage,” the document that serves as the legal contract between the health plan and enrollee.

Formularies are the most common of several tools health plans use to help administer their drug benefits (Hoadley, 2005). They are usually divided into three or more tiers representing different levels of cost-sharing for the enrollee. Enrollee cost-sharing can include co-payments or coinsurance and deductibles for each prescription. Typically, patient out-of-pocket spending is lowest for Tier 1, which includes generic medications, drugs that are relatively inexpensive because they are no longer protected by the original developer’s patents. Drugs in Tier 2 have the next lowest cost sharing obligations and typically are brand-name drugs that the plan “prefers” physicians to prescribe for a particular condition if clinically appropriate.⁴ Cost-sharing for Tier 3 is higher than for the previous two and usually comprises other (i.e. “non-preferred”) brand-name drugs. Some health plans have instituted additional tiers which they reserve for medications whose use they want to monitor particularly closely for various reasons, including cost effectiveness and quality of care reasons. Plans can also use other pharmacy management tools such as prior authorization and step therapy, in which the patient must try the preferred medication(s) in a class before reimbursement of any non-preferred drug is allowed. Enrollee cost-sharing for drugs that do not appear on a formulary, but are covered when medically necessary, can differ from those drugs on the formulary.⁵

Based on the language of the legislation, CHBRP’s analysis assumes that the conditions of the bill are met if a health plan or insurer’s formulary contains at least one drug from each class of FDA-approved medications for AD. Given the current array of FDA-approved drugs, SB 415 would require that formularies include, at least, memantine (the only approved NMDA receptor antagonist) plus one cholinesterase inhibitor.

⁴ Plans may “prefer” a particular drug for various clinical or financial reasons, although the ability to steer enrollees towards a specific product in a class of similar medications provides the health plan with some leverage in negotiating reimbursement rates.

⁵ Current proposed regulations promulgated by the Department of Managed Health Care (DMHC) titled would create standard definitions of various drug benefit management tools, require that enrollees receive certain information about their drug benefits, place limits on patient cost-sharing, and standardize other features of pharmaceutical benefit. “Outpatient Prescription Drug Co-payments, Coinsurance, Deductibles, Limitations and Exclusions, Control #2002-0019, Adopting Section 1300.42.7 in Title 28, California Code of Regulations”.



The bill is silent on the use of pharmacy management tools such as tiered cost-sharing and prior authorization, thus leaving health plans and insurers open to adopt such tools as long as the conditions described above and any other relevant law or regulation is met.

I. MEDICAL EFFECTIVENESS

Results from the Literature Review

The results of the review of the scientific literature on the medical effectiveness of FDA-approved medications for AD are organized into the following major categories of outcomes:

- Cognitive function;
- Clinician and/or caregiver global assessment of outcome;
- Function in activities of daily living (ADL) and instrumental activities of daily living (IADL);
- Behavioral and neuropsychological outcomes, e.g., agitation, sleeplessness, and confusion;
- Caregiver time devoted to the person with AD and caregiver stress; and
- Nursing home placement.

Studies on the effectiveness of the FDA-approved medications for AD were identified from the PubMed and Cochrane databases for the period from January, 1990, through December, 2004, yielding 519 references. The types of publications included in the literature search were randomized controlled trials, clinical trials, meta-analyses, systematic review articles, practice guidelines, and case reports. However, given the existence of eight well-done meta-analyses, the present analysis was able to rely on these meta-analyses to assess the impact of AD medications on most of the outcomes assessed, supplemented by individual randomized trials and systematic reviews published subsequent to the studies included in the meta-analyses, and when necessary, observational studies for the remainder of the outcomes.

A more thorough description of the methods used to conduct the medical effectiveness review and the process used to “grade” the evidence for each outcome measure can be found in Appendix A: Literature Review Methods. Summary tables with detailed findings and evidence from the literature can be found in Appendix B: Summary of the Findings on Medical Effectiveness.

A Note on the Interpretation of the Medical Effectiveness Literature

In assessing the literature on the medical effectiveness of the FDA-approved medications for AD, it is important to distinguish between the *statistical significance* of findings, that is, whether the findings of differences between each medication and placebo could have arisen by chance, and *clinical significance*, that is, whether the difference between the medication and placebo is meaningful to the well-being of persons with AD, their caregivers, and health care providers.

In the literature on the medical effectiveness of the FDA-approved medications for AD, the outcome most frequently assessed is cognitive function. For this outcome, the most frequently used assessment tool is the ADAS-COG, or Alzheimer’s Disease Assessment Scale-Cognitive (Pena-Casanova, 1997). ADAS-



COG has a range of 0-70. In studies using ADAS-COG, a four point change is said to distinguish between those responding to the drug in question and those not responding. Alternatively, one can assess the annual change in the score, said to average between seven to eight points a year. In most of the clinical trials reviewed below and summarized in Appendix B Table B-2 the difference between a drug and placebo was substantially less than the average change over a year and about the same as—or slightly less than—the amount said to indicate that a person with AD was a “responder” to the drug.

There is another way to interpret these results: by translating them into an approximate amount of time in which cognitive function is preserved. Seen in this light, the studies would indicate that, on average, the FDA-approved medications for AD save the equivalent of several months of cognitive function, a statistically significant amount, but one that must be weighed against the average duration of time between onset of disease and death of about eight years.

Although a discussion of the scale properties of the measurement tools used to assess each of the outcomes of AD is beyond the scope of this discussion, for each tool it is important to evaluate the results in terms of whether they represent meaningful results from the perspective of the person with AD, his or her caregivers, and health care providers.

The analysis of medical effectiveness within CHBRP “grades” the evidence for each of the outcome measures based on statistical significance. However, in discussing the results with the content expert, Dr. Kenneth Covinsky, and with others knowledgeable about AD, it became clear that there is a disjuncture between the *statistical significance* with respect to most short-term outcomes of the FDA-approved medications, which indicates that the medications are effective, and the *clinical impression* of such experts that the magnitude of the effect of the medications is relatively modest, albeit measurable and detectable.

Cognitive Outcomes

In the literature on the FDA-approved medications for AD, the largest number of studies were concerned with the cognitive outcomes of the medications. Of these, most were comparisons of individual medications and placebo, all but one of which evaluated cholinesterase inhibitors; however, there were three studies comparing one medication to another (Mossello et al., 2004; Wilcock et al., 2003; Wilkinson et al., 2002).

Among the publications comparing a medication to placebo (Birks et al., 2003; Birks and Harvey, 2003; Courtney 2004; Loy and Schneider, 2004; Pirttila et al., 2004; Ritchie 2004; Suh et al., 2004), in all but 3 of the 39 analyses of cognitive outcomes summarized in Appendix B Table B-2, persons receiving the specific AD medication achieved significantly better cognitive outcomes than those on placebo. In all but 3 of the 38 analyses comparing cholinesterase inhibitors and placebo, persons receiving one of the former class of medications achieved better cognitive outcomes than those on placebo.

Thus, overall, the evidence suggests that medications for AD in general and the cholinesterase inhibitors in particular have a favorable effect on cognitive outcomes compared to placebo.

However, in many of the studies reviewed, the effect is relatively modest. For example, in the meta-analysis conducted by Birks and Harvey (2003), the weighted mean difference between those taking



donepezil and placebo was between -2.0 and -2.9 (favoring the donepezil group) across a possible range of 0-70 in the ADAS-Cog. As noted above, differences in this range are slightly smaller than the amount indicating that an individual is a “responder” to the medication in question.

Among the three studies comparing one FDA-approved medication to another, there were no statistically significant differences between medications with respect to cognitive outcomes, although in the study by Wilcock et al. (2003), there was a slightly better outcome among persons with AD taking galantamine versus donepezil.

Overall, however, in the studies comparing one medication to another, there was a pattern toward no effect or weak evidence of a difference between medications.

Clinician/Caregiver Assessment of Outcomes

Six publications, of which all but one was a meta-analysis, presented evidence on the impact of FDA-approved medications for AD on global assessment of outcomes provided either by the clinician or caregiver for the person with AD (Areosa Sastre et al., 2004; Birks et al., 2003; Birks and Harvey, 2003; Loy and Schneider, 2004; Ritchie et al., 2004; Suh et al., 2004). All of the studies described in the publications were comparisons of an FDA-approved medication for AD and placebo, and of these, all but one were evaluations of cholinesterase inhibitors. There were no studies comparing clinician or caregiver global assessments of outcomes for one such medication to another. Of the 27 analyses summarized in Appendix B Table B-2 with respect to clinician or caregiver global assessment of outcome, in all but 4 analyses, persons with AD receiving one of the FDA-approved medications had an assessment score indicating a better outcome than those receiving placebo or were more likely to have an assessment consistent with improvement. Of the 23 analyses of cholinesterase inhibitors, in all but 4 analyses, persons with AD receiving this kind of medication achieved better outcomes with respect to clinician/caregiver assessments than those receiving placebo.

Overall, then, the evidence suggests that medications for AD have a favorable effect on clinician or caregiver assessment of outcomes compared to placebo.

Daily Functioning

Eight publications, of which three were meta-analyses, presented evidence on the impact of FDA-approved medications for AD on daily functioning among persons with AD (Areosa Sastre et al., 2004; Birks et al., 2003; Birks and Harvey, 2003; Courtney et al., 2004; Loy and Schneider, 2004; Mossello et al., 2004; Suh et al., 2004; Wilcock et al., 2003). Two of the publications were comparisons of one such medication to another (Mossello, 2004; Wilcock, et al., 2003); the remainder compared an FDA-approved medication for AD to placebo, and of these, all but one concerned cholinesterase inhibitors. In most of the analyses comparing an FDA-approved medication to placebo, persons with AD receiving the FDA-approved medications achieved better functional outcomes than those receiving placebo. In the analyses comparing the cholinesterase inhibitors to placebo, in 16 of 21 comparisons, the persons receiving the cholinesterase inhibitors experienced a statistically significant better outcome with respect to daily functioning. In one other publication, in which seven studies were reviewed, at least one study showed a pattern toward a favorable outcome (Loy and Schneider, 2004). Positive outcomes included activities of



daily living (such as providing self-care in bathing and eating), instrumental activities of daily living (such as handling a bank account) and assessments by caregivers and health professionals.

Overall, the evidence from the analyses comparing an FDA-approved medication to placebo with respect to functional status indicates that those receiving such medications experience a favorable outcome.

In the two studies comparing one FDA-approved medication for AD to another, there were three separate analyses. In a comparison of donepezil and galantamine with respect to the Bristol Activities of Daily Living Scale, the difference between the two groups did not reach statistical significance (Wilcock, et al., 2003).. In the study comparing donepezil and rivastigmine, the former group achieved a significantly better outcome with respect to activities of daily living, but the two groups did not differ significantly with respect to instrumental activities of daily living (Areosa Sastre, et al., 2004)..

Thus, overall, there is ambiguous or mixed evidence that one FDA-approved medication results in better functional outcomes than another.

Behavioral and Neuropsychological Outcomes

Six publications presented information on the impact of FDA-approved medications on behavioral and neuropsychological outcomes such as agitation or sleeplessness (Areosa Sastre et al., 2004; Birks and Harvey, 2003; Holmes et al., 2004; Loy and Schneider, 2004; Suh et al., 2004; Wilcock et al., 2003); of these, three are meta-analyses (Areosa Sastre et al., 2004; Birks and Harvey, 2003; Loy and Schneider, 2004), and the remainder are single, randomized control trials. Of the six publications, five compare behavioral and neuropsychological outcomes of an FDA-approved medication to placebo and, of these, all but one concerned the cholinesterase inhibitors, while one (Wilcock, Howe et al., 2003) compares these outcomes among persons receiving donepezil and galantamine.

The results of the studies comparing an FDA-approved medication for AD to placebo for behavioral and neuropsychological outcomes are not as definitive as such studies for cognitive outcomes, clinician or caregiver global assessment, or daily functioning. For example, Birks et al. (2003) reported that donepezil did not result in significantly better NPI (Neuropsychiatric Inventory) scores than placebo, but Holmes et al. (2004) reported that it did. In the five publications comparing an FDA-approved medication for AD to placebo for behavioral and neuropsychological outcomes, there were ten analyses. Of these ten, persons with AD taking an FDA-approved medication experienced significantly better behavioral or neuropsychological outcomes in six analyses and no significant difference in the remainder; although in two of the latter analyses, there was a pattern toward a favorable result that did not reach statistical significance. Of the seven analyses comparing cholinesterase inhibitors to placebo, in three analyses the persons taking the cholinesterase inhibitors had statistically significantly better outcomes with respect to behavioral and neuropsychological parameters and in two others there was a pattern toward a favorable effect.

Thus, overall, the evidence indicates a pattern toward favorable outcomes with respect to behavior and neuropsychological symptoms.



In the one study (Wilcock, Howe et al., 2003) that compared one specific cholinesterase inhibitors (donepezil) to another (galantamine), the two groups did not differ with respect to behavioral and neuropsychological outcomes.

Thus, there is a pattern toward no effect or weak evidence that one medication achieves better behavioral and neuropsychological outcomes than another.

Caregiver Time/Distress

Four publications (Birks and Harvey, 2003; Holmes, et al., 2004; Sano, et al., 2003; Wimo, et al., 2004), including one meta-analysis (Birks and Harvey, 2003), concern the impact of an FDA-approved medication for AD on caregiver time and distress. Of these, all concern cholinesterase inhibitors. All but one of the publications assess the impact of the medications on the amount of time spent care giving. In all of the analyses, the caregivers spend significantly less time taking care of persons with AD receiving one of the cholinesterase inhibitors than those taking placebo. In the two analyses in which the results are reported in terms of minutes/day spent in care giving (both were comparisons of donepezil and placebo), the caregivers of persons with AD receiving donepezil spent from 64.2 to 81.9 fewer minutes in this set of activities than those receiving placebo (Birks and Harvey, 2003; Wimo, et al., 2004). In the one study reporting on caregiver distress using the NPI-D scale (Holmes, et al., 2004); the persons with AD receiving donepezil reported a significantly lower (better) score on the scale than those in the placebo group.

Thus, overall, the evidence indicates a favorable outcome in caregiver time and distress for persons with AD receiving a cholinesterase inhibitor than for those receiving placebo.

Nursing Home Placement

Two publications, neither a meta-analysis, reported the risk of nursing home placement for persons with AD receiving one cholinesterase inhibitor, donepezil, versus placebo. In the first publication (Geldmacher et al., 2003), one study reported longer treatment times with donepezil were significantly associated with greater reductions in the risk of nursing home placement when compared with placebo. In another study, longer treatment times with donepezil were associated with a lowered risk of a first nursing home placement and with permanent nursing home placement when compared with placebo. However, this study was an observational follow-up to a prior randomized controlled trial, and the results reported could be an artifact of differences in follow-up rather than an accurate reflection of the impact of different durations of exposure to the medication. In the second publication, (Courtney et al., 2004), donepezil had no effect on the risk of nursing home placement relative to the placebo group.

Thus, overall, there is ambiguous or mixed evidence that treatment with donepezil affects the risk of nursing home placement compared to placebo.

Conclusions

A review of the evidence of the medical effectiveness of FDA-approved medications for AD, most of which concerns the cholinesterase inhibitors, reveals that the FDA-approved medications for AD have a statistically significant and favorable effect on most outcomes analyzed compared with placebo. However,



an analysis of the specific outcome measures used in the studies and discussion with a content expert in AD indicate that the amount of the benefit is relatively modest in clinical terms: for example, the equivalent of maintaining a specific level on an outcome measure for several months, but no longer than a year. Also, of the double-blind, randomized controlled trials reviewed, only one study measured outcomes for longer than a year and that study showed no effect on the outcomes (Courtney, et al., 2004). However, the disease lasts an average of eight years between onset and death, so long-term outcomes data are essential to assess the effectiveness of the medications.

There were very few studies comparing one FDA-approved medication for AD to another. These studies provide no evidence that one agent achieves better outcomes than another.

From studies comparing FDA-approved medications for AD with placebo, results were favorable for the medications with respect to cognitive outcomes, clinician/caregiver global assessment, daily functioning, and caregiver time spent on the person with AD and caregiver distress.

From the studies comparing FDA-approved medications for AD with placebo, there was a pattern toward favorable results for behavioral and neuropsychological outcomes.

From studies comparing FDA-approved medications for AD to placebo, there was ambiguous/mixed evidence with respect to the hazard or relative risk of nursing home placement.

Another way to place the results of the literature on FDA-approved medications for AD in context is to estimate the number needed to treat (NNT) with the medications for one patient to achieve a certain level of benefit and the number needed to treat for an adverse effect to occur, sometimes referred to as the number needed to harm (NNH). Three studies in the literature make estimates of NNT (Lanctot, Herrmann et al., 2003; Livingston and Katona, 2000; Livingston and Katona, 2004) and two of these also make estimates of the NNH (Lanctot et al., 2003; Livingston and Katona, 2004) (data not in tables). Livingston and Katona (2000) estimated that between 4 and 13 persons would need to be treated with rivastigmine and between 4 and 15 with donepezil to achieve at least a minimal benefit. Lanctot et al. (2003) observed that the NNT for rivastigmine, donepezil, and galantamine to achieve stabilization was 7 persons with AD (95% confidence interval (CI) 6-9), to achieve “minimal” improvement in disease was 12 (95% CI 9-16), and to achieve “marked” improvement was 42 (95% CI 26-114). On the other hand, these authors noted that the NNH was also 12 (95% CI 10-18), the same number as need to achieve “minimal” improvement. Similarly, Livingston and Katona (2004) observed that the NNT was from 3-11 for memantine, although there was no difference in the NNH between this medication and placebo.

The foregoing data on NNT when combined with the data presented in Appendix B Table B-2 indicate that a relatively small proportion of persons with AD receiving the FDA-approved medications experience a large clinical benefit, whereas a relatively large proportion experience some benefit.



II. UTILIZATION, COST, AND COVERAGE IMPACTS

CHBRP assesses the utilization, cost, and coverage impacts of a proposed health benefit(s) mandate based on criteria specified under Assembly Bill 1996 (2002) (AB 1996), *California Health and Safety Code (Section 127660, et seq.)* This section is organized by, and addresses, each criterion specified in the statute.⁶

SB 415 mandates that every health care service plan contracted to provide prescription drug benefits shall include, in its prescription drug formularies, cholinesterase inhibitors and other FDA-approved medications for the treatment of AD. For the purposes of this analysis, the legislation is assumed to require that *at least one drug*, for each class of drugs, is included in drug formularies of insurers for the treatment of AD. Alternative interpretations of SB 415, such as requiring that all FDA-approved drugs for AD be included in health plans' formularies, will produce different cost impacts for this legislation.

The bill is silent on the use of pharmacy management tools such as tiered cost-sharing and prior authorization, thus leaving health plans and insurers open to adopt such tools as long as the conditions described above and any other relevant law or regulation is met.

The population affected by this mandate includes insured individuals with prescription drug coverage enrolled in Knox-Keene and Department of Insurance health service plans, as well as HMO enrollees covered by CalPERS, Medi-Cal, and Healthy Families programs. The disabled population under 65 years of age who are covered by Medicare are excluded because state mandates do not typically override federal regulations. The elderly (65+ years) Medicare and Medi-Cal dually eligible individuals are also excluded because, as of January 2006, Medicare Part D will set the formulary requirements for these individuals. This mandate will take effect in July 2006, if signed.

Present Baseline Cost and Coverage

Current coverage of the mandated benefit (3(i))

Coverage data were collected in March 2005 by CHBRP from six of the seven major California health insurance and managed care organizations. All responding organizations currently include at least one type of cholinesterase inhibitors or other FDA-approved drugs for treatment of AD on their formularies. Additional inquiries of informed sources by CHBRP did not identify any plans that exclude all cholinesterase inhibitors or memantine from their formularies.

SB 415 applies only to plans that already provide a prescription drug benefit. All individuals covered by the public payers included in this CHBRP analysis have prescription drug coverage. Some private healthcare plans in California offer optional plans that do not cover prescription drugs. These optional plans are not subject to this mandate. CHBRP estimates that 95% of all insured populations in California have coverage for prescription drug benefits, and so would receive coverage for these mandated benefits if this bill is signed into law.

⁶ For an overview of the cost impact process, and the kinds of data used, please peruse the *Cost Impact Analysis Summary*. (http://www.chbrp.org/analysis_methodology/cost_impact_analysis.php).



Currently, there are five FDA-approved drugs on the market indicated for the treatment of Alzheimer's: tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), memantine (Namenda), and galantamine (Reminyl). Some insurers require preauthorization for some of the drugs, but at least one drug is covered at standard second tier name-brand copayment. The co-payments and coinsurance amounts that apply to these drugs vary.

Current utilization levels and costs of the mandated benefit (Section 3(h))

The data used in this and the following sections are from the 2003 Milliman national claims database, which includes a total of 7.4 million individuals claims from the commercially insured population in the United States.

Studies of AD indicate a prevalence rate ranging from 0.018 % to 1% in the population ages 0-64 nationally (discussed in the following public health section in detail). No California-specific prevalence rates are currently available. Using Milliman data, the overall number of AD cases in the population under 65 years of age covered by private and public insurers in California is estimated at about 2,000 individuals (0.01%) out of the total insured population who are subject to this mandate (20,014,000). This number translates to an estimated prevalence rate of 0.26% among the insured population ages 45-64, which is within the reported national prevalence rates. An equal rate of AD is assumed for both private and public payers, due to lack of prevalence data for public payers. It is likely that the Medi-Cal program may have a larger number of individuals with AD due to the high rates of disability caused by this disease.

About 1,000 or 0.0054% of the total insured population are estimated to receive FDA-approved drugs for treatment of AD. An additional 700 or 0.0033% also receive these medications but have diagnosis other than AD.

Among the population receiving FDA-approved drugs for the treatment of AD, most receive donepezil (53.4%). Rivastigmine and galantamine are the second and third most frequently received drugs at 23.0% and 22.8% respectively. Memantine is used by 0.6%, and tacrine by 0.2%. This distribution was based on 2003 data; current utilization may differ, but would not affect the conclusions of this report.

The extent to which costs resulting from lack of coverage are shifted to other payers, including both public and private entities. (Section 3(f))

CHBRP estimates no change in availability and subsequent utilization of FDA-approved drugs for treatment of AD, because all California insurers cover at least one such drug on their formularies. There will be no cost shifting among payers due to SB 415.

Public demand for coverage (Section 3(j))

The decisions about the inclusion or exclusion of particular services among health insurers is one measure of the public's demand for them. In the case of cholinesterase inhibitors and NMDA receptor antagonists for AD, CHBRP's survey of the seven largest health plans and insurers in the state and additional inquiries of informed sources indicate that all already meet the conditions that would be required by SB 415.



Impacts of Mandated Coverage

How will changes in coverage related to the mandate affect the benefit of the newly covered service and the per-unit cost? (Section 3(a))

Medical effectiveness of cholinesterase inhibitors and other FDA-approved drugs for treatment of AD is not expected to be affected by this mandate. The current utilization levels are expected to remain the same, leading to the same current levels of medical effectiveness.

There is no evidence that there are current supply constraints on availability of these drugs in the health care market in California or nationally. The mandate is not expected to impact the supply of these drugs, because they are generally covered and available.

The unit costs of cholinesterase inhibitors are not expected to change as a consequence of this mandate, because SB 415 is not expected to change current utilization patterns.

How will utilization change as a result of the mandate? (Section 3(b))

There will not be a change due to SB 415 to current utilization levels.

To what extent does the mandate affect administrative and other expenses? (Section 3(c))

CHBRP estimates no additional impact due to SB 415 on administrative expenses.

Impact of the mandate on total health care costs (Section 3(d))

CHBRP estimates no changes to current total health care costs as a consequence of SB 415.

Costs or savings for each category of insurer resulting from the benefit mandate (Section 3(e))

CHBRP does not estimate any costs or savings to various insurers in California as a consequence of this bill.

Impact on access and health service availability (Section 3(g))

CHBRP does not estimate any changes to access to care and availability of services as a result of this mandate.

III. PUBLIC HEALTH IMPACTS

Present Baseline Health Outcomes



SB 415 will affect California's commercial non-Medicare (and therefore under 65 years of age) population with AD. Although AD is an illness that increases in risk and severity with age (Evans et al, 1989), in rare cases, individuals may get early-onset AD, defined arbitrarily and variously as disease onset before 60 to 65 years of age. (Nussbaum and Ellis, 2003) Certain inherited forms of AD have been diagnosed in individuals as early as their 30s and 40s (Bird et al, 1989).

Measuring the prevalence of AD in a population is a difficult task for many reasons, among them, the differing diagnostic criteria applied, the lack of definitive diagnostic techniques, and difficulties in estimating true onset of illness (Nussbaum and Ellis, 2003; Leifer, 2003; Helmer et al., 2001). The literature review found only a limited number of epidemiological and community studies that attempted to estimate prevalence of AD in the under-65 population, and only two were conducted in the United States (Kokmen et al., 1989; Schoenberg et al., 1985). The estimated prevalence rates range from .018% to 1.000%, depending on the way the study defined early onset. The study age groups ranged from 30 to 60 years old. A community study in Minnesota calculated the prevalence of AD in the 45-59 age group to be 27 per 100,000 (Kokmen et al., 1989). Another study in Mississippi looked at the 40-59 age group and estimated prevalence of AD to be 45 per 100,000 (Schoenberg et al., 1985). A number of prevalence studies have been conducted in Europe: one review of six European studies calculated the average prevalence rate of AD in the 60-69 age group to be 0.3% (Rocca et al., 1991). A community study in Finland looked at primary degenerative dementia, which is expected to correspond to AD in more than 80% of cases, and estimated prevalence in the 30-59 year population to be 18.2 per 100,000 (Sulkava et al., 1985). Finally, one study in France estimated the prevalence of early-onset AD to be 41 per 100,000 in the under 61 years of age population (Campion et al., 1999). Variations in the estimation of prevalence can be explained by differing definitions of early-onset AD which result in different populations studied, as well as different diagnostic techniques used to identify the study populations.

There were no data found on prevalence of AD in California in the under 65 population; however, state-specific projections show that the total prevalence of AD in California was 440,000 in 2000 and is expected to increase by 50% to 660,000 in 2025 (Hebert et al., 2004). Applying the estimated prevalence rates from existing studies above to California census data in 2000, prevalence rates in the under 65 population can be estimated. For example, based on the estimates from the Minnesota study, the prevalence of AD for the 45-59 year old population in California in 2000 (5.7 million people) would be 1,565 cases. However, due to differences in community composition, this only provides a rough estimate of the true prevalence of AD in California. The 2003 Milliman claims data from private and public insurers indicate a prevalence rate of AD in California of 0.01% of all members under of 65 years of age. Variations in prevalence estimates can be explained by different diagnostic methods of identifying AD patients (Kukull et al., 1990; McKhann et al., 1984) and different populations studied - the community studies look at specific age groups in the under-65 population, while the claims data look at all patients under 65 years of age as a group.

In California in 2000, there were a total of 4,398 deaths attributable to AD, making it the eighth leading cause of death in the state. The age-adjusted death rate of AD in California was 15.1 per 100,000 compared with the national death rate of 18.0. In 2000 there were 40 deaths under 65 years of age attributable to AD, which was less than 1% of all AD deaths in California in 2000. (California Department of Health Services, 2000).



Survival time following diagnosis ranges from 3 years to 9 years (Fitzpatrick et al., 2005). Adjusted accelerated life models in one study calculated median survival from dementia onset to death as 7.1 years for AD (Fitzpatrick et al, 2005). Duration of survival depends strongly on the age at diagnosis. Median survival times in one study ranged from 8.3 years after diagnosis at age 65 years, to 3.4 years for persons diagnosed at age 90 years (Brookmeyer et al., 2002). Studies have also found that there is a greater disparity in remaining life years between AD and non-AD populations at younger ages, (Dodge et al., 2003; Larson et al., 2004; Tschanz et al., 2004) presumably because older patients are already at high risk of dying of other causes (Brookmeyer et al., 2002).

Impact of the Proposed Mandate on Public Health

Impact on Community Health (Section 1A)

The review of the effectiveness literature found that the FDA-approved medications for AD have a significant and favorable short-term effect when compared to placebo with respect to cognitive function, clinician/caregiver global assessment, daily functioning, behavioral/neuropsychological outcomes and caregiver time/distress. However, based on the California health plan carrier survey, since most major health plans that cover outpatient prescription drugs already cover at least one FDA-approved medication for the treatment of Alzheimer's, we conclude that this mandate will not increase or decrease access to or utilization of these drugs. Therefore, SB 415 will have no impact on community health.

Impact on Community Health where Gender and Racial Disparities Exist (Section 1B)

No literature was found specific to gender or racial disparities in AD in the under-65 population; however, there is some information on disparities in the general AD population, which is presented below. Given that any disparity that exists in AD patients under 65 years is likely to persist in persons over the age of 65 as the disease progresses, research findings on the general AD population may be applied to estimate any impact of the mandate on gender and racial disparities.

Analysis of mortality data in California suggests underlying gender differences in AD patterns. In general, deaths attributable to AD occur at a higher rate among females than males (Table 1) and among Whites more than any other race/ethnicity category (Table 2). For the most part, the literature review corroborates these findings. The national Milliman claims data discussed above suggest a prevalence rate of .012% for females and .010% for males. Studies have found that prevalence and incidence of AD are higher among women (Gambassi et al., 1999; Hui et al., 2003) compared to males and that females suffer from more severe impairment and accelerated decline (Gambassi et al., 1999). More specifically, the evidence suggests that the incidence of AD is greater for women than men particularly at older ages (Andersen et al, 1999; Fratiglioni et al, 1997; Miech et al, 2002). However, studies have also found that men have higher mortality rates attributable to AD than women (Heyman et al, 1996; Jagger et al., 1995; Lapane et al., 2001; Larsen et al., 2004 Ostbye et al., 1999).

In terms of racial differences in prevalence, the literature review supports the findings from the California data. Studies have found no differences in the rates of AD between Blacks and Whites when controlling for age and education (de la Monte et al., 1989; Fitzpatrick et al., 2004; Froehlich et al., 2001). Finally, recent findings on genetic determinants of AD have concluded that Whites may hold an allele not present in Blacks, which is a potent risk factor for AD (Farrer et al., 1997; Tang et al., 1996; Tang et al., 1998).



The literature review of differences in morbidity and other health outcomes produced only limited findings; this may be due to methodological issues in ascertaining onset of AD and difficulties in conducting longitudinal studies in this population. However, results were mixed among the studies that were identified. Shadlen et al. (1999) concluded that measured cognitive impairment was significantly more severe in Blacks than Whites, once diagnosed with AD, and Sink et al. (2004) found that Black and Hispanic community-dwelling patients with moderate to severe dementia had a higher prevalence of dementia-related behaviors than Whites. In contrast, Ripich et al. (2002) found that there were no differences between Blacks and Whites with AD in their verbal reasoning or linguistic abilities, and Ford et al. (1996) found that Whites and Blacks with AD did not differ significantly on cognitive test scores or functional impairment variables.

A large body of literature is devoted to understanding racial disparities in cognitive test performance, as this is one of the main criteria for diagnosis of AD. Most studies have concluded that a variety of factors such as SES and education contribute to racial disparities in testing scores and controlling for these variables greatly reduces the observed disparity (Froehlich et al, 2001). One study found no significant disparity between African Americans and European Americans with AD on cognitive test performance when controlling for education (Carlson et al, 1998) and another study determined that Black patients presented with less cognitive decline than White patients (Fillenbaum et al., 1990).

Another major finding among studies of AD disparities in testing outcomes is false-positive diagnoses of Alzheimer's. A screening device sensitive enough to pick up early cases will classify some people with no disease as impaired, and the risk of misclassification is higher for Blacks. Fillenbaum et al. (1990) found that 6 % of non-impaired Whites and 42 % of non-impaired Blacks were incorrectly classified by the Mini-Mental State Examination (MMSE). There have been consistently higher false-positive rates for Blacks than for Whites on numerous mental status examinations (Fillenbaum et al., 1990).

No literature was identified on racial or gender disparities in access to or utilization of medication to treat AD. However, there is evidence of some disparity with regards to healthcare treatment between men and women. Young (2003), building upon prior research findings, concluded that female patients (NCHS, 1989) and patients with dementia (Ernest and Hay, 1994) comprised a large proportion of nursing home residents. Her findings show that women with AD were more likely to be institutionalized than men with AD, despite the fact that they were in better health upon entrance than men. There is very limited literature on racial disparities in institutionalization among Alzheimer's-specific populations (Gaugler et al., 2004), but most studies show that Blacks in the general population, as well as those with dementia, have significantly lower rates of institutionalization than Whites, despite worse physical and functional status (Hinrichsen and Ramirez, 1992; Wallace et al, 1998; Belgrave et al., 1993)..

Although there is some evidence of gender and racial disparities in the prevalence of AD, there is no evidence that this mandate would increase baseline utilization of pharmacotherapies for the treatment of AD. Therefore, we conclude that SB 415 will have no public health impact on gender or racial disparities.

Reduction of Premature Death and the Economic Loss Associated with Disease (Section 1C)

The health outcomes examined in this report represent measures of quality of life and are not measures of premature death related to the mandate. The literature review identified studies that suggested that in all



age groups, patients with AD have decreased survival compared to survival in the overall U.S. population (Larson et al, 2004; Dodge et al, 2003). For example, Larson et al (2004) found that median survival time for men at 70 years of age was 4.4 years for those with AD compared with 9.3 years for the U.S. population. Similar findings were evident in a community study in Pennsylvania (Dodge et al, 2003). In the non AD cohort, men at 70 years of age had 13.7 years of remaining life compared to men of the same age with AD who had only 6.8 years of remaining life on average. While the literature points to a high risk of death associated with AD, we have no evidence that coverage of pharmacotherapy will delay death. Furthermore, since there is evidence that the mandate will not change utilization of pharmacotherapy, we conclude that SB 415 will have no impact on mortality associated with AD.

A literature review was conducted to address the potential impact of the mandate on economic loss associated with early-onset AD. However, no studies or data were found on the economic loss specific to the under-65 population. Direct costs of AD are estimated to be \$50-\$100 billion annually for treatment according to estimates used by the Alzheimer's Association and the National Institute on Aging (Kirchstein, 2000). Indirect costs are measured in terms of productivity losses, and all studies include productivity of both patient and caregiver. Harrow et al (2004) estimated the annual cost per care recipient for informal care to be \$23,436, based on a replacement-wage-rate approach. Souetre et al (1995) calculated indirect care costs by the loss of earnings for both patients and caregivers and concluded that it accounted for 40 % of total costs for AD patients. A study commissioned by the Alzheimer's Association (Koppel, 2002) reported that AD costs American businesses \$61 billion a year, of which \$36.5 billion were costs related to lost productivity, absenteeism and worker replacement of caregivers of AD patients. It is clear that a significant economic loss is associated with AD; however, because there is no evidence to suggest that the mandate will alter current utilization of pharmacotherapy, we conclude that SB 415 will not have an impact on the reduction of economic loss associated with AD.



Table 1: Alzheimer's Disease Deaths by Race, California 1999-2000

| Race | No. of Total Deaths Attributable to AD | % | Age-Adjusted Death Rate | No. of Total Deaths under 65 Years Attributable to AD | % | Death Rate |
|-------------|---|----------|--------------------------------|--|----------|-------------------|
| White | 3,824 | 87.0% | 17.8 | 29 | 72.5% | Unreliable |
| Black | 196 | 4.4% | 15.1 | 0 | 0% | Unreliable |
| Hispanic | 266 | 6.0% | 7.1 | 7 | 17.5% | Unreliable |
| Asian/Other | 112 | 2.5% | 4.3 | 4 | 10.0% | Unreliable |

Source: California Department of Health Services: 2000

Table 2: Alzheimer's Disease Deaths by Gender, California 1999-2000

| Gender | No. of Total Deaths Attributable to AD | % | Age-Adjusted Death Rate | No. of Total Deaths under 65 Years Attributable to AD | % | Death Rate |
|---------------|---|----------|--------------------------------|--|----------|-------------------|
| Male | 1,388 | 32% | 18.0 | 17 | 42.5% | Unreliable |
| Female | 3,010 | 68% | 17.4 | 23 | 57.5% | Unreliable |

Source: California Department of Health Services: 2000



APPENDICES

Appendix A

Literature Review Methods

SB 415 is an act to add Section 1373.15 to the Health and Safety Code and to add Section 10124.1 to the Insurance Code, relating to health care coverage. The proposed bill "... *would require a health care service plan and a health insurance policy providing coverage for prescription drugs, to include medications in that benefit for the treatment of Alzheimer's disease.*" Section 1373.15 states that, "*Every health care service plan contract that provides prescription drug benefits, except a standardized health care service plan contract, that is issued, amended, renewed, or delivered in this state on or after July 1, 2006 shall include in its prescription drug formularies, cholinesterase inhibitors and other medications approved by the federal Food and Drug Administration for the treatment of Alzheimer's disease.*" Section 10124.1 states that, "*Every group or individual policy of health insurance that provides hospital, medical, or surgical benefits that is issued, amended, renewed, or delivered in this state on or after July 1, 2006, that also includes a prescription drug benefit, shall offer coverage for cholinesterase inhibitors and other medications approved by the federal Food and Drug Administration for the treatment of Alzheimer's disease.*"

Appendix A describes the literature search for studies that evaluate the medical effectiveness of the cholinesterase inhibitors approved by the Food and Drug Administration (FDA), including tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl), as well as the single NMDA-receptor antagonist currently approved by the FDA, memantine (Namenda). The outcomes included in the literature search included *patient health outcomes*, including physiologic, physical, behavioral (sleeplessness, agitation, wandering, anxiety, depression, discomfort), cognitive function, functioning in activities of daily living, and social participation; *health care outcomes*, including utilization of home care, attendant services, and nursing home care and residential care services; *caregiver health outcomes*, including anxiety, stress, and depression; and *caregiver quality of life*, including work absence.

To "grade" the evidence for all outcome measures, the CHBRP effectiveness team uses a system⁵ with the following categories:

1. Favorable (statistically significant effect): Findings are uniformly favorable, and many or all are statistically significant.
2. Pattern⁶ toward favorable (but not statistically significant): Findings are generally favorable, but there may be none that are statistically significant.

⁵ The foregoing system was adapted from the system used by the U.S. Preventive Services Task Force, available at <http://www.ahcpr.gov/clinic/3rduspstf/ratings.htm>. The medical effectiveness team also considered guidelines from the Centers for Medicare & Medicaid Services, (available at <http://www.cms.hhs.gov/mcac/8b1-i9.asp>) and guidelines from the Blue Cross and Blue Shield Association (available at <http://www.bcbs.com/tec/teccriteria.html>).

⁶ In this instance, the word "trend" may be used synonymously with "pattern."



3. Ambiguous/mixed evidence: Some findings are significantly favorable, and some findings with sufficient statistical power show no effect.
4. Pattern toward no effect/weak evidence: Studies generally find no effect, but this may be due to a lack of statistical power.
5. No effect: There is statistical evidence of no clinical effect in the literature with sufficient statistical power to make this assessment.
6. Unfavorable: No findings show a statistically significant benefit, and some show significant harms.
7. Insufficient evidence to make a “call”: There are very few relevant findings, so that it is difficult to discern a pattern.

Studies of the effectiveness of the foregoing agents were identified from PubMed and Cochrane databases (January, 1990–December, 2004). The search terms used to elicit studies relevant to the mandate, that is those that were relevant to studies about the FDA-approved drugs specifically for Alzheimer’s, were:

Medical Subject Headings

Tacrine
Galantamine
Memantine
Alzheimer Disease with Subheadings blood, urine, cerebrospinal fluid, enzymology, immunology, metabolism, pathology
Brain
Behavior and Behavior Mechanisms
Cognition
Depression
Treatment Outcome
Follow-Up Studies
Health Status
Quality of Life
Outcome Assessment
Sleep
Sleep Disorders
Caregivers
Activities of Daily Living
Rehabilitation
Human Activities
Nursing Homes
Residential Facilities
Dyskinesias
Socialization
Interpersonal Relationships
Morbidity
Mortality



Keywords

Below is a list of keywords used in PubMed search to retrieve newly published articles that haven't been indexed with MeSH terms, or because no MeSH terms are available.

Tacrine
Cognex
Aricept
Donepezil
Exelon
Rivastigmine
Reminyl
Galantamine
Namenda
Memantine
Alzheimer Disease
Alzheimer*
AD
Memory
Sleep
Caregiver*
Stress
Movement
Anxiety
Anxious
Discomfort
Walk*
Wander*
Mobil*
Pain
Distress
Discomfort

The asterisk (*) indicates that the word has been truncated, meaning that the search retrieves all variations with the same root. For example, effect* would retrieve effect, effects, effectiveness, effective, etc.

The types of publications included in the literature search were:

Randomized Controlled Trials
Clinical Trials
Reviews
Journal Articles
Case Reports
Practice Guidelines



The literature review resulted in 519 references. However, in CHBRP analyses, we rely on a hierarchy of study designs. In this hierarchy, meta-analyses and systematic reviews of randomized trials are given the greatest weight, followed by individual randomized trials and then by such other study designs as observational studies and case reports. Among the 519 references, there were 8 meta-analyses of randomized trials (all of the randomized trials were also among the 519 articles). Given the existence of these meta-analyses, the present analysis was able to rely on the foregoing meta-analyses for most of the outcomes assessed, supplemented by individual randomized trials published subsequent to the studies included in the meta-analyses for select outcomes, and observational studies for the remainder of the outcomes. The complete articles for the 8 meta-analyses and 11 other relevant publications were retrieved and reviewed by at least two persons. Because tacrine (Cognex) is infrequently prescribed now due to high rates of hepatotoxicity, this review is limited to the three other cholinesterase inhibitors, donepezil (Aricept), galantamine (Reminyl), and rivastigmine (Exelon) and to the one NMDA agonist, memantine (Namenda).



Appendix B
Summary of Findings on Effectiveness of Alzheimer’s Medications

Table B-1. Summary of Published Studies on Effectiveness of Approved Medications in Treatment of Alzheimer’s Disease (AD)

| Citation | Type of Study | Intervention vs. Comparison Group | Length of Study(ies) | Population Studied | Location |
|-----------------------------------|---|---|-----------------------------|--|--------------------------|
| Birks and Harvey, 2003 | Meta-analysis of 16 double-blind RCTs, analyzed separately by dose and duration | Donepezil (5 or 10 mg/day) vs. placebo | 12, 24, 52 weeks | Mild/moderate, or severe dementia due to AD | U.S., Japan, Europe |
| Wimo al., 2004 | Double-blind RCT | Donepezil (5 or 10 mg/day) vs. placebo | 52 weeks | Caregivers of patients with mild/moderate dementia due to AD | Europe (5 countries) |
| Geldmacher et al., 2003 | Observational follow-up to RCT | Donepezil (5 or 10 mg/day) vs. no treatment | 24, 48, or 96 weeks | Mild/moderate dementia due to AD | U.S. (multiple sites) |
| Courtney et al., 2004 | Double-blind RCT | Donepezil (5 or 10 mg/day) vs. placebo | 114 weeks | Mild/moderate dementia due to AD | England (multiple sites) |
| Holmes et al., 2004 | Double-blind RCT | Donepezil (10 mg/day) vs. placebo | 24 weeks | Mild/moderate dementia due to AD | England (multiple sites) |
| Loy and Schneider, 2004 | Meta-analysis of 7 double-blind RCTs, analyzed separately by dose and duration | Galantamine (24 or 36 mg/day) vs. placebo | 12, 21, 26, or 29 weeks | Mild/moderate dementia due to AD | North America and Europe |
| Bullock et al., 2004 ⁷ | Open-label extension of double-blind RCT | Galantamine/galantamine (24 mg/day) vs. placebo/galantamine | 12 months | Mild/moderate dementia due to AD + cerebrovascular disease | North America and Europe |

RCT = randomized controlled trial

⁷ Study not included in Table B-2. The reported results are small sig. difference each group compared to baseline, but figure in publication shows very small difference in final result of two groups and indicates that use past 7.5 months results in downward trajectory of treatment effect on cognition.



Table B-1 (Cont'd).

| Citation | Type of Study | Intervention vs. Comparison Group | Length of Study(ies) | Population Studied | Location |
|--|--|--|------------------------------|--|--|
| Pirttila et al., 2004 ⁸ | Open-label extension of 2 double-blind RCTs | Galantamine (24 mg/day) observed vs. predicted | 36 months | Mild/moderate dementia due to AD | Europe |
| Sano et al., 2003 | Double-blind RCT | Galantamine (24 mg/day) vs. placebo | 6 months | Mild/moderate dementia due to AD | Europe and Canada |
| Suh et al., 2004 | Double-blind community-controlled trial | Galantamine (8, 16, or 24 mg/day) vs. community comparison (no AChEI meds) | 16 weeks | Mild/moderate dementia due to AD | Korea |
| Birks et al., 2003 | Meta-analysis of 7 double-blind RCTs, analyzed separately by dose and duration | Rivastigmine (1-4 or 6-12 mg/day, maximum tolerated) vs. placebo | 9, 13, 18, 26 weeks | Probable AD | Europe and North America |
| Ritchie et al., 2004 | Meta-analysis of 15 double-blind RCTs, analyzed separately by drug and dose | Donepezil (5,10 mg/day), rivastigmine (1-4,6-12 mg/day), or galantamine (8, 16, 18, 24, 32 mg/day) vs. placebo | 10, 12, 15, 18, 24, 26 weeks | Mild/moderate or severe dementia due to AD | Europe, North America, Australia, Africa |
| Lanctot et al., 2003 ⁹ | Meta-analysis of 16 double-blind RCTs, analyzed jointly | Donepezil (5,10 mg/day), rivastigmine (1-4,6-12 mg/day), or galantamine (8, 16, 18, 24, 32 mg/day) vs. placebo | 12-52 weeks | Diagnosis of AD (mild/moderate/severe) | Japan, U.S., Europe, South Africa, Australia |
| Livingston and Katona, 2000 ³ | Meta-analysis of 3 double-blind RCTs | Donepezil (5,10 mg/day) or rivastigmine (1-4,6-12 mg/day) vs. placebo | 24 to 26 weeks | Mild/moderate dementia due to AD | North America and Europe |

Inappropriate use of the last observation carried forward (LOCF) protocol over-inflates results in a study where cognition is declining over time.

⁹ These 3 meta-analyses are based on studies which are included in the Cochrane Systematic Reviews for the individual drugs. The main results are not summarized in Table B-2, as they would be redundant. However, all three include a “numbers needed to treat/harm” methodology, the results of which are discussed in the text of this report.



Table B-1 (Cont'd).

| Citation | Type of Study | Intervention vs. Comparison Group | Length of Study(ies) | Population Studied | Location |
|--|--|---|------------------------------|--|-------------------------------|
| Wilcock et al., 2003 | Double-blind RCT | Donepezil (5 or 10 mg/day) vs. galantamine (8 or 12 mg/day) | 52 weeks | Mild/moderate dementia due to AD | UK |
| Wilkinson et al., 2002 | Rater-blinded, randomized open-label study | Donepezil (10 mg/day) vs. rivastigmine (up to 12 mg/day) | 12 weeks | Mild/moderate dementia due to AD | UK, South Africa, Switzerland |
| Mossello et al., 2004 | Observational study | Donepezil (5-10 mg/day) vs. rivastigmine (6 - 12 mg/day) | 9 months | Mild/moderate dementia due to AD | Italy |
| Areosa Sastre et al., 2004 | Meta-analysis of 9 double-blind RCTs, analyzed separately by dose & duration | Memantine (10, 20, 30 mg/day) vs. placebo | 6, 12, 24, 28 weeks | Mild/moderate or severe dementia due to AD &/or vascular disease | Europe and U.S. |
| Livingston and Katona, 2004 ³ | Meta-analysis of 2 double-blind RCTs | Memantine (10 or 20 mg/day) vs. placebo | 12 and 28 weeks | Moderate/severe AD | U.S. and Latvia |
| Qizilbash et al., 1998 ¹⁰ | Meta-analysis of 12 double-blind RCTs | Tacrine (varied dosages) vs. placebo | 3, 4, 6, 8, 12, 30, 36 weeks | Probable AD (no severity info provided) | not provided |

¹⁰ Tacrine studies were not included in this report, as the drug is infrequently prescribed currently, due to unacceptable levels of serious side effects (e.g., liver toxicity).



Table B-2. Summary of Evidence of Effectiveness by Outcome for Approved Medications in Treatment of Alzheimer’s Disease (AD)

Cognitive Outcomes

Favorable for comparison between FDA-approved AD medications and placebo.

Pattern toward no effect/weak evidence for comparisons between FDA-approved AD medications.

| Citation | Results | Categorization of Results (Significance, Direction) |
|----------------------------|---|--|
| Birks and Harvey, 2003 | <u>Donepezil</u> ADAS-Cog: WMD -2.0 to -2.9 MMSE: WMD 1.1 to 1.8 | 4 analyses: all sig, fav 5 analyses: all sig, fav |
| Courtney et al., 2004 | <u>Donepezil</u> MMSE: MD 0.8 (0.5, 1.2) | sig, fav |
| Loy and Schneider, 2004 | <u>Galantamine</u> ADAS-Cog: WMD -1.3 to -3.3 ADAS-Cog, ≥ 4 pt improvement: OR 2.2 to 2.7 | 9 analyses: all sig, fav 4 analyses: 3 sig, fav 1 NS (8 mg/d) |
| Pirttila et al., 2004 | <u>Galantamine</u> ADAS-Cog: MD 11.2 (p < 0.001) (compared with predicted values from Stern equation; Stern et al., 1994) | sig, fav Diff equivalent to 18 mos. “savings” of cog. function. |
| Suh et al., 2004 | <u>Galantamine</u> ADAS-Cog: MD -8.4 to -10.3 | 3 doses: sig, fav |
| Birkss et al., 2003 | <u>Rivastigmine</u> ADAS-Cog: WMD -0.3 to -2.1 MMSE: WMD -0.4 to -0.8 | 6 analyses: 5 sig, fav 1 NS (1-4 mg) 2 analyses: both sig, fav |
| Ritchie et al., 2004 | <u>Donepezil</u> ADAS-Cog: WMD -2.2 to -3.0 <u>Galantamine</u> ADAS-Cog: WMD -2.6 to -3.2 <u>Rivastigmine</u> ADAS-Cog: WMD -1.1 to -3.2 | 2 analyses: both sig, fav 3 analyses: all sig, fav 2 analyses: both sig, fav |
| Wilcock et al., 2003 | <u>Donepezil vs. galantamine</u> MMSE: MD -1.1 (p < 0.1) ADAS-Cog, no deterioration: 31.7% vs. 44.9% (p < 0.1) | NS, favors galantamine NS, favors galantamine |
| Wilkinson et al., 2002 | <u>Donepezil vs. rivastigmine</u> ADAS-Cog: MD -0.2 (-1.9, 1.6) | NS |
| Mossello et al., 2004 | <u>Donepezil vs. rivastigmine</u> MMSE: MD 0.5 | NS |
| Areosa Sastre et al., 2004 | <u>Memantine</u> Pooled*: SMD -0.3 (-0.4, -0.2) | 1 analysis: sig, fav |

Abbreviations of outcome measures are defined immediately following Table B-2.

WMD = weighted mean difference; MD = mean difference; OR = odds ratio.

*Pooled scales include ADAS-Cog, SIB, and SKT.



Table B-2 (Cont'd).

Clinician/Caregiver Global Assessment

Favorable for comparison between FDA-approved AD medications and placebo.

| Citation | Results | Categorization of Results (Significance, Direction) |
|----------------------------|--|--|
| Birks and Harvey, 2003 | <u>Donepezil</u> CIBIC-Plus: OR 2.1 to 2.7 CDR-SB: WMD -0.2 to -0.5 | 4 analyses: all sig, fav 4 analyses: 3 sig, fav 1 NS, fav |
| Loy and Schneider, 2004 | <u>Galantamine</u> CIBIC-plus/ADCS-CGIC: OR 1.6 to 2.1 | 3 analyses: all sig, fav |
| Suh et al., 2004 | <u>Galantamine</u> CIBIC-plus: treatment group, 43 to 54% rated as improved, control group, 11% rated as improved | 1 study: sig, fav |
| Birks et al., 2003 | <u>Rivastigmine</u> CIBIC-plus: OR 0.68 to 0.98 | 6 analyses: 4 sig, fav 2 NS (1-4 mg) |
| Ritchie et al., 2004 | <u>Donepezil</u> CGI: OR 2.3 to 2.4 <u>Galantamine</u> CGI: OR 1.4 to 1.5 | 2 analyses: both sig, fav 3 analyses: 2 sig, fav 1 NS, fav |
| Areosa Sastre et al., 2004 | <u>Memantine</u> CIBIC-Plus: WMD -0.27 to -0.3 CGI: OR 3.3 (1.7, 6.3) | 3 analyses: all sig, fav 1 analysis: sig, fav |



Table B-2 (Cont'd).

Daily Functioning

Favorable for comparison between FDA-approved AD medications and placebo.

Ambiguous/mixed evidence for comparisons between FDA-approved AD medications.

| Citation | Results | Categorization of Results (Significance, Direction) |
|----------------------------|--|---|
| Birks and Harvey, 2003 | <u>Donepezil</u> PDS: MD 3.8 (1.7, 5.9) CMCS: MD -2.4 (-0.5, -4.3) DAD: MD 4.83 to 8.0 IADL: MD -6.3 to -8.2 Functional decline: OR 0.53 (0.36, 0.78) | 1 study: sig, fav 1 study: sig, fav 2 analyses: both sig, fav 2 analyses: both sig, fav 1 study: sig, fav |
| Courtney et al., 2004 | <u>Donepezil</u> BADLS: MD 1.0 (0.5, 1.6) BADLS disab: RR 1.0 (0.7, 1.5) | 1 study: sig, fav 1 study: NS |
| Loy and Schneider, 2004 | <u>Galantamine</u> ADCS-ADL: MD -0.6 to -3.1 DAD: MD 2.8 to 4.8 | 3 analyses: 2 sig, fav, 1 NS 3 analyses: 2 sig, fav, 1 NS, fav |
| Suh et al., 2004 | <u>Galantamine</u> DAD: MD 7.2 to 12.9 | 1 study: sig, fav |
| Birks et al., 2003 | <u>Rivastigmine</u> PDS: WMD 0.4 to -2.2 | 5 analyses: 3 sig, fav 2 NS (1-4 mg) |
| Wilcock et al., 2003 | <u>Donepezil vs. galantamine</u> BrADL: MD 0.2 (p>0.5) | NS |
| Mossello et al., 2004 | <u>Donepezil vs. rivastigmine</u> ADL: MD 0.4 (p = 0.02) IADL: MD 0.3 | sig, favors donepezil NS |
| Areosa Sastre et al., 2004 | <u>Memantine</u> ADCS-ADL: WMD 0.1 to 1.7 NOSGER: WMD -0.1 (-0.7, 0.4) | 2 analyses: 1 sig, fav; 1 NS 1 analysis: NS |



Table B-2 (Cont'd).

Behavioral and Neuropsychological Outcomes

Pattern toward favorable for comparison between FDA-approved AD medications and placebo.

Pattern toward no effect/weak evidence for comparisons between FDA-approved AD medications.

| Citation | Results | Categorization of Results (Significance, Direction) |
|--------------------------------|---|--|
| Birks and Harvey, 2003 | <u>Donepezil</u> NPI: SMD -0.2 (-0.3, 0.01) | 1 analysis: NS, fav |
| Holmes, Wilkinson et al., 2004 | <u>Donepezil</u> NPI: MD -6.2 (p = 0.02) | 1 study: sig, fav |
| Loy and Schneider, 2004 | <u>Galantamine</u> NPI: MD 0.3 to -2.1 | 4 analyses: 2 sig, fav 1 NS, fav 1 NS |
| Suh, Yeon Jung et al., 2004 | <u>Galantamine</u> BEHAVE-AD: MD -5.4 to -6.0 | 1 study: sig, fav |
| Wilcock, Howe et al., 2003 | <u>Donepezil vs. galantamine</u> NPI: actual results not reported | NS |
| Areosa, McShane et al., 2004 | <u>Memantine</u> NPI: WMD -3.5 to -3.6 Pooled*: SMD -1.2 (-1.5, -0.9) | 2 analyses: sig, fav 1 anal, 2 studies: sig, fav |

SMD = standardized mean difference

*Pooled results used NOSIE and SCAG

Caregiver Time/Distress

Favorable for comparison between FDA-approved AD medications and placebo.

| Citation | Results | Categorization of Results (Significance, Direction) |
|------------------------|--|--|
| Birks and Harvey, 2003 | <u>Donepezil</u> Min/day: -81.9 (-153.1, -10.7) | 1 study: sig, fav |
| Wimo et al., 2004 | <u>Donepezil</u> Min/day: -64.2 (-120.5, -7.8) | 1 study: sig, fav |
| Holmes et al., 2004 | <u>Donepezil</u> NPI-D: MD -3.0 (p = 0.01) | 1 study: sig, fav |
| Sano et al., 2003 | <u>Galantamine</u> Min/day: MD 32 (p = 0.01) | 1 study: sig, fav |



Table B-2 (Cont'd).

Nursing Home Placement

Ambiguous/mixed evidence for comparisons between FDA–approved AD medications and placebo.

| Citation | Results | Categorization of Results (Significance, Direction) |
|-------------------------|--|--|
| Geldmacher et al., 2003 | <u>Donepezil</u> 1st NHP: HR 0.4 to 0.7 Permanent NHP: HR 0.4 to 0.7 | 6 treatment times: longer treatment associated with greater reductions in risk. All but 1 HR: sig, fav |
| Courtney et al., 2004 | <u>Donepezil</u> NHP: RR 1.0 (0.7, 1.2) | 1 study: NS |
| | | |

NHP = Nursing home placement; HR = Hazard ratio from proportional hazard models of time to NHP

Outcome Measures Listed in Table B-2

Cognitive

- ADAS-Cog: Alzheimer’s Disease Assessment Scale (Rosen et al., 1984)
- MMSE: Mini-Mental State Examination (Folstein, Folstein et al., 1975)
- SIB: Severe Impairment Battery (Schmitt et al., 1997)
- SKT: Syndrom-Kurztest (Kim et al., 1993)

Behavioral/Neuropsychological

- BEHAVE-AD: Behavior Pathology in Alzheimer’s Disease Rating Scale (Reisburg et al., 1996)
- NOSIE: Nurses Observation Scale for Inpatient Evaluation (Honigfeld, 1974)
- NPI: Neuropsychiatric Inventory (Cummings et al., 1994)
- SCAG: Sandoz Clinical Assessment Geriatric Scale (Shader et al., 1974)

Global

- CDR-SB: Clinical Dementia Rating-Sum of the Boxes (Berg, 1988)
- CGIC: Clinical Global Impression of Change (Schneider et al., 1997)
- CIBIC: Clinician’s Interview-Based Impression of Change (Knopman et al., 1994)

Daily Functioning/Disability

- ADCS-ADL: Alzheimer’s disease Cooperative Study–Activities of Daily Living (Galasko et al., 1997)
- ADL: Activities of Daily Living (Katz et al., 1963)
- BrADL: Bristol Activities of Daily Living Scale (Bucks et al., 1996)
- DAD: Disability Assessment for Dementia Scale (Gelinas et al., 1999)
- CMCS: Caregiver-Modified Crichton Scale (Wilkin and Thompson, 1989)
- IADL: Instrumental Activities of Daily Living (Lawton and Brody, 1969)
- NOSGER: Nurses’ Observation Scale for Geriatric Patients (Spiegel et al., 1991)
- PDS: Progressive Deterioration Scale (DeJong et al., 1989)

Caregiver Distress

- NPI-D: – Neuropsychiatric Inventory Distress Scale (Cummings et al., 1994)



Appendix C

Cost Impact Analysis: General Caveats and Assumptions

This appendix describes general caveats and assumptions used in conducting the cost impact analysis. For additional information on the cost model and underlying methodology, please refer to the CHBRP Web site, http://www.chbrp.org/analysis_methodology/cost_impact_analysis.php

The cost analysis in this report was prepared by Milliman and the University of California, Los Angeles, with the assistance of CHBRP staff. Per the provisions of AB 1996 (California Health and Safety Code, Section 127660, et seq.), the analysis includes input and data from an independent actuarial firm, Milliman. In preparing cost estimates, Milliman and UCLA relied on a variety of external data sources. The *Milliman Health Cost Guidelines* (HCG) were used to augment the specific data gathered for this mandate. The HCGs are updated annually and are widely used in the health insurance industry to estimate the impact of plan changes on health care costs. Although this data was reviewed for reasonableness, it was used without independent audit.

The expected costs in this report are not predictions of future costs. Instead, they are estimates of the costs that would result if a certain set of assumptions were exactly realized. Actual costs will differ from these estimates for a wide variety of reasons, including:

- Prevalence of mandated benefits before and after the mandate different from our assumptions.
- Utilization of mandated services before and after the mandate different from our assumptions.
- Random fluctuations in the utilization and cost of health care services.

Additional assumptions that underlie the cost estimates presented here are:

- Cost impacts are only shown for people with insurance.
- The projections do not include people covered under self-insurance employer plans because those employee benefit plans are not subject to state-mandated minimum benefit requirements.
- Employers and employees will share proportionately (on a percentage basis) in premium rate increases resulting from the mandate. In other words, the distribution of premium paid by the subscriber (or employee) and the employer will be unaffected by the mandate.

There are other variables that may affect costs, but which Milliman did not consider in the cost projections presented in this report. Such variables include, but are not limited to:

- Population shifts by type of health insurance coverage. If a mandate increases health insurance costs, then some employer groups or individuals may elect to drop their coverage. Employers may also switch to self-funding to avoid having to comply with the mandate.
- Changes in benefit plans. To help offset the premium increase resulting from a mandate, members or insured may elect to increase their overall plan deductibles or copayments. Such changes would have a direct impact on the distribution of costs between the health plan and the insured person, and may also result in utilization reductions (i.e., high levels of patient cost sharing result in lower utilization of health care services). Milliman did not include the effects of such potential benefit changes in its analysis.



- Adverse Selection. Theoretically, individuals or employer groups who had previously foregone insurance may now elect to enroll in an insurance plan post-mandate because they perceive that it is to their economic benefit to do so.
- Health plans may react to the mandate by tightening their medical management of the mandated benefit. This would tend to dampen our cost estimates. The dampening would be more pronounced on the plan types that previously had the least effective medical management (i.e., FFS and PPO plans).
- Variation in existing utilization and costs, and in the impact of the mandate, by geographic area and delivery system models: Even within the plan types we modeled (HMO, PPO, POS, and FFS), there are variations in utilization and costs within California. One source of difference is geographic. Utilization differs within California due to differences in the health status of the local commercial population, provider practice patterns, and the level of managed care available in each community. The average cost per service would also vary due to different underlying cost levels experienced by providers throughout California and the market dynamic in negotiations between health plans and providers.

Both the baseline costs prior to the mandate and the estimated cost impact of the mandate could vary within the state due to geographic and delivery system differences. For purposes of this analysis, however, we have estimated the impact on a statewide level.



Appendix D

Information Submitted by Outside Parties for Consideration for CHBRP Analysis

In accordance with its policy to analyze evidence submitted by outside parties during the first two weeks of each 60-day review of a proposed benefit mandate, CHBRP received the following submissions:

No information was submitted to date.

CHBRP analyzes all evidence received during the initial public submission period according to its relevance to the proposed legislation and the program's usual methodological criteria. For more information about CHBRP's methods, to learn how to submit evidence relevant to an on-going mandate review, or to request email notification of new requests CHBRP receives from the California Legislature, please visit: <http://www.chbrp.org>.



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A group of faculty and staff undertakes most of the analysis that informs reports by the California Health Benefits Review Program (CHBRP). The CHBRP **Faculty Task Force** comprises rotating representatives from six University of California (UC) campuses and three private universities in California. In addition to these representatives, there are other ongoing contributors to CHBRP from UC. This larger group provides advice to the CHBRP staff on the overall administration of the program and conducts much of the analysis. The CHBRP **staff** coordinates the efforts of the Faculty Task Force, works with Task Force members in preparing parts of the analysis, and coordinates all external communications, including those with the California Legislature. The level of involvement of members of CHBRP's Faculty Task Force and staff varies on each report, with individual participants more closely involved in the preparation of some reports and less involved in others.

As required by CHBRP's authorizing legislation, UC contracts with a certified actuary, Milliman, to assist in assessing the financial impact of each benefit mandate bill. Milliman also helped with the initial development of CHBRP's methods for assessing that impact.

The **National Advisory Council** provides expert reviews of draft analyses and offers general guidance on the program to CHBRP staff and the Faculty Task Force. CHBRP is grateful for the valuable assistance and thoughtful critiques provided by the members of the National Advisory Council. However, the Council does not necessarily approve or disapprove of or endorse this report. CHBRP assumes full responsibility for the report and the accuracy of its contents.

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