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Factors associated with use of medications with potential to impair cognition or cholinesterase inhibitors among Alzheimer's disease patients

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Abstract

Background: The aim of this study was to use a signal detection method to examine the prevalence of, and patient characteristics associated with, medication with potential to impair cognition and cholinesterase inhibitor use in patients with Alzheimer's disease.

Methods: A cross-sectional study was conducted of 1,954 patients with a diagnosis of probable or possible Alzheimer's disease. Concurrent medications were measured, specifically; (I) a medication with potential to impair cognition or (2) a cholinesterase inhibitor. Predictor variables included age, gender, ethnic group, education, age of symptom onset, number of prescriptions, number of medical diagnoses, Mini-Mental State Examination (MMSE), Blessed-Roth Dementia Rating Scale (BRDRS), probable versus possible AD diagnosis.

Results: Fifteen percent of the Alzheimer's disease patients were on a medication with potential to impair cognition, and 44% were on a cholinesterase inhibitor. Patient characteristics associated with the prescription of a medication with potential to impair cognition included total number of prescription medications, low education, low MMSE, older age, reported lack of vitamin use, and more medical diagnoses. Patient characteristics associated with the prescription of a cholinesterase inhibitor included reported use of vitamins, the total number of prescription medications, fewer medical diagnoses, lower age of symptom onset, and higher education.

Conclusions: Determining the patient characteristics associated with the prescription of a medication with potential to impair cognition can help clinicians identify patients who are at risk for drug-related morbidity. Patient characteristics unassociated with dementia appear to influence the prescription of cholinesterase inhibitors. Signal detection analysis is well suited to this type of research.

Keylvord,: Alzheimer's disease; inappropriate medications; cholinesterase inhibitors; Beers criteria; signal detection; receiver operating characteristic analysis

1. Introduction

Inappropriate medication use, especially in the elderly, has been a topic of increasing concern. Although older AmLricans (aged 65 years and older) account for 13% of the total US population, they consume more than 25% of all prescription medications and can have increased rates of adverse effects [I]. One of the challenges in this area has been to develop criteria for inappropriate medication use. Although lists of potentially inappropriate medications cannot capture all of the complex factors that are involved in clinical decision making, they can be useful in gauging potentially inappropriate medication use. The most studied

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of these is the Beers list of explicit criteria for inappropriate prescribing in older patients. These criteria, first published in 1991 [2] and updated in 1997 [3] and 2003 [4] were originally developed for nursing home patients. However, they have been used to evaluate patients in board and care facilities [5], outpatient settings [6,7], and home health care settings [8] as well as nursing homes [9]. The criteria were developed initially by Beers on the basis of a literature review and evaluated by experts in geriatrics and pharmacology using a modified Delphi method [3]. The patient-based prevalence of potentially inappropriate use of medications found in these studies ranges from 14% to 40% with higher percentages generally observed in nursing homes and lower percentages seen in community samples [10,11], although 2 Canadian studies observed lower rates in nursing homes than in the community [12,13]. One representative study found that 21% of community-dwelling elderly patients received at least 1 potentially inappropriate medication [6]. A similar prevalence was found in a European population [14]. The patient characteristics associated with a higher risk of receiving Beers-criteria medications include poor overall health [6,10-12], depression [14], polypharmacy [6,10-12,14], and possibly female gender [6,10-12]. Age has had mixed results as a predictive factor, with some studies reporting older patients to be at lower risk [12-14] and others at higher risk [10,15,16] of receiving a Beers-criteria medication.

Psychotropic medications are the most commonly prescribed class of Beers-criteria medications in the elderly [13] (23%,44%, and 51% of potentially inappropriate medications in long-term care, office-based settings and outpatient departments, respectively) [15], with benzodiazepines, amitriptyline, and propoxyphene being the most commonly given medications with cognitive adverse effects [10,11,16]. One study found that 33% of community-dwelling elderly who were taking psychotropic drugs received medications that were generally inappropriate [16]. Although these studies did not target demented patients, they were part of the subject population in many of these studies. One report assessed anticholenergic use and potential drug-drug interactions in demented and non demented populations [17]. In this study, we evaluate the amount of medication with potential to impair cognition use in demented patients.

We had 3 objectives for this study. The first was to evaluate the use of a subset of Beers-criteria medications that can interfere with cognition in patients with possible or probable Alzheimer's disease (AD). The physicians in our research group reviewed the list of Beers-criteria medications and defined a subset of medications that can interfere with cognition. We are interested in several questions: How commonly are AD patients on potentially inappropriate medications that can interfere with cognition? What patient characteristics CO1Tespond with the prescription of Beers-criteria medications that can interfere with cognition?

Our second objective was to examine the prevalence of, and patient characteristics associated with, the prescription of cholinesterase inhibitors in AD patients. Few studies have examined the complex factors involved in the prescription of a therapeutic agent. During the period of our analysis, cholinesterase inhibitors were prescribed increasingly. By identifying the patient variables associated with the prescription of a relatively new class of medications, we hoped to characterize patients who are most likely to receive new treatments early. These patients provide an interesting contrast to the patients prescribed a potentially inappropriate medication identified in the first part of this study.

Our third objective was to use an innovative signal detection method called a receiver operating characteristic curve (ROC) analysis to meet objectives 1 and 2 above.

2. Methods

The 1,954 AD patients in this study were seen in 1 of 11 Alzheimer's Disease Research Centers or Alzheimer's Disease Centers of California. Patients were self-referred or refelTed by outside clinicians to one of these centers for further evaluation of possible dementia and potential involvement in research projects. All patients who presented for their first evaluation at one of the sites between December 31, 1997 and December 31, 2001 and had an initial consensus diagnosis of probable or possible AD by National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria [18] were included in the study. The patients' capacity to consent to this study was judged by a multidisciplinary consensus panel. If a patient was judged to be incapable of providing informed consent, a surrogate decision maker was evaluated, and if deemed appropriate and approved by the patient, assigned research durable power of attorney duties. This project was reviewed and approved by the appropriate institutional review boards. The demographic characteristics of the subjects are presented in Table 1.

Data from the initial evaluation were used to diagnose and determine the medications of the patient. Data were retrieved from the Minimum Uniform Data Set (MUDS), which is maintained by the Institute for Health and Aging for the Alzheimer's Disease Research Centers of California. This data set includes the conculTent medications recorded at the time of the visit as well as other demographic and clinical status measures.

We were interested in the subset of the Beers criteria medications with interference with cognition as a potential side effect. This included the majority of Beers-criteria medications (15 of 25). The revised list from 1997 was used, and only the medications deemed potentially inappropriate independent of diagnoses were used (Table 2).

The 1997, and not the 2003 criteria were used for several reasons: The 2003 criteria were not published until after our

Table I

Patient demographics

	All patients	On medication with potential to impair cognition	On cholinesterase inhibitor
No. of patients	1,954	296	865
Male	630 (32%)	69 (23%)	314 (36%)
Female	1,324 (68%)	227 (77%), *p* ::s 0.0004	55! (64%), *p* $ 0.001
Probable AD	1,293 (66%)	182(61%),p::So.07	587 *(68%),p* ::s 0.160
Possible AD	66] (34%)	114 (39%)	278 (32%)
Caucasian	1,391 (71%)	*206(70%),p::So.51*	662 (77%), *p* ::s 0.0001
Hispanic	270 (!4%)	*48(16%),p::So.19*	107 *(12%),p* ::s 0.010
African-Ameriean	126 (6%)	21 (7%), *p* ::s 0.62	40 *(5%),p* $ 0.004
Asian American	126 (6%)	16 *(5%),p* ::s 0.43	39 *(5%),p* ::s 0.002
Other ethnicity	41 (2%)	5 (2%)	17 (2%)
Taking vitamins	1,014 (52%)	140 (47%), *p* ::s 0.20	(524) *61%,p::s0.0001*
Mean age at enrollment	77.6 (8.1)	78.8 *(8.1),p* ::s 0.01	*77.0(7.5),p::S0.001*
Mean years of education	12.5 (4.2)	12.0 (4.4), *p* ::s 0.03	13.0 *(3.9),p* ::s 0.00!
Mean age at symptom onset	73.6 (8.6)	74.5 *(8.6),p* ::s 0.04	72.6 (8.3), *p* ::s 0.001
Mean no. of prescriptions	4.4 (2.5)	6.0 (2.8), *p* ::s 0.0001	4.7 (2.5), *p* $ 0.001
Mean no. of medical diagnoses	1.6 (].4)	1.8 *(1.4),p* $ 0.03	*1.4(1.3).p$0.001*
Mean MMSE	18.2 (6.9)	17.4 (7.6), *p* ::s 0.04	*!7.9(6.8),p::S0.08*
Mean BRDRS	5.3 (3.4)	6.0 (3.8), *p* $ 0.0004	5.4 *(3.5),p* ::s 0.29

NOTE Numbers in parentheses are one standard deviation for reported means. Percentages in parentheses are percentages of patients with the charaeteristic out of the total number of patients in each column. *p* value determined from univariate logistie regressions.

study was completed, the 2003 criteria rely more heavily than the 1997 criteria on diagnosis-specific potentially inappropriate medications (which is not as well suited to the analysis we used) and to facilitate comparison to the past literature on this topic. In the Beers criteria, benzodiazepines included individual medications as being potentially inappropriate if they were above a certain dose. We did not have records on specific doses of medications, so we were unable to determine if patients were above a certain dose. We also do not have information on as needed versus scheduled use. However, we felt that benzodiazepines were an important class of medications to analyze and so we included these medications in our analyses irrespective of dose.

The entire MUDS was reviewed, and variables that were judged as clinically significant were included in the analysis. These variables were age, gender, ethnic group, education, age of symptom onset, number of prescriptions, number of medical diagnoses, MMSE [19], BRDRS [20], and probable versus possible AD diagnosis. Data from the initial patient evaluation were used in the analysis.

Two families of multivariate statistical methods are used commonly to identify subgroups of individuals at elevated risk for a particular outcome. Linear models, including logistic regression analysis, are most commonly used. The other family, recursive partitioning, includes classification and regression trees (CART), y automatic interaction detection, and signal detection methods [21] .In this study, we chose to use a signal detection method, rather than logistic regression analysis, for several reasons. First, although logistic regression analysis is preferred for the testing of a priori hypotheses, signal detection techniques are designed for exploratory, hypothesis-generating studies such as this

Table 2

Type of medication used in patients taking a medication with potential to impair cognition

Medication	Percentage taking
Propoxyphene and combination produets	6.1
Indomethaein (Indocin, Indocin SR)	1.4
Pentazocine (Talwin)	0
Methocarbamol (Roxabin), carisoprodol (Soma), oxybutynin (Ditropan), chlorzoxazone (Paraflex), metaxalone (Skelaxin), and cyclobenzaprine (Flexeril)	18.2
Flurazepam (Dalmane)	1.7
Amitriptyline (Elavil), chlordiazepoxide amitriptyline (Limbitrol), and perphenazine amitriptyline (Triavi!)	8.8
Doxepin (Sinequan)	2.7
Meprobamate (Mi!town, Equanil)	0.7
Lorazepam (Ativan), oxazepam (Serax), alprazolam (Xanax), temazepam (Restoril), zolpidem (Ambien). triazolam (Halcion)	53.0
Chlordiazepoxide (Librium), chlordiazepoxide (Librax), and diazepam (Valium)	7.1
Reserpine (Serpasil), reserpine hydrochlorothiazide (Aldoril)	1.0
Dicyclomine (Bentyl), hyoscyamine (Lev sin, Levsinex), propantheline (Pro-Banthine), belladonna alkaloids Donnatal and others, cJidinium-ch]ordiazepoxide (Librax)	5.1
Antihistamines including chlorpheniramine (Chlor Trimeton), diphenhydramine (Benadry1), hydroxyzine (Visaril, Atarax), cyproheptadine (Periactin), promethazine (Phenergan), tripelennamine, and dexehlorphenirmaine (Polaramine)	10.8
All barbiturates except Phenobarbital	0
Meperidine	0

NOTE Because some patients were taking more than I medication with potential to impair cognition, the total percentage sums to greater than 100%.

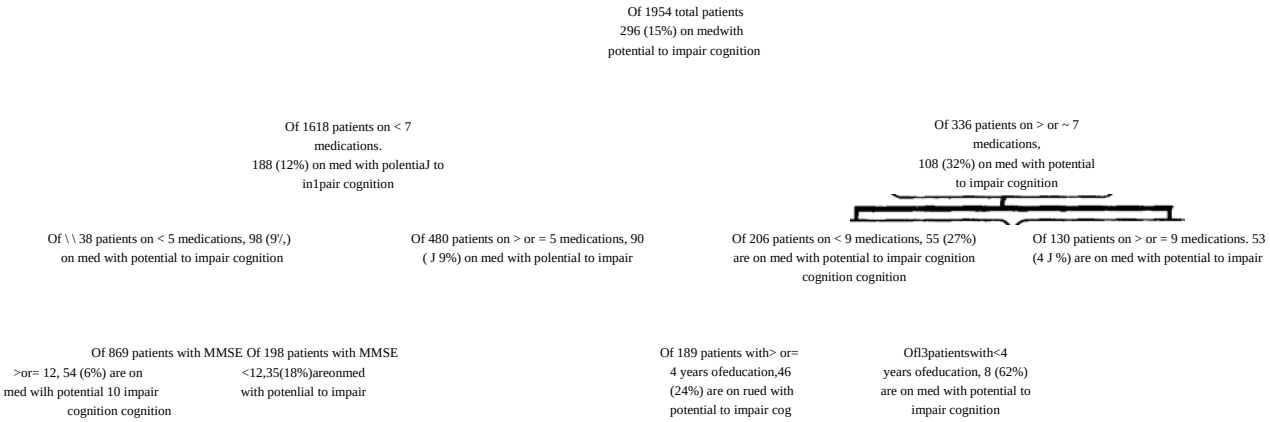

Fig I. ROC analysis of medications with potential to impair cognition.

one. The recursive partitioning process of signal detection techniques automatically and systematically examines a series of interactions [21] .In contrast, stepwise forward regression requires that the investigator enter alllower-order interaction terms before considering higher-order interactions [21] .These explicit decisions can affect the magnitude of the estimated weights and thus the identified predictors [22]. Second, if there are reasons to believe that predictors are collinear (as in this study), signal detection may be preferred to logistic regression, because collinear predictors can substantially bias the estimated weights for the predictors in all-in logistic regression, independent of the actual relationship between predictor and outcome [21,23,24]. Third, in stepwise-forward logistic regression, the main effect terms making up an interaction must be entered before the interaction term itself, which lowers statistical power to detect interaction terms [21,25].

The specific signal detection analysis we used is called a "receiver operating characteristic curve (ROC) analysis" because it calculates ROC curves to identify subgroups of a population at higher or lower risk for a dichotomous outcome of interest (in our case, use of a potentially inappropriate medication and the use of a cholinesterase inhibitor)

[21,23].

We used an ROC analysis to identify patient characteristics associated with prescription of either a potentially inappropriate medication or of a cholinesterase inhibitor. The procedure constructs ROC curves for each potential predictor variable and determines which variable best separates the larger group into 2 subgroups with the greatest purity of the dichotomous outcome of interest (i.e., the largest difference of prevalence) [21,23]. Each splitting variable must achieve a level of statistical significance of $p < 0.01$ or lower. After a split has been made, the program repeats the analysis on each of the subgroups to further divide the sample into subgroups having improved purity for the outcome of interest. The process repeats until the program can not identify a predictor that achieves signifi cance of $p < 0.01$, or the subgroup to be analyzed has 10 or fewer subjects, or after the program has reached 3 levels of analysis (i.e., creating a maximum of 8 subgroups). For continuous predictor variables (e.g., age), the procedure calculates ROC curves first for the lowest value in the data set, then for the lowest value plus 1, then plus 2, and so on, and ultimately selects the value with the best sensitivity and specificity. The ROC procedure can be set to differentially weight the analysis for sensitivity and specificity. Our analyses were set to equally weigh sensitivity and specificity thereby achieving both maximum sensitivity and maximum specificity. The ROC analysis software was developed at the Sierra-Pacific MIRECC at the Palo Alto Veterans Affairs hospital. The program is public domain and may be accessed at *http://mirecc.stanford. edu.*

3. Results

3.1. *Potentially inappropriate medication use*

In Fig. 1 at the top of the analysis, we can see that overall, 15% of patients were prescribed a potentially inappropriate medication that could interfere with cognition. Benzodiazepines were the most commonly prescribed class of medications. Looking at the first cutpoint in the ROC analysis, the number of prescriptions ("RxCount") ;::: or less than 7 medications best separates patients who are and are not prescribed a medication with potential to impair cognition (32% vs. 12%). After another split by number of prescriptions, those patients with education less than 4 years or patients with a MMSE score less than 12 were more likely to receive a medication with potential to impair cognition. Taking the extreme categories from Fig. I, a patient on 7 or 8 medications and who had less than 4 years of education was 10 times more likely to be on a medication with potential to impair cognition as a patient on less than 5 medications with a MMSE score of 12 or greater (62% vs. 6%).

The number of prescriptions was an important variable at

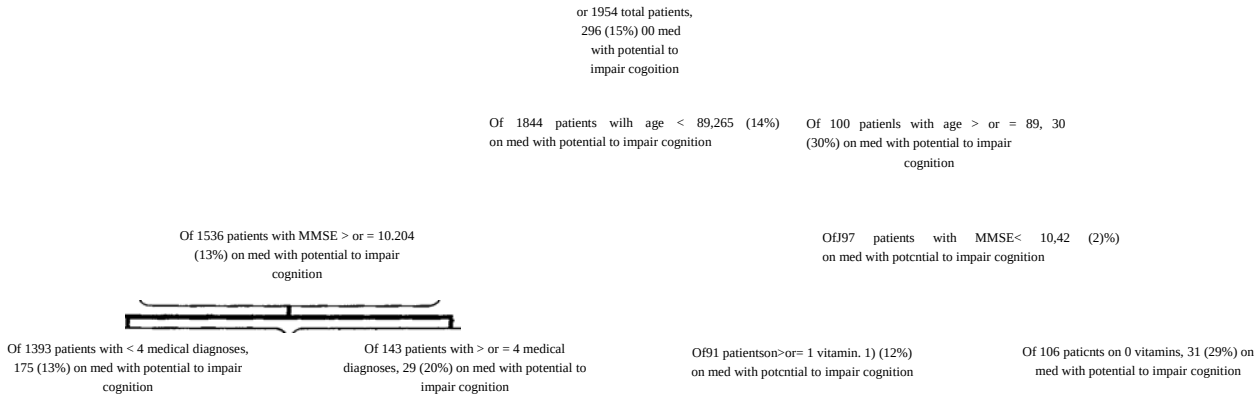

Fig 2. ROC analysis of medications with potential to impair cognition excluding number of prescriptions.

several steps in the analysis, as we expected based on the results of previous studies and because our outcome variable affects this variable. (Because we are looking at the possibility of being prescribed a certain medication, being prescribed one of these medications will affect the total number of prescriptions.) We therefore wanted to reanalyze the data without the influence of prescription number and so Fig. 2 is the same analysis as Fig. 1, excluding the number of prescriptions from the analyses.

If we drop the number of prescriptions from the analysis (Fig. 2), age, with patient age greater than or equal to 89 years, is the most predictive of which patients were more likely to receive a medication with potential to impair cognition (30% vs. 14%). Among the patients less than 89 years, prescription of a medication with potential to impair cognition was more likely if they had a MMSE score less than 10 and were not taking vitamins. In patients with an MMSE score ~ 10, ~4 medical diagnoses was associated with prescription of a medication with potential to impair cognition.

3.2. *Cholinesterase inhibitor use*

Forty-four percent of the patients were on a cholinesterase inhibitor at the time of their initial evaluation (Fig. 3). The greatest predictor of whether a patient was on a cholinesterase inhibitor was whether the patient was taking vitamins. Vitamin takers were more likely to be prescribed a cholinesterase inhibitor. Total number of prescriptions also predicted who was on a cholinesterase inhibitor. If we look at the ROC analysis without the inclusion of number of prescriptions (Fig. 4), we see that additional predictors of being on a cholinesterase inhibitor are fewer medical diagnoses, lower age of symptom onset, and education ~14 years. Looking at the most widely separated groups in Fig. 4, we see that a patient on vitamins, with fewer than 2 medical diagnoses and with symptom onset at less than 74 years old, was almost 3 times as likely to be on a cholinesterase inhibitor than a patient not on vitamins, with less than 14 years of education, with age of symptom onset at 80 years or older (65% vs. 23%).

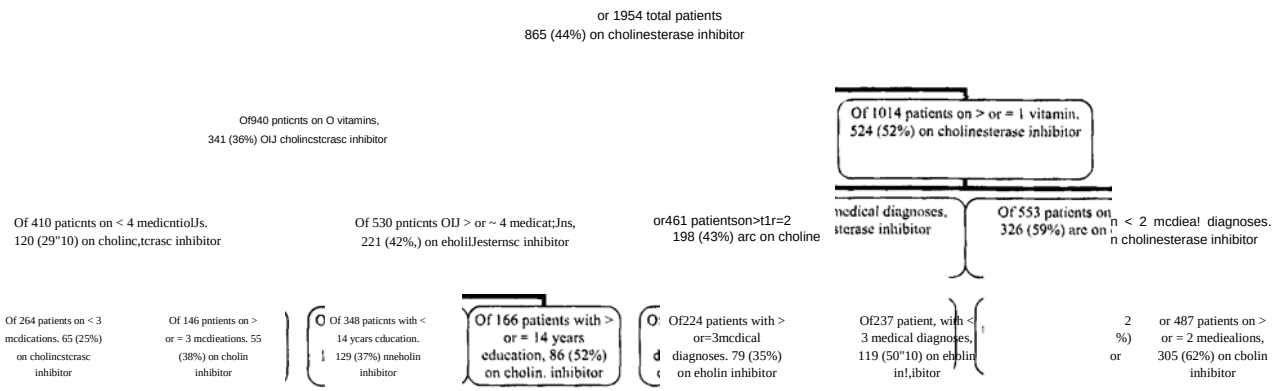

Fig 3. ROC analysis of cholinesterase inhibitor use.

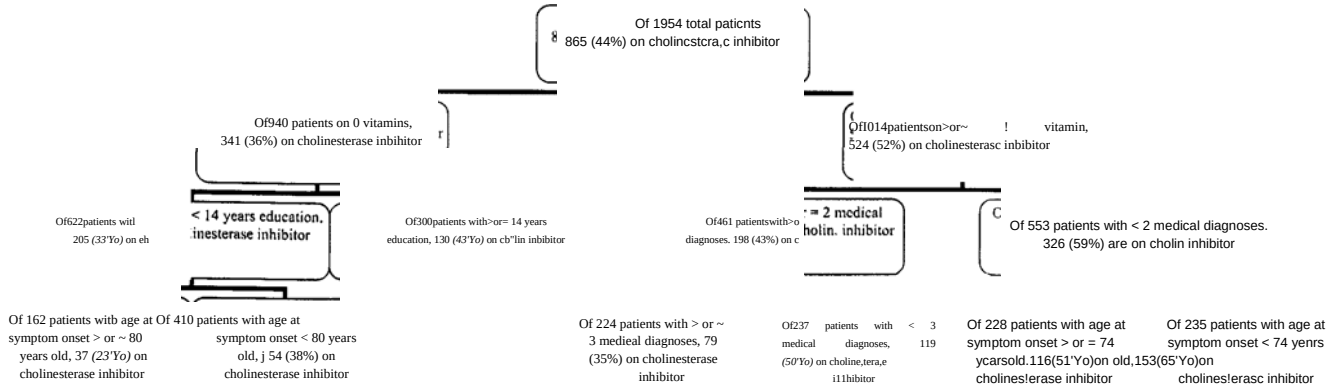

Fig 4, ROC analysis of cholinesterase inhibitor use excluding number of prescriptions.

3.3. *Variables chosen for analysis*

Univariate logistic regressions were performed on all of the independent variables that we selected for our analysis (Table 1). With the exception of one split on the basis of vitamin use at the third level of analysis of Fig. 2, all of the independent variables identified in the ROC analysis were significant in univariate logistic regressions. Note that this minor discrepancy does not mean that the ROC analysis was incorrect in this instance. Within the subgroup defined by the previous 2 splits, and removing the effect of number of prescriptions, the third level split on the basis of vitamin use in Fig. 2 was statistically significant at $p < 0.0\ 1$ in the ROC analysis.

3.4. *Center effects*

To test whether assessment center had an effect on our outcomes of interest, we reperformed with ROC analyses discussed above with the inclusion of assessment center as a variable. There were no differences on the 2 analyses on prescription of a medication with potential to impair cognition (Figs. I and 2) in the reanalysis. There was an effect of center on cholinesterase inhibitor use, but the effect was minor (at the third and final split level of the analysis). Patients not on vitamins with 4 or more prescriptions were more likely to be on a cholinesterase inhibitor if they were seen at the Martinez, Caljfornia sjte. Patients not on vitamins who had less than 14 years of education were more likely to be on a cholinesterase inhibitor if they were seen at the Martinez, California site. Otherwise, the analyses with and without assessment center were identical.

4. Discussion

Overall, 15% of patients were prescribed a potentially inappropriate medication that could interfere wjth cognition. This is on the low end of the range reported in previous studies of outpatient and nursing home elderly (14% to 40%) [10,11]. However, we would expect the number found in our study to be lower than that of previous studies for several reasons: We were only looking at a subset of the Beers criteria medications, dementia patients are hopefully less likely than non-demented patients to receive a medication that may interfere with cognition, and the patient population we analyzed is a research population that is likely highly motivated and more closely monitored compared to the general population. However, as previously noted, a significant proportion of subjects in previous studies on this topic suffered from dementia. We were unable to remove low dose benzodiazepines from our analysis as specified in the Beers criteria [3], and so 15 % may be an overestimation, especially since benzodiazepines were the most commonly prescribed class of Beers criteria medications in our sample. This is a serious limitation as benzodiazepines were the largest category of medications with potential to impair cognition prescribed. 7% of the patients were on both a medication with potential to impair cognition and a cholinesterase inhibitor. Note that we use the term "potential to impair cognition." The Beers criteria are guidelines and there may be instances where the best choice for an individual patient is a Beers criteria "potentially inappropriate" medication.

Our results agree with previous studies that the strongest single predictor for a patient being on a medication with potential to impair cognition is being on a high number of medications. Being on 7 or more medications almost tripled a patient's chance of being on a medication with potential to impair cognition. Our results also support previous papers that have reported older age and more medical diagnoses as significant predictors of being on a medication with potential to impair cognition. Lower education and lower MMSE have not been as consistently reported. It appears that older, sicker, less-educated dementia patients are at particular risk for receiving a medication that can impair cognition. Not taking vitamins is also a predictor of being on a medication with potential to impair cognition. This has not, to our knowledge, been reported. This information could help clinicians involved in quality improvement projects. For example, if a pharmacy wanted to assess whether patients with

dementia are on medications with potential to impair cognition, they could prioritize resources to patients identified in this study at particularly high risk for being on such a medication.

The patient characteristics that predicted cholinesterase inhibitor treatment are quite different than those that predicted medication with potential to impair cognition use. Taking vitamins was the single best predictor of a patient taking a cholinesterase inhibitor. Other predictors included fewer medical diagnoses, earlier symptom onset, and higher education. These characteristics are likely markers for healthier, health-literate patients who may be more likely to request a new medication from their physician. The process of the prescription of therapeutic medications is an under-researched topic.

Overall, 44% of our patients were taking a cholinesterase inhibitor. This is, however, a group of dementia patients referred to a research clinic during the years 1998 to 200 1 , and as such it represents a particular group of patients during a specific period. Preceding and during this period, more cholinesterase inhibitors were made available (tacrine in 1993, donepezil in 1996, rivastigmine in 2000, and galantamine in 2001), and the prescription of this class of medications gained acceptance in the medical community. We do not know how many patients during this period were on cholinesterase inhibitors in a general community sample or how the prescription rates have changed since then. Also, these results were obtained on a specific population and may not be generalizable to other populations. Another limitation of our study is, because it is cross-sectional, we can note associations, but we cannot assign causality. For example, low MMSE score could increase the chance of being prescribed a potentially inappropriate medication or it could be the result of the administration of a medication that interferes with cognition. Also, we do not know the temporal relationship of when medications were prescribed.

Signal detection analysis is well suited to the questions addressed in this study. It indicates not only which patient characteristics are associated with the outcome of interest, it gives the cutpoints that maximally sepaI-ate the patients on the outcome of interest. It also indicates which patients are at high or low risk for an outcome within groups already defined as high or low risk in previous levels of the analysis. The resulting "tree" display is clinically relevant and easy to understand for practicing clinicians.

A significant number of our dementia patients were on a potentially inappropriate medication that could interfere with cognition. These patients are likely to be at higher risk for adverse effects, as they tend to be on more medications, tend to be older, and have more medical diagnoses. Cholinesterase inhibitor use was associated with patient characteristics that are likely markers for patients who are more likely to seek new treatments for a disorder. Many of the patient chaI.acteristics associated with inappropriate medication use were the opposite of those associated with cholinesterase inhibitor use. The research on this topic demonstrates the complexity of medical care delivery to the elderly, the continuing need for highly trained prescribing physicians, and the need to develop new statistical methods to investigate the complex factors that influence medication prescription.

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