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Month/Year of Review: January 2012
PDL Class: Drugs for Alzheimer's disease (AD)

Date of Last Review: October 2006
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Current Preferred Agents:
Galantamine
Donepezil (Aricept®)
Memantine (Namenda®)

Current Non-Preferred Agents:
Rivastigmine (Exelon Patch®)
Donepezil ODT (Aricept ODT®)

Previous Recommendations

- There is insufficient evidence that any one of the AD drugs, donepezil, galantamine, rivastigmine, tacrine, or memantine is superior to the others in terms of efficacy or effectiveness.
- There is no evidence that any of the AD drugs prevent the progression of disability or delay institutionalization.
- Tacrine has an increased incidence of liver enzyme elevation compared to the other AD drugs.
- There is insufficient evidence that donepezil, galantamine, rivastigmine, or memantine has less adverse effects than each other.
- Memantine may have some pharmacological differences from the other medications, but there is inadequate data to conclude that these are clinically significant differences.

PA Criteria/QL:
Patient must have an OHP covered diagnosis

Methods:
A MEDLINE Ovid search was conducted using all treatments for AD and including: Alzheimer's Dementia, Alzheimer$, dementia$, anticholinergic agents, Anticholinergic$, donepezil, galantamine, memantine, rivastigmine. The search was limited to randomized controlled trials and meta-analysis, English language, and to studies conducted in humans from October 2009 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Systematic Reviews:
In April 2010, the AHRQ produced a comprehensive review of evidence based literature for Alzheimer's Dementia in preventing AD and cognitive decline (Appendix B).[1] This systematic review evaluated current evidence for interventions to prevent the onset of AD, as well as assessed research on risk factors and protective factors for the development of AD for possible development of recommendations for behavioral, lifestyle, or pharmaceutical interventions. This review did not evaluate treatment strategies or tolerability in established AD or treating symptoms associated with AD. Cholinesterase inhibitors were evaluated for any effect on the progression to AD or dementia as well as the ability to maintain or improve cognitive ability in patients who met diagnostic criteria for mild cognitive impairment. However, evidence was insufficient to currently support the use of pharmaceutical agents to prevent cognitive decline or onset of AD.

New Guidelines

The National Institute for Health and Clinical Excellence (NICE) revised evidence-based treatment guidelines in March 2011 using a rigorous literature search and critical appraisal method for donepezil, galantamine, rivastigmine, and memantine for the treatment of AD.[2] Recommendations include the following:

- The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine, and rivastigmine are recommended as options for managing mild to moderate AD.
- Memantine is recommended as an option for managing people with moderate AD who are intolerant or have a contraindication to AChE inhibitors or severe AD.
- Choice of AChE inhibitor should normally be started based on the lowest acquisition cost. An alternative agent can be used when if advantageous based on adverse effect profile, adherence, medical comorbidity, and possible drug interactions.
- There is insufficient evidence to differentiate between the AChE inhibitors in terms of clinical effectiveness.
- There is no evidence to suggest that AChE inhibitors affect survival or delay institutionalization.
- Fewer side effects are noted in patients treated with rivastigmine patches than with oral rivastigmine.
- Combination treatment with memantine and AChE inhibitors cannot be recommended because of lack of evidence of additional clinical efficacy compared with memantine monotherapy.

New FDA-approved drugs:

Aricept® (donepezil) 23mg, a new dosage strength of donepezil, was FDA approved in 2010 and is indicated for moderate to severe AD who have been on a dose of donepezil 10mg for at least three months.[3] Donepezil 23 mg was compared to donepezil 10 mg in 1,371 patients during a 24-week, randomized, double-blind trial.[4] The primary outcome was the Severe Impairment Battery (SIB) measure of cognition and the Clinician's Interview-Based Impression of Change Plus Caregiver Input Scale (CBIC-plus) measure of global function. The mean change of SIB score was significantly greater with donepezil 23 mg than with donepezil 10 mg (2.6 vs. 0.4, $p<0.001$). The CIBIC+ score was not different between the groups. There is no accepted clinically important change for SIB.[5]

In addition, a totally of 296 (30.2%) patients withdrew from the donepezil 23 mg group, and 87 (17.9%) patients withdrew from the donepezil 10mg group. About 19% of the discontinuations in the donepezil 23 mg group were due to adverse effects, compared to 8% in the donepezil 10mg group. The most common adverse effects in the 23mg and 10mg daily groups were nausea (11.8% vs. 3.4%), vomiting (9.2% vs. 2.5%), diarrhea (8.3% vs. 5.3%), anorexia (5.3% vs. 1.7%), and dizziness (4.9% vs. 3.4%).[3, 4]

FDA approval of donepezil 23mg was based on results from post hoc analysis showing an improvement in both SIB and CIBIC+ score with donepezil 23 mg in patients with more advanced AD

New Randomized Controlled Trials (RCT):

The MEDLINE search retrieved 172 full citations. After a review of citations and abstracts, 15 studies were identified for assessment. After a full review of citations and abstracts, six new head-to-head randomized control trials (RCT) were reviewed, including the study supporting approval of donepezil 23mg (Appendix A). Two small studies (Farlow 2010; Choi 2011) examined the benefit of adding memantine to the rivastigmine (Exelon®) patch. Neither study resulted in improved effectiveness, but one study observed increased adverse events with dual therapy (Farlow 2010). Another small RCT (Modrego 2010) compared memantine and donepezil head-to-head with clinical effectiveness as a secondary outcome. No significant difference was found between the two drugs in patients with mild to moderate AD. Finally, two small, separate ad hoc studies from the 2007 IDEAL trial looked at rivastigmine patch versus capsule data. The first (Lee 2011) examined the effect of body weight on adverse events and tolerability with both formulations. The other (Grossberg 2011) looked at the outcome of improved quality of life but observed no difference between the capsule and patch, although both were significant over placebo.

New FDA Indications:
None identified.

New FDA safety alerts:

Medication	Alert Date	FDA Alert
Rivastigmine transdermal system (Exelon Patch®)	August 2010	**Warnings and Precautions:** **Medication errors resulting in overdose.** Medication errors with Exelon patches have resulted in serious adverse events; some cases have required hospitalization, and rarely, led to death. The majority of medication errors have involved not removing the old patch when putting on a new one and the use of multiple patches at one time. Patients and caregivers must be given proper instruction on the dosage and administration of Exelon patches. **Adverse Reactions:** **Additional adverse reactions reported.** The following additional adverse reactions have been observed with Exelon capsules/oral solution. Confusion, abnormal liver function tests, duodenal ulcers.
Donepezil	November 2010	**Precaution:** **Drug interaction with ramelteon (Rozerem®).** Donepezil increases systemic exposure of ramelteon; patients should be closely monitored when ramelteon is co administered with donepezil.

Recommendations:

1. No further research or review needed.
2. Make Aricept 23mg non-preferred due to increased adverse drug events.
3. Add ProDUR edits to prevent duplicate therapy.

References:
1. Williams J, Plassman B, Burke J, Holsinger T, Benjamin S. Preventing Alzheimer's Disease and Cognitive Decline. Evidence Report/Technology Assessment No. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-1.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0008821/. Accessed January 24, 2012.

2. NICE. TA217 Alzheimer's disease - donepezil, galantamine, rivastigmine and memantine: guidance. *NICE*. 2011. Available at: http://www.nice.org.uk/. Accessed January 24, 2012.

3. Center for Drug Evaluation and Research. Application Number: 022568. Summary Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022568Orig1s000SumR.pdf.

4. Farlow MR, Salloway S, Tariot PN, et al. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. *Clin Ther*. 2010;32(7):1234-1251.

5. New dose of Aricept (donepezil): 23 mg. Pharmacist's Letter/Prescriber'sLetter 2010;26(9):260905.

Appendix A: Abstracts of new randomized controlled trials.

1. Modrego PJ, Fayed N, Errea JM, Rios C, Pina MA, et al. Memantine versus donepezil in mild to moderate alzheimer's disease: A randomized trial with magnetic resonance spectroscopy. European Journal of Neurology [Internet]. 2010; 17(3):405-12.

BACKGROUND AND PURPOSE: To compare memantine with the most prescribed cholinesterase inhibitor (donepezil) from a clinical viewpoint when administered in early phases of Alzheimer disease (AD), and to find out whether memantine may produce changes in brain metabolite concentrations in comparison with donepezil.
METHODS: In this comparative rater-blinded parallel group randomized trial we recruited a consecutive sample of patients with probable mild to moderate AD. At baseline we carried out neuropsychological assessment with mini-mental, Clinical Dementia Rating Scale (CDR), Blessed Dementia Rating Scale, Alzheimer's Disease Assessment Scale, cognitive part (ADAS-cog), neuropsychiatric inventory (NPI), and disability assessment for dementia (DAD), as well as (1)H magnetic resonance spectroscopy (MRS) in several areas of the brain. Patients were randomized to receive either donepezil or memantine for 6 months. After this elapse of time we repeated the same procedures and observed the changes in clinical scales (ADAS-cog, NPI, DAD), as well as the changes in metabolite levels in every area of exploration (temporal, pre-frontal, posterior cingulated (PCG), and occipital), especially those of N-acetyl-aspartate (NAA) which is regarded as a surrogate marker of neuronal density.
RESULTS: A total of sixty-three patients completed the trial. We did not see significant differences in clinical scales and metabolite levels between those on donepezil (n = 32) and those on memantine (n = 31). In general, more patients worsened than improved on either of the drugs. The changes in the NAA/creatine ratio in the PCG correlated significantly with the changes in the ADAS-cog (P = 0.004).
CONCLUSIONS: Donepezil and memantine have similar modest clinical and spectroscopic effect on mild to moderate AD. MRS could be useful to monitor progression of the disease.

2. Farlow MR, Alva G, Meng X, Olin JT. A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate alzheimer's disease: A post hoc analysis. Curr Med Res Opin [Internet]. 2010; 26(2):263-9.

OBJECTIVE: To investigate the tolerability and efficacy of the rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease receiving concomitant memantine.
RESEARCH DESIGN AND METHODS: Post hoc analysis of a 25-week, randomized, prospective, open-label, parallel-group study. Patients receiving donepezil were switched to rivastigmine patches (4.6 mg/24 h) immediately or following a 7-day withdrawal for 4 weeks (core phase), before titrating up to 9.5 mg/24 h for a further 20-week extension phase. Prior memantine therapy was continued throughout.
MAIN OUTCOME MEASURES: Tolerability (adverse events [AEs], serious AEs [SAEs] and discontinuations) and efficacy (cognition, global functioning and activities of daily living [ADLs]) were assessed for the rivastigmine transdermal patch, with or without concomitant memantine.
RESULTS: Overall, 135 and 126 patients received rivastigmine with and without memantine, respectively. Of these, 122 (90.4%) and 118 (93.7%) patients with and without memantine, respectively, completed the core phase; 120 and 114 patients, respectively, entered the extension phase, and 90 (75.0%) and 86 (75.4%) completed the study. The incidences of AEs (73.3 vs. 67.5%) and SAEs (10.4 vs. 7.1%) were both slightly larger in patients receiving concomitant memantine, but the differences were not statistically significant (95% CIs: -5.2, 16.9 and -3.6, 10.1 for AEs and SEAs, respectively). The incidence of gastrointestinal AEs was low in both groups. Discontinuation due to AEs was higher in patients who received memantine (17.0 vs. 11.9%). Changes in cognitive and global function were similar between groups. ADL scores worsened in both groups; significantly more in those treated with memantine.
CONCLUSION: Use of the rivastigmine transdermal patch in patients on established memantine appears to be well-tolerated, with only modest, non-significant increases in AEs compared with monotherapy, and did not seem to affect cognition or global functioning adversely.

3. Choi SH, Park KW, Na DL, Han HJ, Kim E-, Shim YS, Lee J-. Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate alzheimer's disease: A multicenter randomized, open-label, parallel-group study. Curr Med Res Opin [Internet]. 2011; 27(7):1375-83.

OBJECTIVE: To compare the tolerability and efficacy of combination therapy of memantine plus rivastigmine patch with rivastigmine patch monotherapy in patients with mild to moderate Alzheimer's disease (AD).
RESEARCH DESIGN AND METHODS: In this multicenter, randomized, open-label study, patients entered an 8-week run-in period (a 5 cm 2 rivastigmine patch for 4 weeks, then a 10 cm(2) patch for 4 weeks) followed by 16 weeks of memantine plus rivastigmine patch or rivastigmine patch monotherapy. The primary outcome measure was the retention rate at the end of the trial. Clinical trial registration: clinicaltrials.gov. NCT01025466.
RESULTS: Overall, 88 and 84 patients received rivastigmine patch with and without memantine, respectively, and of these, 77 (87.5%) and 70 (83.3%) patients completed the study. The difference in retention rate was not significant (95% confidence interval: -6.3-14.7%). The incidence of adverse events (AEs) (53.4 vs. 50.6%) and discontinuation due to AEs (6.8 vs. 4.8%) were not different between patients with and without memantine. The most frequent AEs were skin irritation in patients with and without memantine (42.0 vs. 34.9%, p = 0.71), but discontinuation due to skin irritation was rare (4.5 vs. 2.4%, p = 0.74). The incidence of gastrointestinal AEs was very low in patients with and without memantine (nausea, 2.3 vs. 1.2%; vomiting, 1.1 vs. 1.2%). The Korean Version of the Cohen Mansfield Agitation Inventory scores favored rivastigmine patch monotherapy at the end of treatment (p = 0.01). Changes in other efficacy measures were similar between the groups.
CONCLUSION: There were no significant differences in tolerability and safety between the treatment groups. The combination therapy of memantine plus rivastigmine patch did not show an advantage over rivastigmine patch monotherapy on efficacy analyses. The sample size for comparing tolerability may have been too small to detect a difference of efficacy between the two groups.

4. Lee J, Sevigny J. Effects of body weight on tolerability of rivastigmine transdermal patch: A post-hoc analysis of a double-blind trial in patients with alzheimer disease. Alzheimer Dis Assoc Disord [Internet]. 2011; 25(1):58-62.

OBJECTIVE: The rationale for the development of the rivastigmine transdermal patch was to improve upon an efficacious therapy by mitigating certain adverse events, such as nausea and vomiting. This may be particularly important in Alzheimer disease patients with low body weights, who may be more susceptible to these adverse events. This analysis compared the effect of body weight on tolerability in Alzheimer disease patients receiving rivastigmine capsules or rivastigmine patch. Using data from a 24-week trial, adverse events and discontinuations were evaluated in patients stratified on the basis of extreme low weight (<50 kg), medium weight (50 to 80 kg), and high weight (>80 kg) at baseline. Rivastigmine patch was generally well tolerated, regardless of patient body weight. Among patients receiving rivastigmine patch, lower body weight, as stratified, was not associated with a higher adverse event rate; however, there was an association between a higher adverse event rate and low body weight among patients receiving rivastigmine capsules. Discontinuations because of adverse events were not directly related to weight.A lower incidence of adverse events was apparent with transdermal delivery of rivastigmine compared with oral administration.

5. Grossberg G, Xiangyi Meng, Olin JT. Impact of rivastigmine patch and capsules on activities of daily living in alzheimer's disease. Am J Alzheimers Dis Other Demen [Internet]. 2011; 26(1):65-71.

BACKGROUND: Rivastigmine patches provide similar efficacy to rivastigmine capsules with a lower incidence of gastrointestinal side effects in patients with probable Alzheimer's disease (AD).
METHODS: Post hoc analysis of a 24-week, prospective, international, randomized, double-blind, placebo- and active-controlled trial. Patients (n = 892) with probable AD received rivastigmine transdermal patches (9.5 mg/24 hours [10 cm(2)]), rivastigmine capsules (6 mg twice daily), or placebo, and impact on activities of daily living (ADLs) was assessed utilizing 3 subscales: basic, high-level function, and autonomy.
RESULTS: At week 24, both rivastigmine groups demonstrated significantly superior performance in Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Total Score versus placebo (rivastigmine patch, P = .013; capsules, P = .039). Overall, both rivastigmine formulations provided benefits in ADL subscales. For basic ADLs, rivastigmine capsules performed significantly better than placebo (P = .012). For high-level function ADLs, rivastigmine patch performed better than placebo (P = .056). For autonomy ADLs, rivastigmine patch performed significantly better than placebo (P = .017).
CONCLUSION: Rivastigmine patches and capsules provide significant effects in both total and subscale ADLs in patients with probable AD.

6. Farlow MR, Salloway S, Tariot PN, Yardley J, Moline ML, et al. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe alzheimer's disease: A 24-week, randomized, double-blind study. Clin Ther [Internet]. 2010; 32(7):1234-51.

BACKGROUND: Currently approved Alzheimer's disease (AD) treatments have been reported to provide symptomatic benefit, without proven impact on clinical progression. We hypothesized that the loss of initial therapeutic benefit over time may be mitigated by higher doses of a cholinesterase inhibitor.
OBJECTIVE: The aim of this study was to determine the effectiveness and tolerability of increasing donepezil from 10 to 23 mg/d in patients with moderate to severe AD.
METHODS: This randomized, double-blind study was conducted at 219 sites in Asia, Europe, Australia, North America, South Africa, and South America from June 6, 2007, to March 27, 2009. Patients aged 45 to 90 years with probable AD, Mini-Mental State Examination score 0 to 20 (moderate to severe impairment), and who were

receiving donepezil 10 mg once daily for > or =12 weeks before the start of the study were eligible. Patients (n = 1467) were randomly assigned to receive high-dose donepezil (23 mg once daily) or standard-dose donepezil (10 mg once daily) for 24 weeks. Co-primary effectiveness measures were changes in cognition and global functioning, as assessed using least squares mean changes from baseline (LSM [SE] A) scores (last observation carried forward) on the Severe Impairment Battery (SIB; cognition) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input scale (CIBIC+; global function rating) overall change score (mean [SD]) at week 24. Treatment-emergent adverse events (TEAEs) were assessed using spontaneous patient/caregiver reporting and open-ended questioning; clinical laboratory testing (hematology, biochemistry, and urinalysis panels analyzed by a central laboratory); 12-lead ECG; and physical and neurologic examinations, including vital sign measurements.
RESULTS: The effectiveness analyses included 1371 patients (mean age, 73.8 years; 62.8% female; 73.5% white; weight range, 34.0-138.7 kg). A total of 296 of 981 patients (30.2%) withdrew from the donepezil 23-mg/d group; 87 of 486 patients (17.9%) withdrew from the donepezil 10-mg/d group. At study end (week 24), the LSM (SE) Delta in SIB score was significantly greater with donepezil 23 mg/d than with donepezil 10 mg/d (+2.6 [0.58] vs +0.4 [0.66], respectively; difference, 2.2; P < 0.001). The between-treatment difference in CIBIC+ score was nonsignificant (4.23 [1.07] vs 4.29 [1.07]). In post hoc analysis, LSM Delta in SIB score and CIBIC+ treatment effect at end point were greater with donepezil 23 mg/d than 10 mg/d in patients with more advanced AD compared with less impaired patients (SIB, +1.6 [0.78] vs -1.5 [0.88], respectively [P < 0.001]; CIBIC+, 4.31 [1.09] vs 4.42 [1.10] [P = 0.028]). TEAEs were reported in 710 of 963 patients (73.7%) who received donepezil 23 mg/d and in 300 of 471 patients (63.7%) who received donepezil 10 mg/d. With donepezil 23 mg/d, mild, moderate, and severe TEAEs were reported in 297 (30.8%), 332 (34.5%), and 81 (8.4%) patients, respectively; with donepezil 10 mg/d, these proportions were 147 (31.2%), 119 (25.3%), and 34 (7.2%). The 3 most common severe AEs reported with the 23-mg/d dose were nausea (9 patients [0.9%] vs 1 [0.2%] with the 10-mg/d dose), dizziness (7 [0.7%] vs 1 [0.2%]), and vomiting (6 [0.6%] vs 0). The most commonly reported TEAEs considered probably related to treatment with the 23-mg/d dose were nausea (59 patients [6.1%] vs 9 [1.9%] with the 10-mg/d dose), vomiting (48 [5.0%] vs 4 [0.8%]), and diarrhea (31 [3.2%] vs 7 [1.5%]).Thirteen deaths were reported during the study or within 30 days of study discontinuation (23 mg/d, 8 patients [0.8%]; 10 mg/d, 5 patients [1.1%]); all were considered unrelated to the study medication.
CONCLUSIONS: In this study in patients with moderate to severe AD, donepezil 23 mg/d was associated with greater benefits in cognition compared with donepezil 10 mg/d. The between-treatment difference in global functioning was not significant in the overall population. Patients with more advanced AD appeared to benefit from donepezil 23 mg/d on the assessment of global functioning, but this observation requires additional studies for confirmation.

Appendix B: Abstract of new Systematic Review.

1. Williams JW, Plassman BL, Burke J, Holsinger T, Benjamin S. Preventing Alzheimer's Disease and Cognitive Decline. Evidence Report/Technology Assessment No. 193. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290-2007-10066-I.) AHRQ Publication No. 10-E005. Rockville, MD: Agency for Healthcare Research and Quality. April 2010.

OBJECTIVES: To assess whether previous research on purported risk or protective factors for Alzheimer's disease (AD) and cognitive decline is of sufficient strength to warrant specific recommendations for behavioral, lifestyle, or pharmaceutical interventions/modifications targeted to these endpoints.
METHODS: A group of experts in the field developed the list of factors to be evaluated in preparation for an upcoming National Institutes of Health (NIH) Office of Medical Applications of Research (OMAR) State-of-the-Science Conference addressing the prevention of AD and cognitive decline. We grouped the factors into the following categories: nutritional factors, medical conditions and prescription and non-prescription medications, social/economic/behavioral factors, toxic environmental factors, and genetics. Outcomes of interest were the development of AD or cognitive decline. Both observational and intervention studies were evaluated. Studies were evaluated for eligibility and quality, and data were abstracted on study design, demographics, intervention or predictor factor, and cognitive outcomes.
RESULTS: A total of 25 systematic reviews and 250 primary research studies were included. Only a few factors showed a consistent association with AD or cognitive decline across multiple studies, including both observational studies and randomized controlled trials (when available). Such factors associated with increased risk of AD and cognitive decline were: diabetes, epsilon 4 allele of the apolipoprotein E gene (APOE e4), smoking, and depression. Factors showing a fairly consistent association with decreased risk of AD and cognitive decline were: cognitive engagement and physical activities. A consistent association does not imply that findings were robust, as the data were often limited, and the quality of evidence was typically low. In addition, the modification of risk for reported associations was typically small to moderate for AD, and small for cognitive decline. Some of the factors that did not show an association with AD or cognitive decline in this review may still play an influential role in late-life cognition, but there was not sufficient

evidence to draw this conclusion. Many of the factors evaluated are not amenable to randomization, so rigorous observational studies are required to assess their effect on AD and cognitive decline.
CONCLUSIONS: The current research on the list of putative risk or protective factors is largely inadequate to confidently assess their association with AD or cognitive decline. Further research that addresses the limitations of existing studies is needed prior to be able to make recommendations on interventions.