OREGON DUR BOARD NEWSLETTER©

AN EVIDENCE BASED DRUG THERAPY RESOURCE

Volume 6, Issue 7 | Also available on the web and via e-mail list-serve at http://pharmacy.oregonstate.edu/drug_policy/newsletter_email.htm | August 2004

Three New Classes Added to OHP Drug List

By Kathy L. Ketchum, BPharm, MPA:HA, OSU College of Pharmacy

This is the third article examining Oregon's landmark evidence-based OHP Drug List and will focus on the most recent Health Resources Commission (HRC) reports on angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs) and beta-blockers (BBs). [1, 2] A quality rating is provided for the evidence comparing a drug to other drugs rather than grading the evidence of efficacy compared to placebo. All studies were evaluated based on established standards for study design.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

The report described the relative effectiveness and safety in adults of the 10 ACEIs currently marketed in the United States for the following: hypertension, heart failure (HF), high cardiovascular (CV) risk, recent myocardial infarction (MI), and diabetic or non-diabetic nephropathy in the ambulatory setting.

The literature search identified 6,096 studies from all sources. Only 120 studies met inclusion criteria and were evaluated for the report (19 head-to-head trials, 44 placebo or active controlled trials, 8 systematic reviews and 1 observational study for adverse events). Efficacy measures varied somewhat by indication, but focused on mortality and other long-term outcomes rather than intermediate outcomes (i.e. reductions in blood pressure). The findings are summarized in Table 1.

TABLE 1 – SUMMARY OF COMPARATIVE EVIDENCE FOR ACEIS [3, 4]

Indication	Evidence Quality	Findings
Hypertension	Poor	No long-term outcomes assessed in head-to-head trials. There is no evidence to suggest that one ACEI is superior to another and there are no clear safety differences.
High CV Risk	Fair	There were no head-to-head trials. Ramipril (>10mg), perindopril and enalapril all reduce major CV events and CV mortality in patients with coronary artery disease. Only ramipril at doses >10mg reduced all-cause mortality in a single large study (NNT = 56).
Recent MI	Fair	In "good" quality placebo-controlled trials, captopril, lisinopril, ramipril (>10mg) and trandolapril all reduce mortality and heart failure in patients with recent MI. One small trial (n=225) comparing captopril to enalapril favored enalapril for all-cause mortality. Another trial found no significant difference in mortality between captopril and perindopril.
Heart Failure	Fair	Benazepril, captopril, enalapril, lisinopril, perindopril, quinapril, and ramipril reduce morbidity and mortality. The evidence was rated "good" for functional outcomes as 15 short-term head-to-head trials found no differences in symptoms for captopril, enalapril, fosinopril, lisinopril quinapril and ramipril.
Diabetic Nephropathy	Poor	No head to head trials. Captopril reduced End Stage Renal Disease (ESRD) and death, but only in patients with long-standing type 1 diabetes mellitus. ACEIs reduce albuminuria in type 2 diabetics, but have not been shown to prevent ESRD.
Non-diabetic nephropathy	Poor	1 placebo controlled trial of benazepril found it reduced the risk of ESRD by 50% in patients with renal insufficiency from various causes and no hypertension. 21% of patients had diabetic nephropathy.

Safety was evaluated using withdrawal rates as well as rates for specific adverse effects. Observational studies were included for this part of the review. There was no evidence to indicate one ACEI is safer than any other. There were no differences between ACEIs reported based on age. There was evidence that ACEIs are as effective in African Americans as Caucasians, but no data to suggest any ACEI is superior. There is evidence suggesting that ACEIs may be less effective in women for HF.

CALCIUM CHANNEL BLOCKERS

Similarly, the HRC reviewed the evidence for relative effectiveness and safety of nine CCBs marketed in the United States for the following: hypertension, angina, supraventricular arrhythmias, and heart failure (systolic dysfunction). The literature search produced 3,480 citations, of which 127 were included for evaluation. These included 91 unique trials (13 head-to-head, 57 active controlled and 21 placebo controlled). The HRC Subcommittee further divided this class into two subclasses – the dihydropyridines and the non-dihydropyridines.

Efficacy measures again varied by indication, and focused on long-term outcomes such as all-cause mortality, CV mortality and CV events. The efficacy findings are summarized in Table 2.

TABLE 2 – SUMMARY OF COMPARATIVE EVIDENCE FOR CCBS [5, 6]

Indication	Evidence Quality	Findings
Hypertension	Poor	No head-to-head trials. Evidence for amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine and verapamil from 12 long-term, active-controlled trials was insufficient to clearly differentiate one CCB from another for effectiveness or safety. No evidence was found for bepridil or felodipine.
Chronic Stable Angina	Good	Consistent evidence from 13 head-to-head trials does not differentiate among amlodipine, diltiazem, nisoldipine, nicardipine and nifedipine or between dihydropyridines and non-dihydropyridines for efficacy. Only indirect evidence was found for bepridil and verapamil and no evidence for felodipine or isradipine.
Supraventricular arrhythmias	Fair to Good	Consistent results in 3 fair quality head-to-head trials found no differences in efficacy or safety of diltiazem and verapamil for chronic atrial fibrillation. Evidence for other supraventricular arrhythmias was inadequate.
Systolic dysfunction co-morbid with hypertension, angina or atrial fibrillation	Fair	Consistent indirect evidence across six "fair-good" quality placebo-controlled trails of amlodipine and felodipine showed that both had neutral effects on all-cause mortality or combined fatal/non-fatal CV events. The evidence from 9 "fair" quality active or placebo-controlled trials indicates no difference among amlodipine, felodipine, nifedipine or nisoldipine on symptoms or exercise tolerance.

Safety was evaluated using withdrawal rates as well as rates for specific adverse effects in the studies reviewed for efficacy. However, in light of limited time and budget, observational studies were not included due to the large volume of data required to review. Thus, the relative safety of long-acting products over immediate release preparations was not fully addressed. There was not sufficient evidence to clearly differentiate one CCB over another for specific patient subgroups based on age, race, or gender.

BETA-BLOCKERS

The HRC reviewed the evidence for relative effectiveness and safety for 10 beta-blockers for the following: hypertension, stable angina, post-

coronary artery bypass graft, silent ischemia, recent MI, HF, atrial arrhythmias, migraine, and esophageal varices. Three beta-blockers (timolol, betaxolol, acebutolol) were inadvertently omitted from the literature search. The literature search produced 4,198 total citations.

Studies of adult patients were evaluated and again focused on long-term outcomes where possible. Considerable discussion and debate of the evidence for beta-blocker use in heart failure took place in the Subcommittee. The results are summarized in Table 3.

TABLE 3 – SUMMARY OF COMPARATIVE EVIDENCE FOR BETA-BLOCKERS [7, 8]

Indication	Evidence Quality	Findings
Hypertension	Poor	No head-to-head trials of long-term (> 6 months) health outcomes. Reliable indirect comparisons were not possible from 3 long-term placebo-controlled trials of atenolol and propranolol. No evidence of mortality benefit was found for use of beta-blockers in otherwise healthy patients with essential hypertension.
Angina	Poor	Atenolol, bisoprolol, carvedilol, labetolol, metoprolol immediate-release (IR), metoprolol extended-release (ER), nadolol, pindolol, penbutolol, propranolol IR and propranolol ER all reduced angina attacks in patients with stable angina in short-term studies. No differences were found in 4 head-to-head trials and no long-term studies met inclusion criteria.
Post coronary artery bypass graft	Poor	Beta-blockers have not been shown to improve mortality in post-CABG patients.
Silent ischemia	Poor	No head-to-head trials. One good quality, placebo-controlled trial found that atenolol reduced ischemic events in patients with mild or no angina.
Recent MI	Fair	Carvedilol, metoprolol IR and propranolol all decrease mortality in patients with recent MI compared to placebo. Similar mortality reductions were reported for atenolol and propranolol in one head-to-head trial.
Heart failure	Fair - Good	Bisoprolol, carvedilol, and metoprolol ER have similar effects on symptoms and all-cause mortality when compared to placebo. 1 fair quality head-to-head trial (COMET) favored carvedilol over metoprolol IR on the primary endpoint of all-cause mortality in patients with mild-mod HF. Only carvedilol and metoprolol ER reduced mortality in severe HF, but the current evidence does not distinguish a difference between them.
Atrial arrhythmia	Poor	There are no head-to-head trials. Limited evidence from placebo-controlled trials shows that atenolol, nadolol, pindolol, and propranolol, but not labetalol, were effective for rate control in atrial fibrillation. No beta-blocker was effective in preventing recurrence. No mortality or CV mortality data was identified.
Migraine prophylaxis	Poor	4 "fair" quality head-to-head trials of atenolol, metoprolol ER and IR each compared to propranolol did not clearly differentiate one drug from the others. Bisoprolol was effective compared to placebo and pindolol was not.
Bleeding esophageal ulcers	Poor	The current evidence does not distinguish a difference among atenolol, nadolol, propranolol, and propranolol ER.

Safety was evaluated using withdrawal rates and rates of specific adverse events. The Subcommittee concluded there was not evidence to distinguish one beta-blocker drug from others in terms of safety or when used in specific subgroups of patients by age, gender race or comorbidities.

CONCLUSION

The evidence findings of three classes recently reviewed by the HRC were reported. Complete evidence reports are posted to the www.oregonrx.org website under the "Oregon's Research" button. The Department of Human Services uses these findings in combination with drug cost to create the OHP Drug List (Table 4).

TABLE 4 – OHP DRUG LIST AUGUST 1, 2004

LONG-ACTING OPIOIDS	
methadone	$20
levorphanol	$90
Oramorph SR	$140
morphine-LA	$145
Avinza	$200
SKELETAL MUSCLE RELAXANTS	
cyclobenzaprine	$15
baclofen	$40
NSAIDS	
piroxicam	$2
ibuprofen	$5
naproxen	$10
TRIPTANS – cost for 9 tabs	
Imitrex	$140
Maxalt, Maxalt MLT	$145, $135
Zomig, Zomig ZMT	$140, $145
PPIs	
Prilosec OTC*	$20
URINARY INCONTINENCE	
oxybutynin IR	$10
ESTROGENS	
estradiol (oral)	$10
Menest	$25
Prefest	$30
Cenestin	$30
Premarin (oral)	$30
Prempro	$35
Premphase	$40
STATINS	
Lovastatin	$50
Altocor	$60
Lescol, Lescol XL	$55, $60
Lipitor	$70
Pravachol	$100
Zocor	$105

CALCIUM CHANNEL BLOCKERS	
verapamil IR	$5
diltiazem IR	$10
verapamil SA	$15
nifedipine IR	$15
Sular	$35
nicardipine IR	$35
Norvasc	$60
ACE INHIBITORS	
captopril	$5
enalapril	$10
captopril/HCTZ	$10
lisinopril	$10
Uniretic	$30
Lotensin/HCTZ	$35
Aceon	$40
Monopril	$40
Monopril/HCTZ	$40
BETA-BLOCKERS	
atenolol	$5
metoprolol IR	$5
propranolol	$5
pindolol	$5
nadolol	$20
labetolol	$25
bisoprolol	$25
propranolol LA	$25
Innopran XL	$25
Toprol XL	$30
ORAL HYPOGLYCEMICS	
tolbutamide	$3
glipizide	$4
glyburide	$10
glyburide, micronized	$10

Prices reflect average 30-day cost (excluding rebate) to OHP 1/1/04-3/31/04 unless otherwise noted. OHP patients have lower copays for generics (bolded).

* A NATION-WIDE SHORTAGE EXISTS; GENERIC OMEPRAZOLE IS AN ALTERNATIVE.

REFERENCES:

1. Ketchum, K. "HRC Reports Evidence in First Classes for OHP Drug Plan", Oregon DUR Board Newsletter. 4:4 Jun 2002 . Accessed 7/14/04. pharmacy.oregonstate.edu/drug_policy/news/5_7/5_7.html.
2. Ketchum, K. "The OHP Preferred Drug List: What is it, what's on it and why?", Oregon DUR Board Newsletter. 5:7 Sep 2003. Accessed 7/14/04. pharmacy.oregonstate.edu/drug_policy/news/4_4/4_4.html.
3. Oregon Health Resources Commission Angiotensin-Converting Enzyme Inhibitors (ACEIs) Subcommittee Report, November 2003. Accessed 7/14/04. www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
4. Oregon Health & Science University Evidence-based Practice Center, Drug Class Review on Angiotensin Converting Enzyme Inhibitors Oct 2003. Accessed 7/14/04. www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
5. Oregon Health Resources Commission Calcium Channel Blocker Subcommittee Report, October 2003. Accessed 7/14/04. www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
6. Oregon Health & Science University Evidence-based Practice Center, Drug Class Review on Calcium Channel Blockers. Sep 2003. Accessed 7/14/04. www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
7. Oregon Health Resources Commission Beta-Blocker Subcommittee Report, March 2004. Accessed 7/14/04. www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
8. Oregon Health & Science University Evidence-based Practice Center, Drug Class Review on Beta-Blockers. Sep 2003. Accessed 7/14/04. www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Reviewed by Roger Chou, MD, Marian McDonagh, PharmD, and Kim Peterson, MS, all at the OHSU Evidence-based Practice Center.

Oregon DUR Board Newsletter
Produced by the
OREGON STATE UNIVERSITY - COLLEGE of PHARMACY
Marquam II - 2611 SW 3rd Avenue Suite 280Z
Portland, OR 97201-4952
Managing Editor: Kathy L. Ketchum
Ketchumk@ohsu.edu or 503-494-1589