

WYOMING DRUG UTILIZATION REVIEW

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Essential Hypertension

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Definition of Essential Hypertension¹. Secondary causes of hypertension have been ruled out including renal parenchymal disease, renovascular disease, pheochromocytoma, Cushing syndrome, primary aldosteronism, coarctation of the aorta, and hereditary salt retention syndromes. Normal blood pressure is defined as an average resting blood pressure less than 120/80, stage one hypertension 140-159/90-99, and stage two hypertension is greater than 160/100. The blood pressure should be taken while the patient is seated and resting for at least 5 minutes and repeated with an average of the two given as the blood pressure.

History of Hypertension. In 1733, a pastor by the name of Stephen Hales records the first blood pressure by using an intra-arterial manometer on a horse. This device stood approximately 9 foot tall and was not terribly useful. Then in 1905 Kaorotkoff described the auscultory method of blood pressure measurement that is being used today. Of note, Karotkoff and most researchers use Karotkoff's first and fifth sounds (When the sound is first heard and when the sound is last heard, not when the sound changes) as their standards. Interest in hypertension as a cause of disease started in the early 1900's. In 1912 Janeway read a paper before the American Medical Association on 100 patients who died of hypertension. Although many physicians recognized hypertension as a problem little could be done because of a lack of effective treatments. In 1941 Flexnor read a paper before the Southern Medical Society that suggested 15% of all deaths were from hypertension. In 1945 President Franklin Roosevelt died from a hypertensive induced cerebral hemorrhage.

The Medical Treatment of Hypertension. In the early 1700s, a bounding pulse was treated with phlebotomy. Since that time, numerous medications have been tried for hypertension including tincture of iodine, spirits of nitre, sodium nitrite, nitroglycerin, veratrum viride, and morphine. All of these met with limited success because of side effects and/or extremely short duration of action. In 1903 Pauli describes the use of potassium cyanate. Few physicians utilized potassium cyanate because of the narrow therapeutic window and high death rate. In the 1930s several surgeons suggested lumbodorsal sympathectomy. Although this relieved hypertension, the patients found they could not stand without fainting. The first breakthrough in the treatment of hypertension occurred in 1949 when Wakil reported on the use of Rauwolfia Serpentina to treat hypertension. Two years later the pharmaceutical company Ciba refines Rauwolfia Serpentina into reserpine. Shortly thereafter Apresoline, the ganglionic blockers phenoxybenzamine and hexamethonium, and chlorothiazide were introduced. Searching for a medication with less side effects, once daily dosing, and that reliably reduced blood pressure; central alpha agonists, beta blockers, alpha adrenergic blocking agents, angiotensin converting enzyme inhibitors, calcium antagonist, and angiotensin II receptor blockers were introduced.

Hypertension and the Evidence. In the early 1900s actuarial data suggested hypertension lead to increased morbidity and mortality. This data was only used for insurance purposes until the 1960's when the Framingham study² showed clear evidence that hypertension lead to stroke, congestive heart failure, and coronary artery disease. Demonstrat-

ing that high blood pressure leads to an increased risk of morbidity and mortality led to an assumption that lowering the blood pressure would reduce those risks. And, in fact, the first outcome study was completed in the 1960's. The Veterans Administration cooperative study³ clearly showed that the treatment of diastolic hypertension with hydralazine or a diuretic reduced morbidity and mortality. Other studies including MRFIT, the Oslo study, SHEP, and others revealed most antihypertensives decreased morbidity and mortality. Many studies have shown the benefit of weight loss. The treatment of hypertension led to a marked decrease in stroke but only a minor decrease in cardiovascular disease. This led the researchers to develop newer antihypertensive agents in an attempt to decrease cardiovascular disease and develop an agent that could be taken once daily and with limited side effects. Then in 2002, the ALLHAT study⁴ (Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial, an eight year study with 42,418 participants) revealed the relative effectiveness of 4 different antihypertensive medications. This study compared a dihydropyridine calcium channel blocker (amlodipine), an alpha-blocker (doxazosin), an angiotensin converting enzyme inhibitor (lisinopril), and a diuretic (chlorthalidone). The alpha-blocker arm of the study was stopped early because of a 25% increase in cardiovascular disease and a 200% increase in congestive heart failure. The study also revealed that the diuretic was as good as or better than all the other medications in all other outcomes. Finally a medication met the criteria as a perfect antihypertensive agent. It could be taken once daily, it had few side effects, and it reduced morbidity over all other antihypertensive medications (except angiotensin II blockers). The VALUE trial⁵ compared a calcium channel blocker with an angiotensin receptor II blocker and found them to be equally efficacious. Currently a diuretic is the drug of choice in the treatment of hypertension unless the patient cannot tolerate a diuretic. In addition a diuretic has been the drug of choice for the past 20 years. A 22-pound weight loss yields about the same blood pressure lowering and decrease in both mortality and morbidity as any of the medications⁴.

Treatment of Hypertension in the Wyoming MEDICAID Population. When we examine the use of antihypertensive medications in the Wyoming MEDICAID population we find that less than 25% of the patients were on a diuretic. Switching these patients to a diuretic or adding a diuretic could save 27 patients from heart failure, 25 patients from cardiovascular disease, and 6 patients from a stroke annually. Total savings would be \$500,000.00⁷. Cost of antihypertensive medications for Wyoming MEDICAID recipients is \$2,000,000.00/ yr.

Wyoming MEDICAID hypertension medication usage. ACEI: 20,464; ARB: 7,582; ACEI/ARB with a diuretic: 5,200; Alpha-blocker: 1,948; Beta-blockers: 12,643; Calcium blockers: 11,702; Diuretics: 9,479.

Conclusions. Weight loss and regular exercise should be the treatment of choice for hypertension. When that fails a diuretic should be added. Those patients not currently taking a diuretic would benefit from adding or switching to a diuretic. Alpha-blockers should be avoided because of poor outcomes.

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The table provides cost estimates for a one month supply of drugs for essential hypertension. The price list is from www.drugstore.com.

Diuretics	Cost
Chlorthalidone 500 mg	7.99
chlorthalidone 25 mg	8.99
Dyazide 25/37.5	16.48
Enduron 2.5 mg	18.99
Enduron 10 mg	75.96
hydrochlorothiazide 25 mg	8.99
hydrochlorothiazide 12.5 mg	13.99
Microzide 12.5 mg	22.81
indapamide 2.5 mg	7.99
Lozol 2.5 mg	36.99
Maxide	18.94
Mykrox 0.5 mg	38.49
Zaroxolyn 2.5 mg	52.99
Zaroxolyn 5 mg	57.99
Demadex 5 mg	25.06
Edecrin 25 mg	35.91
furosemide 40 mg	8.99
Lasix 40 mg	11.44
Spironolactone 25 mg	9.99
Other	Cost
Hydralazine 25 mg	8.80
Inspira 50 mg	99.99
Inversine 2.5 mg	73.99
Loniten 10 mg	103.94
minoxidil 10 mg	35.99
reserpine 0.25 mg	11.90
Central alpha agonists	Cost
Clonidine 0.2 mg	10.99
Catapres 0.2mg	77.75
Catapres TTS II	87.24
Guanabenz 4 mg	55.35
Guanabenz 8 mg	93.66
Wytensin 4 mg	59.99
Wytensin 8 mg	88.99
Guanfacine 1 mg	20.99
Guanfacine 2 mg	25.99
Tenex 1 mg	59.99
Tenex 2 mg	100.73
methyl dopa 250 mg	12.99
methyl dopa 500 mg	13.99
Calcium channel blockers	Cost
Norvasc 5 mg	42.99
Norvasc 10 mg	60.99
Procardia 30 mg	44.02
Procardia 60 mg	85.89
Adalat CC 30 mg	41.59
Adalat CC 90 mg	81.99
Nifedipine 30 mg	25.99
Nifedipine 90 mg	60.99
DynaCirc 5mg	49.04
DynaCirc 10 mg	87.40
Plendil 5 mg	34.99
Plendil 10 mg	59.99
Cardene SR 30 mg	53.99
Cardene SR 60 mg	97.99
Sular 20 mg	38.84
Sular 40 mg	45.99
Verapamil CR 120 mg	17.99

Calcium channel blockers	Cost
Verapamil CR 240 mg	12.99
Verapamil ER 120 mg	25.99
Verapamil ER 240 mg	37.99
Calan SR 120 mg	39.23
Covera HS 180 mg	44.47
Covera HS 240 mg	60.99
Isoptin SR 120 mg	35.99
Isoptin SR 240 mg	49.94
Verelan p.m. 120 mg	42.39
Verelan p.m. 240 mg	75.49
diltiazem SR 60 mg	29.99
diltiazem SR 120 mg	64.99
Cardizem CD 120 mg	31.99
Cardizem CD 360 mg	94.99
Cardizem LA 120 mg	39.89
Cardizem LA 420 mg	78.58
Cartia XT 120 mg	31.99
Cartia XT 300 mg	69.99
Diltia XT 120 mg	27.99
Diltia XT 240 mg	34.99
Dilacor XR 120 mg	42.99
Dilacor XR 240 mg	59.99
Tiazac 120 mg	37.43
Tiazac 360 mg	81.11
Beta blockers	Cost
Atenolol 100 mg	13.99
Tenormin 100 mg	58.56
propranolol 40 mg	7.99
propranolol 80 mg	12.99
Inderal LA 80 mg	45.10
Inderal LA 160 mg	73.03
Inopran XL 80 mg	39.09
Inopran XL 120 mg	40.24
Acebutalol 400 mg	21.99
Acebutalol 1200 mg	66.92
Sectral 400 mg	98.18
Sectral 1200 mg	294.54
Betaxolol 10 mg	28.75
Betaxolol 20 mg	36.59
Bisoprolol 10 mg	33.99
Zebeta 10 mg	45.10
Cartelol 5 mg	41.24
Coreg 25 mg	94.99
Corgard 40 mg	54.99
Corgard 80 mg	69.99
Kerlone 10 mg	33.99
Levetol 20 mg	51.83
Lopressor 100 mg	88.13
Metoprolol 100 mg	13.99
Toprol XL 100 mg	31.99
Nadolol 80 mg	17.77
Nadolol 160 mg	33.59
Normodyne 200 mg	50.99
Normodyne 300 mg	66.99
Pindolol 10 mg	15.13
Timolol 10 mg	15.99
Timolol 20 mg	31.99
Trandate 200 mg	50.99
Trandate 400 mg	66.99

Angiotensin II receptor blockers	Cost
Atacand 16 mg	41.99
Atacand 32 mg	55.99
Avapro 150 mg	45.99
Avapro 300 mg	52.99
Benicar 20 mg	43.01
Benicar 40 mg	43.00
Cozaar 50 mg	43.99
Cozaar 100 mg	59.99
Diovan 80 mg	46.99
Diovan 320 mg	187.96
Micardis 40 mg	44.80
Micardis 80 mg	46.37
Teveten 400 mg	30.99
Teveten 600 mg	41.00
Angiotensin Converting Enzyme Inhibitors	Cost
Accupril 20 mg	35.99
Accupril 40 mg	35.99
Aceon 4 mg	41.77
Aceon 8 mg	51.93
Altace 5 mg	76.99
Altace 10 mg	92.99
captopril 50 mg	12.99
captopril 100	16.99
Capoten 50 mg	119.87
Capoten 100 mg	146.99
enalapril 5 mg	10.99
enalapril 20 mg	10.99
Vasotec 5 mg	33.99
Vasotec 20 mg	47.99
lisinopril 10 mg	18.99
lisinopril 40 mg	24.99
Prinivil 10 mg	29.50
Prinivil 40 mg	47.99
Zestril 10 mg	30.99
Zestril 40 mg	47.99
Lotensin 20 mg	33.99
Lotensin 40 mg	33.99
Mavik 2 mg	29.99
Mavik 4 mg	29.99
Monopril 20 mg	71.99
Monopril 40 mg	69.99
Univasc 7.5 mg	34.14
Univasc 30 mg	53.98
Alpha blockers	Cost
Cardura 2 mg	36.75
Cardura 8 mg	41.08
Doxazosin 2 mg	19.99
Doxazosin 8 mg	23.99
Hytrin 1 mg	63.65
Hytrin 10 mg	63.65
Terazosin 1 mg	13.99
Terazosin 10 mg	13.99
Minipress 3 mg	46.94
Minipress 5 mg	78.58
Prazosin 2 mg	16.99
Prazosin 5 mg	25.99

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Current Treatment Guidelines for COPD

Brett Brasfield, PharmD Candidate

The Institute for Clinical Systems Improvement¹ and the National Heart, Lung and Blood Institute² have recently issued guidelines for the treatment of COPD. The tables below are adapted from each of these sources.

Inhaled bronchodilators are the first-line treatment of an acute exacerbation of COPD.³ Albuterol is preferred due to its rapid onset of action. Serial administration is indicated until relief of symptoms is achieved or until side effects such as tachycardia or tremor develop. If side effects develop before clinical improvement, ipratropium bromide should be added to increase bronchodilation, while allowing for a lower dose of albuterol.¹ If the patient is too dyspneic or coughing too severely to retain a MDI inhalation, nebulization is necessary. Xopenex (levalbuterol), the R isomer of albuterol, has theoretical advantages over albuterol, but greater bronchodilation has not been shown in studies.¹ Oral prednisone at 30-60 mg per day can be added if necessary. Inhaled corticosteroids can also be used. Both can be used concomitantly with the inhaled steroid serving to lower the needed dose of systemic steroid.¹

Antibiotics should not be used for an acute exacerbation of COPD if a virus is clearly the cause. An antibiotic may be warranted in the case of prolonged illness with purulent sputum.¹ Amoxicillin, trimethoprim/sulfamethoxazole, doxycycline, and erythromycin are often effective. Second-generation cephalosporins, azithromycin, clarithromycin, and amoxicillin/clavulanate are often effective if a resistant organism acquired from the community is suspected.¹

References

1. Institute for Clinical Systems Improvement (ICSI). Chronic obstructive pulmonary disease. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI);2003 Dec. 67 p. [113 references]
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization, National Heart, Lung and Blood Institute; 2004. 100 p.

Abbreviations: FEV₁ – Forced expiratory volume in one second; FVC – Forced vital capacity

Therapy at Each Stage of Stable COPD ¹					
	0: At Risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
Characteristics	Chronic symptoms	FEV ₁ /FVC < 70% FEV ₁ > 80% With or without symptoms	FEV ₁ /FVC < 70% 50% < FEV ₁ < 80% With or without symptoms	FEV ₁ /FVC < 70% 30% < FEV ₁ < 50% With or without symptoms	FEV ₁ /FVC < 70% FEV ₁ < 30% or FEV ₁ < 50% Predicted plus chronic respiratory failure symptoms
	Avoidance of risk factor(s); Influenza vaccination.				
		Add short-acting bronchodilator when needed.			
			Add regular treatment with one or more long-acting bronchodilators.		
				Add inhaled glucocorticosteroids if repeated exacerbations.	
					Add long-term oxygen if chronic respiratory failure.

Step-Care Pharmacologic Treatment of Stable COPD ²		
Step	Pharmaceutical Intervention	Dosing and Comments
1	Inhaled short-acting bronchodilator	Albuterol preferred – 2-4 puffs Q 4-6 H PRN
2	Continue PRN inhaled short-acting bronchodilator + one of the following as a scheduled dose: Preferred: salmeterol or formoterol Alternatives: albuterol, ipratropium or albuterol + ipratropium or levalbuterol	1 puff BID 2-4 puffs QID 2-4 puffs QID 0.63-1.25 mg Q 6-8 H via nebulizer
3	Continue step 2 therapy and perform a corticosteroid trial. Assess symptoms before and after trial period.	Prednisone PO 30-40 mg/day for 2-4 weeks or an inhaled corticosteroid for 6-12 weeks. Beclomethasone at 1600 mg per day or equivalent dose of another inhaled steroid is required.
	Positive Response	Negative Response
4	≥ 15% improvement in post-bronchodilator FEV ₁ Taper off or discontinue oral corticosteroid and prescribe or continue inhaled corticosteroids.	< 15% improvement in post-bronchodilator FEV ₁ Discontinue corticosteroids and consider theophylline as adjunctive therapy with inhaled beta ₂ -agonists and/or ipratropium. The therapeutic range of theophylline is 10-20 mcg/ml, but 5-15 mcg/ml may be equally efficacious. Discontinue theophylline if not effective.

Wyoming Drug Utilization Review Website
www.uwyo.edu/DUR

Wyoming Preferred Drug List Website
www.uwyo.edu/PDL

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