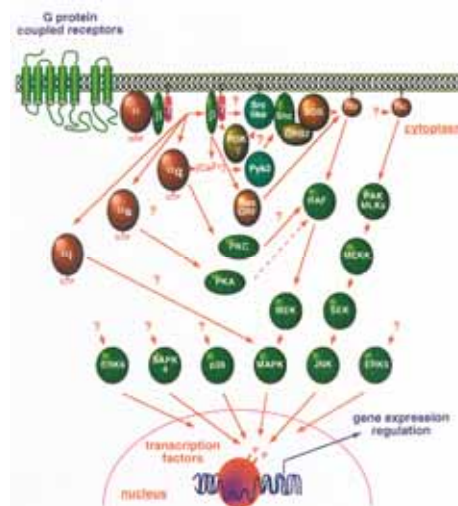# Layered Approaches to Studying Drug Responses

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Chief of Medicine
VA Boston Health Care System
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Conflict of Interest: US Federal Grant Funding

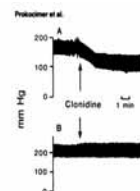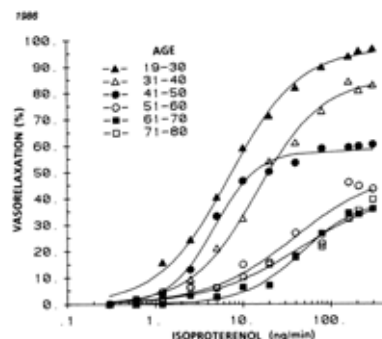---

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Blood Pressure in rats Harboring Pheochromocytoma

Definition of a Clinical Pharmacologist

A clinical pharmacologist is a clinician who understands the dose response curve.

John Ruedy ~ 1960's

Beta Receptor Mediated Vascular Relaxation with Aging

Improving Drug Therapy Decisions

- Educating clinicians about drugs
  - Teaching at site of care: Ogilvie RI, Ruedy J. An educational program in digitalis therapy. JAMA 222:50-5, 1972.
  - Courses, seminars, road shows: (BC Therapeutics Initiative)
  - Newsletters, books, journals etc
- Guidelines
  - Challenge to remember and apply to individual patients, and often have insufficient information

Multiple Therapeutic Guidelines

- National Guideline Clearinghouse

- http://www.guideline.gov.laneproxy.stanford.edu/

- Chemicals and Drugs (MeSH Category) - List all 1066 guidelines

- Cardiovascular Agents - List all 116 guidelines

- Anti-Arrhythmia Agents - 15 guidelines
  Antihypertensive Agents - 30 guidelines
  Calcium Channel Blockers - 34 guidelines
  Cardiotonic Agents - 5 guidelines
  Fibrinolytic Agents - 32 guidelines
  Sclerosing Solutions - 1 guideline
  Vasoconstrictor Agents - 15 guidelines
  Vasodilator Agents - 10 guidelines

Why Hypertension?

We selected hypertension as a model for guideline implementation because…

- Hypertension is highly prevalent in adult medical practice
- There are excellent evidence-based guidelines for management
- There is also evidence that the guidelines are not well-followed

Algorithm for Treatment of Hypertension (JNC 7)
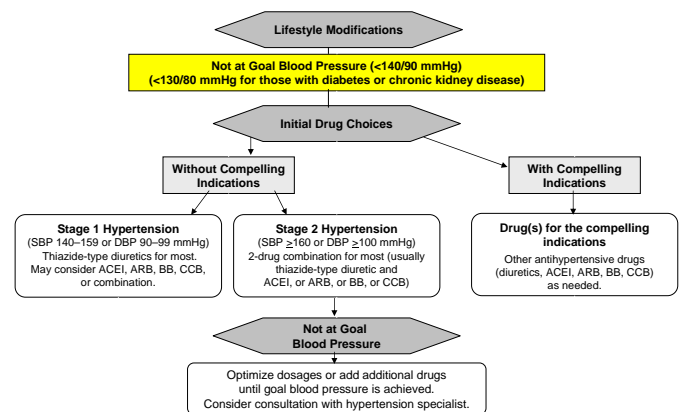
Compelling Indications for Individual Drug Classes

- Heart Failure
  - Beta blockers, ACEI, ARB, Aldo Antagonist
- Post-MI
  - Beta blockers, ACEI
- Post-MI
  - Beta blockers, ACE, CCB
- Diabetes
  - Thiazides, beta blockers, ACEI, ARB, CCB
- Chronic kidney disease
  - ACEI, ARB

Additional Considerations in Antihypertensive Drug Choice
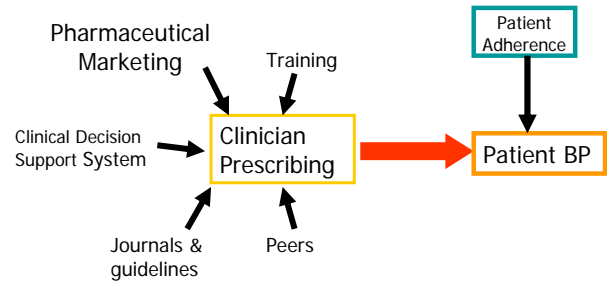
Potential favorable effects
- Thiazide diuretics in osteoporosis
- Beta blockers in treatment of atrial tachyarrhythmias/fibrillation, migraine prophylaxis, essential tremor etc
- Calcium channel blockers in Raynaud's syndrome and some arrhythmias
- Alpha1 receptor antagonists in benign prostatic hyperplasia

Additional Considerations in Antihypertensive Drug Choice

Potential unfavorable effects

- Thiazides used cautiously in gout or history of hyponatremia
- Beta blockers generally avoided in asthma or high degree heart block
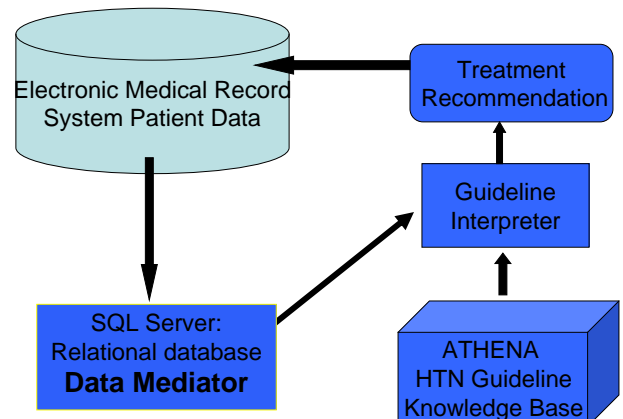- ACEIs and ARBs contraindicated in pregnant women

Conceptualization of Impact of Decision Support System

Pharmaceutical Marketing

Training

Patient Adherence

Clinical Decision Support System → Clinician Prescribing → Patient BP

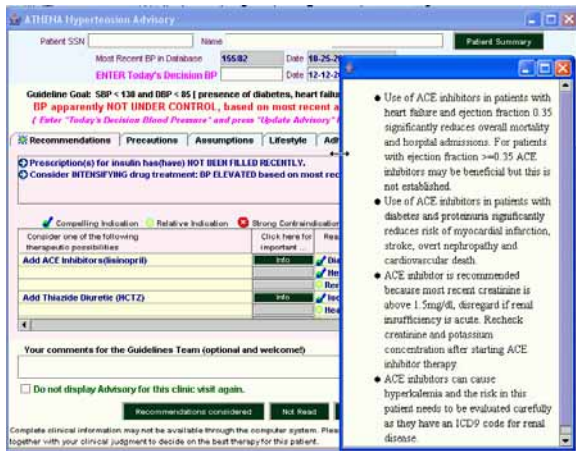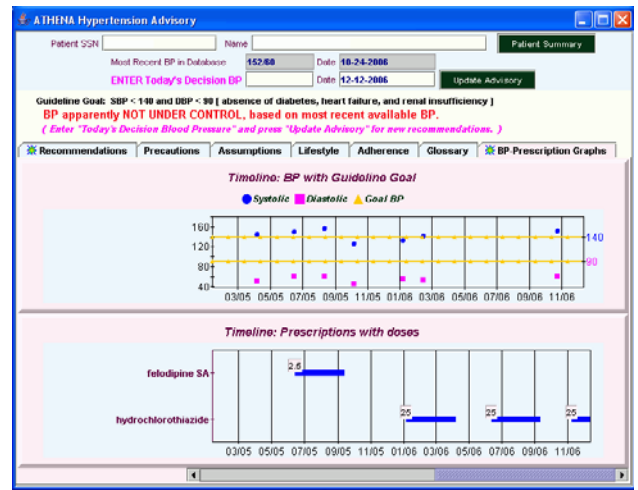Journals & guidelines

Peers

What is ATHENA DSS?

- Automated decision support system (DSS)
  - Knowledge-based system automating guidelines
    - Built with EON technology for guideline-based decision support, developed at Stanford Medical Informatics
  - For patients with primary hypertension who meet eligibility criteria
- Patient specific information and recommendations at the point of care
- Purpose is to improve hypertension control and prescription concordance with guidelines

ATHENA Architecture

Electronic Medical Record System Patient Data

Treatment Recommendation

Guideline Interpreter

SQL Server: Relational database **Data Mediator**

ATHENA HTN Guideline Knowledge Base

What the Clinician Sees…
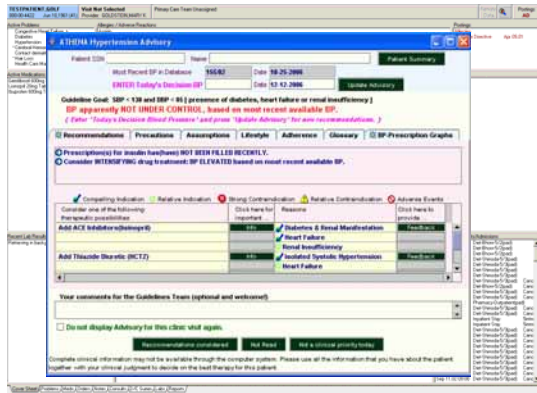
See Rules document for details on knowledge in ATHENA DSS

ACP

BMJ Clinical Evidence

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Study Design

- Multicenter Randomized Controlled Trial
- Subjects: Primary care clinicians (attending physicians, registered nurse practitioners & physician assistants)
- Unit of Randomization: clinician-clusters
- Setting: VA primary care clinics in 3 distinct medical centers: Palo Alto (CA), San Francisco (CA) & Durham (NC)
- Duration: 15 months

Primary Outcomes

1. Clinician Prescribing
   - Rate of intensification of antihypertensive drug therapy at first visit when patient's blood pressure (BP) was above target

2. Patient outcome
   - Change in Systolic Blood Pressure (SBP) from baseline to endpoint

Study Sample

- 91 clinician-clusters
  - 47 ATHENA
  - 44 Active control
- SBP analysis
  - 34,427 visits of 11,473 patients
- Intensification of therapy analysis
  - 9,492 patients with a BP above target

Baseline Comparison

	ATHENA GROUP	ACTIVE CONTROL
	47 clusters 5,254 pts	44 clusters 6,219 pts
SBP mean (SD)	140 (3)	139 (3)
DBP mean (SD)	76 (3)	76 (3)
BP > Target	61.8%	61.3%
Number anti-hypertensive drugs mean (SD)	1.5 (0.17)	1.5 (0.16)

No significant difference between study groups

Mean Number of Visits

ATHENA Group   3.3 (SD 0.64)
Active Control   3.3 (SD 0.48)

Rate of Intensification of Therapy

- 1st visit with BP above target
- **Odds Ratio 1.26 (95% CI 1.01 - 1.57)**
  - **ATHENA Group 30.5%**
  - **Active Control Group 25.7%**

Layers of Clinical Pharmacology

- Molecular Pharmacology
- Animal Models
- Human Pharmacology
- Clinical Trials
- Pharmaco-epidemiology
- Pharmaco-genomics
- Pharmaco-economics