Clinical Effectiveness, Clinical Utility and Comparative Effectiveness: An Evolving Landscape

Gurvaneet Randhawa, MD, MPH
Center for Outcomes and Evidence
Senior Advisor on Clinical Genomics and Personalized Medicine

SACGHS: June, 2009

“ In theory, theory is just like practice. In practice, it ain’t.”

– Yogi Berra

Lost in (Research) Translation

Three major hurdles:

- Pre-clinical to clinical efficacy
- Clinical efficacy to effectiveness
- Effectiveness to implementation & use

Efficacy vs. Effectiveness

- Observed benefits and harms of an intervention in clinical practice differs from expected (from efficacy studies)

- Why?

Patient Factors Influencing Effectiveness of Therapies

- Biology
  - Age
  - Sex
  - Co-morbidities
  - Disease severity
  - Genetic variations
- Other: adherence, cost, preferences, drug-drug interactions

Other Factors Influencing Effectiveness

- Natural history of disease
  - surrogate vs. health outcomes
- Provider: training/skills, experience (e.g. volume of procedures), preferences, time, coverage, liability
- Hospital: volume, availability of devices/tests/therapies, specialty care (e.g. anticoagulation clinics)

Example: Warfarin

- Reduces thromboembolic events
- Commonly prescribed
- Narrow therapeutic index: excessive anti-coagulation can lead to bleeding
- Challenges: INR monitoring, drug-drug and diet-drug interactions, adherence

INR Monitoring

- Target range: week – 85%, month – 50%
- Self-monitoring may be useful
- Meta-analysis of 14 RCTs on self-monitoring (± self-adjusting dose) shows:

SM: ↑ mean INR in target range (6/11-signf.)

SM: ↓ thromboembolic events (OR=0.45)

SM: ↓ major hemorrhage (OR=0.65)

SM: ↓ mortality (OR=0.61)

Lancet 2006; 267:404-11

Distinguishing Effectiveness from Efficacy Trials

- Primary care population
- Stringency of inclusion/exclusion criteria
- Health outcomes
- Length of study
- Assessment of adverse events
- Adequate sample size
- Intention to treat analysis

AHRQ EPC report, 2006

Trade-offs

- Efficacy trials: high internal validity, poor applicability, small sample, fast, less cost
- Effectiveness trials: high applicability, large sample, slow, expensive

Health Utility: Outcome Measure

- Measures preference for health state [perfect health=1, death=0]
- Can be measured as an outcome in a study
- Calculate quality-adjusted life year (QALY), DALY etc.
- QALY often used in modeling studies (DA, CEA) to compare different interventions

Clinical Utility

- EGAPP: includes effectiveness and net benefit, sometimes efficacy
- Examples: health outcomes, information useful for clinical decision making, end diagnostic odyssey, improve adherence

Genetics in Medicine; 2009

- Conceptually closer to a “decision” rather than “outcome” of an intervention

From Outcomes to Decisions

- Efficacy: outcomes in ideal setting
- Effectiveness: outcomes in real-world
- Comparative efficacy (head-head trials)
- Comparative effectiveness

Decision-making Questions

- What are the (health) benefits?
- What are the harms?
- Will there be net benefit in the real-world?
- What is the incremental benefit?
- What is the feasibility?
- What is the cost-effectiveness and cost?
- Other issues: preferences, convenience, coverage/reimbursement etc.

EB(D)M ≠ RCT

- USPSTF recommendations in absence of RCT data
  - cervical cancer screening
  - PKU screening
- EPC report on obesity Rx:
  - surgery more effective for BMI>40

AHRQ website

Comparative Effectiveness

- What?

  Clinical interventions: test, device, drug, dietary supplement, biologic, surgical procedure, counseling/behavioral intervention etc.

Methods (how?)

- Design:

a) Experimental: RCT (head-to-head, effectiveness), cluster randomized trials

b) Observational: cohort, case-control

c) Modeling

d) Systematic reviews, meta-analyses

- Analytic techniques: approaches to minimize bias and confounding (improve internal validity)

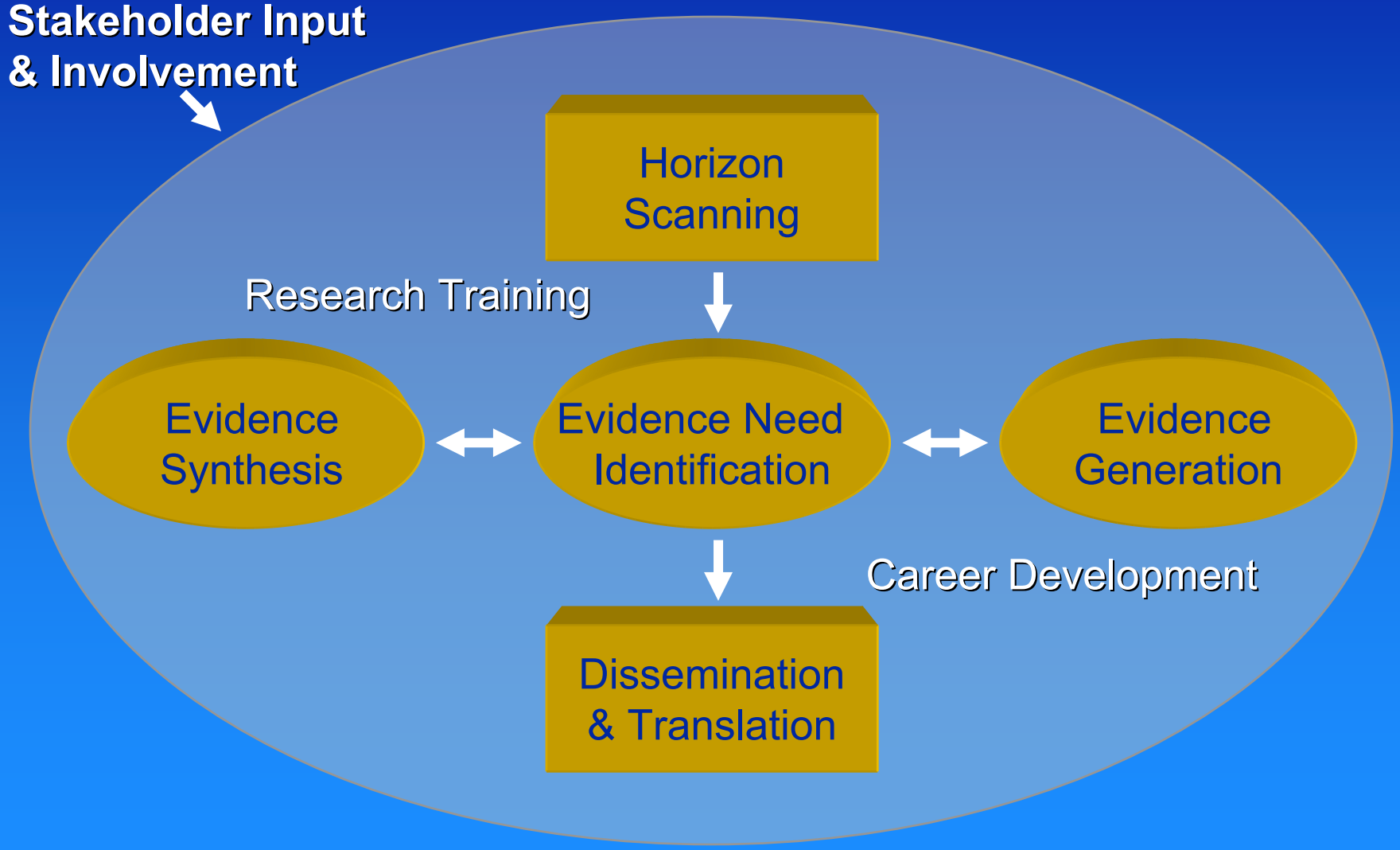
Comparative Effectiveness Research at AHRQ

- Created in 2005, authorized by Section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003
- AHRQ shall conduct and support research on:
  - "the outcomes, comparative clinical effectiveness, and appropriateness of health care items and services (including prescription drugs)"
- Goal: to provide patients, clinicians and policy makers with reliable, evidence-based healthcare information

Effective Health Care Program

- **To improve the quality, effectiveness, and efficiency of health care delivered through Medicare, Medicaid, and S-CHIP programs**
  - Focus is on what is known ***now***: ensuring programs benefit from ***past*** investments in research and what research ***gaps*** are critical to fill
  - Focus is on ***clinical effectiveness***

Conceptual Framework



Output

Number 12

Effective Health Care

Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis

Executive Summary

Background

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The clinical complications of osteoporosis include fractures, disability, and chronic pain. Approximately 44 million people in the United States are affected by osteoporosis or low bone density. It is

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic

Number 8

Effective Health Care

Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes

Executive Summary

Background

Type 2 diabetes is characterized by insulin resistance accompanied by progressive deficiency in insulin secretion. Type 2 diabetes is an increasingly common disease that is closely associated with obesity. In 2005, the prevalence of Americans with diagnosed type 2 diabetes was 2.4 percent for adults aged 20-39 years, 10 percent for adults aged 40-59 years, and 21 percent for adults aged 60 years or over. From 1980 through 2004, the number of Americans diagnosed with diabetes more than doubled, from 5.8 million to 14.7 million. Observational studies and clinical trials show that improved glycemic control reduces microvascular complications (e.g., complications involving the eyes, kidneys, or nerves) and may reduce macrovascular complications (e.g., heart attack); however, the effects of specific oral diabetes medications on these outcomes are less certain.

As new classes of medications have become available for the treatment of diabetes, clinicians and patients have faced a bewildering array of oral medications with different mechanisms of action. The first oral diabetes medications were sulfonylureas, which were introduced into the market in 1955. The second-generation sulfonylureas, which are used today, were

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

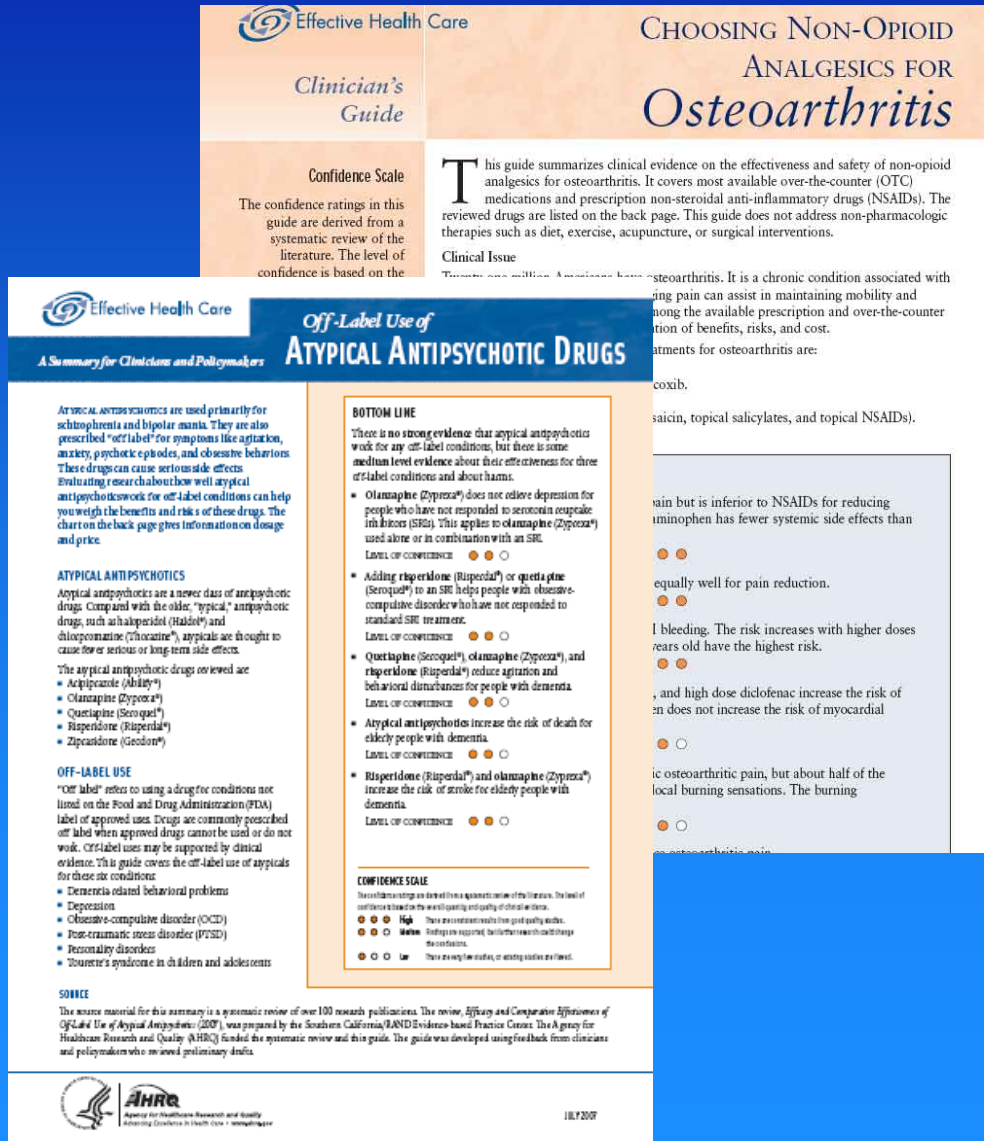
The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective Health Care

Educating Clinicians

- Concise
- Actionable
- Paired with consumer guides
- Convey level of uncertainty/certainty of findings



Effective Health Care

Clinician's Guide

CHOOSING NON-OPIOID ANALGESICS FOR *Osteoarthritis*

Confidence Scale

The confidence ratings in this guide are derived from a systematic review of the literature. The level of confidence is based on the

This guide summarizes clinical evidence on the effectiveness and safety of non-opioid analgesics for osteoarthritis. It covers most available over-the-counter (OTC) medications and prescription non-steroidal anti-inflammatory drugs (NSAIDs). The reviewed drugs are listed on the back page. This guide does not address non-pharmacologic therapies such as diet, exercise, acupuncture, or surgical interventions.

Clinical Issue

Effective Health Care

A Summary for Clinicians and Policymakers

Off-Label Use of ATYPICAL ANTIPSYCHOTIC DRUGS

ATYPICAL ANTIPSYCHOTICS are used primarily for schizophrenia and bipolar mania. They are also prescribed "off label" for symptoms like agitation, anxiety, psychotic episodes, and obsessive behaviors. These drugs can cause serious side effects. Evaluating research about how well atypical antipsychotics work for off-label conditions can help you weigh the benefits and risks of these drugs. The chart on the back page gives information on dosage and price.

ATYPICAL ANTIPSYCHOTICS

Atypical antipsychotics are a newer class of antipsychotic drugs. Compared with the older, "typical," antipsychotic drugs, such as haloperidol (Haldol®) and chlorpromazine (Thorazine®), atypicals are thought to cause fewer serious or long-term side effects.

The atypical antipsychotic drugs reviewed are
- Aripiprazole (Abilify®)
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Ziprasidone (Geodon®)

OFF-LABEL USE

"Off label" refers to using a drug for conditions not listed on the Food and Drug Administration (FDA) label of approved uses. Drugs are commonly prescribed off label when approved drugs cannot be used or do not work. Off-label uses may be supported by clinical evidence. This guide covers the off-label use of atypicals for these six conditions:
- Dementia-related behavioral problems
- Depression
- Obsessive-compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD)
- Personality disorders
- Tourette's syndrome in children and adolescents

BOTTOM LINE

There is **no strong evidence** that atypical antipsychotics work for any off-label conditions, but there is some **medium level evidence** about their effectiveness for three off-label conditions and about harms.

- **Olanzapine** (Zyprexa®) does not relieve depression for people who have not responded to serotonin reuptake inhibitors (SRIs). This applies to **olanzapine** (Zyprexa®) used alone or in combination with an SRI.
  LEVEL OF CONFIDENCE ● ● ○
- Adding **risperidone** (Risperdal®) or **quetiapine** (Seroquel®) to an SRI helps people with obsessive-compulsive disorder who have not responded to standard SRI treatment.
  LEVEL OF CONFIDENCE ● ● ○
- **Quetiapine** (Seroquel®), **olanzapine** (Zyprexa®), and **risperidone** (Risperdal®) reduce agitation and behavioral disturbances for people with dementia.
  LEVEL OF CONFIDENCE ● ● ○
- **Atypical antipsychotics** increase the risk of death for elderly people with dementia.
  LEVEL OF CONFIDENCE ● ● ○
- **Risperidone** (Risperdal®) and **olanzapine** (Zyprexa®) increase the risk of stroke for elderly people with dementia.
  LEVEL OF CONFIDENCE ● ● ○

CONFIDENCE SCALE

● ● ● High
● ● ○ Medium
● ○ ○ Low

SOURCE

The source material for this summary is a systematic review of over 100 research publications. The review, *Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics* (2007), was prepared by the Southern California/RAND Evidence-based Practice Center. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians and policymakers who reviewed preliminary drafts.

AHRQ Agency for Healthcare Research and Quality

ain but is inferior to NSAIDs for reducing
minophen has fewer systemic side effects than
equally well for pain reduction.
l bleeding. The risk increases with higher doses
ears old have the highest risk.
, and high dose diclofenac increase the risk of
en does not increase the risk of myocardial
ic osteoarthritic pain, but about half of the
local burning sensations. The burning

Challenge of Genomics

- Large volume of gene-based information
- Relatively quick and easy to generate
- Little information on outcomes
- Paucity of information on added value
- Concern of rapid and inappropriate dissemination
- Limited skills and training of providers to tackle genomics, especially primary care
- Healthcare system is ill-equipped

Future Steps

- Randomized effectiveness trials when feasible
- Improve observational study design and analysis methods to minimize bias and confounding (improve internal validity)
- Invest in electronic infrastructure to enhance clinical data collected for studies

  - example distributed research methods
- Consistency and transparency in using comparative effectiveness to make decisions
- Build public-private partnerships (CED?)
- Invest in clinical decision support tools

Thank you!

Effective Health Care:
http://effectivehealthcare.ahrq.gov