Knowledge Translation on Medication Benefits and Harms

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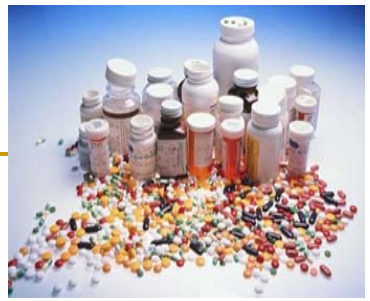
Disclosure

- Clinician
  - Hospital-based internal medicine & clinical pharmacology
- Researcher
  - Optimizing decision-making around drug therapy
    - Research all publicly funded
- Drug Policy Advisor
  - Member of CEDAC, CED formerly known as DQTC, regional formulary process
  - Chair or member of multiple federal, provincial, regional committees related to optimizing drug therapy



Main Points

- Many issues with medications requiring further clarification of benefits and harms
- Knowledge translation requires:
  - Useful knowledge development
  - Translation and implementation
  - High quality evaluations
- No magic bullets
  - But we are like first-year students at Hogwarts

PREXIGE®

Strong and sustained relief of *acute* and *chronic* OA pain of the knee.[1,2]

- **Superior** GI safety profile demonstrated vs. traditional NSAIDs (naproxen and ibuprofen)[3§]
  - 79% reduction in the rate of ulcer complications in the non-aspirin population.
    (Incidence was 29/9,117 vs. 83/9,127 and 14/6,950 vs. 64/6,968, $p<0.0001$ for overall and non-aspirin populations);
    Aspirin population: $p=0.4876$
- **Compelling** CV safety profile demonstrated vs. traditional NSAIDs (naproxen and ibuprofen)[4§]
  - Comparable rate of MI, strokes and CV death in overall population (Incidence was 59/9,117 vs. 50/9,127, $p=0.5074$)

Once Daily Dosing:

- **Short** plasma half-life (mean 4 hrs)[1†]
- **Persists** in the synovial fluid of joints[5†]

§ 52-week, randomized, double-blind, double-dummy, multicentre, parallel-group study involving 18,325 patients (≥50 years) with OA, undertaken as two substudies of identical design and size. Patients were randomized to treatment groups: lumiracoxib 400mg OD (or recurrent-ided dose), naproxen 500mg BID or ibuprofen 800mg TID.

† Clinical significance is unknown.

Risk of Serious Cardiovascular Events

As a group, selective COX-2 inhibitors, including PREXIGE® (lumiracoxib), are associated with an increased risk of adverse cardiovascular events, a risk that is similar to those associated with most NSAIDs.

PREXIGE® (lumiracoxib) is indicated for the acute and chronic treatment of the signs and symptoms of osteoarthritis of the knee in adults.

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first.

Use of PREXIGE® should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events.

PREXIGE®, as a NSAID, does NOT treat clinical disease or prevent its progression. It only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Evidence from clinical studies and postmarket experience suggests that use in the geriatric population is associated with differences in safety. Safety and efficacy have not been established in the pediatric population.

Most common adverse events (defined as being reported by ≥5% in any group) occurring with lumiracoxib 100mg OD were headache (8%) and nasopharyngitis (8%).

Contraindications

PREXIGE® is contraindicated in:

- The peri-operative setting of coronary artery bypass graft surgery (CABG). Although PREXIGE® has NOT been studied in this patient population, another selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications
- The third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition
- Women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants
- Severe uncontrolled heart failure
- Known hypersensitivity to PREXIGE® (lumiracoxib) or to any ingredient in the formulation or component of the container. PREXIGE® 100mg tablets contain lactose and should not be used in patients with rare hereditary problems of galactose intolerance, severe lactase deficiency, or glucose galactose malabsorption
- History of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma)). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind
- Active gastric/duodenal/peptic ulcer, active gastrointestinal (GI) bleeding
- Cerebrovascular bleeding or other bleeding disorders
- Inflammatory bowel disease
- Severe liver impairment (Child-Pugh >9) or active liver disease
- Severe renal impairment (creatinine clearance <30 mL/min or <0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored)
- Known hyperkalemia
- Children and adolescents less than 18 years of age

WARNINGS AND PRECAUTIONS

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure.

PREXIGE® is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Caution should be exercised in prescribing PREXIGE® to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as PREXIGE®, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure.

Randomized clinical trials with PREXIGE® have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing PREXIGE®.

Risk of Gastrointestinal (GI) Adverse Events.

Use of NSAIDs, such as PREXIGE®, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

For complete information regarding PREXIGE®, please refer to approved Product Monograph.

NOVARTIS

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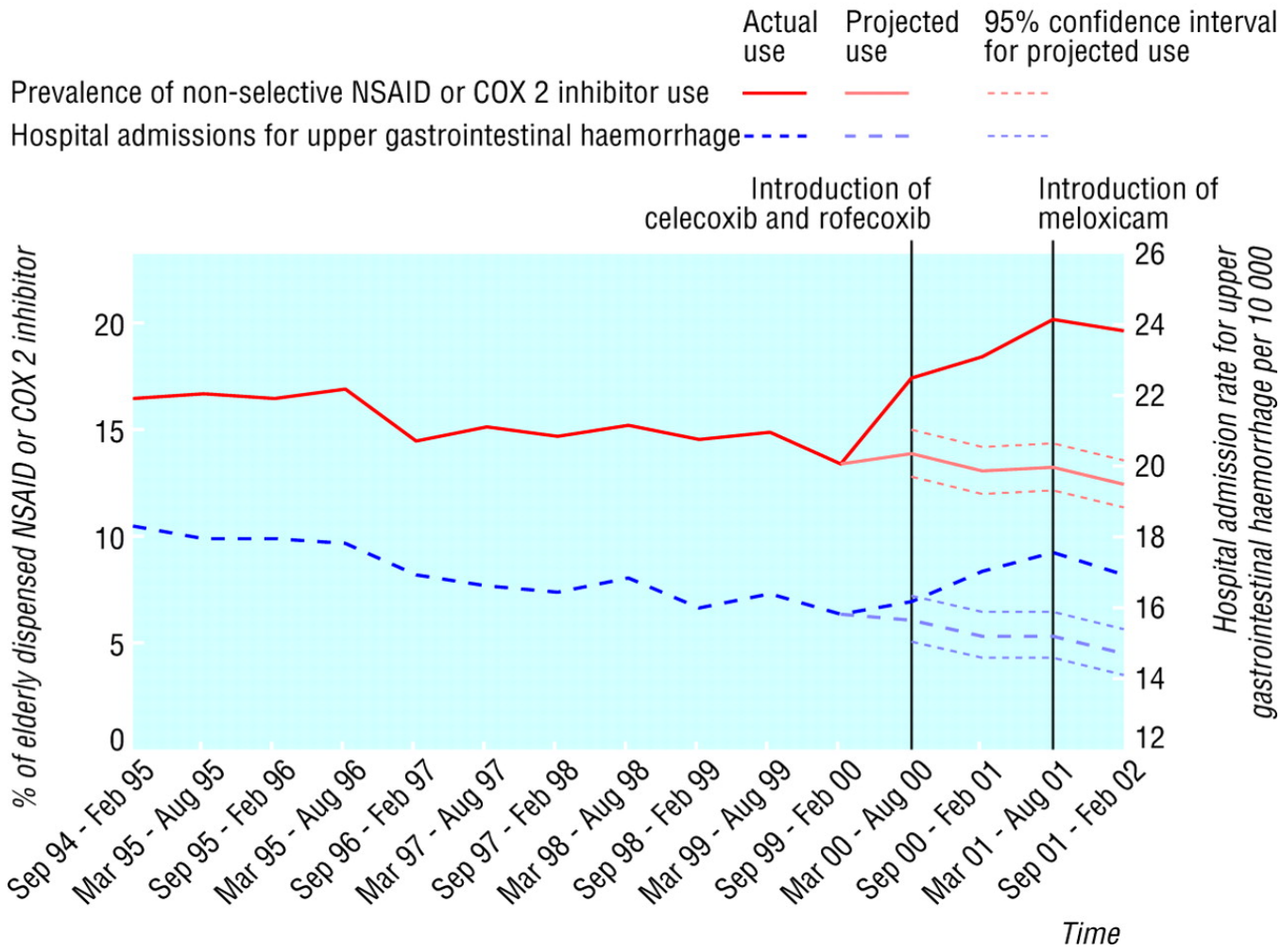
PRX-07-01-PP010062E

COX-2 NSAIDs: Jan 2007

- Better analgesic than placebo
  - But not better than older NSAIDs
  - Much more expensive
    - Expanded from $40 million to $100 million in 5 yr
- Minor decrease in serious GI events
  - Ablated in patients on low dose aspirin
- Small increase in cardiovascular events*
  - Suggested in original COX pharmacology
    - Could have been approx 11,000 additional events in Canada over 5 yr lifespan of rofecoxib (Vioxx)

NSAIDs and Hospitalisation for Upper Gastrointestinal Haemorrhage among elderly people in Ontario



Mamdani, M. et al. BMJ 2004;328:1415-1416

Lumiracoxib (Prexige)

- NOC November 2006
- To CEDAC May 2007
- Key Question was relative benefit:harm
  - Which is the more common cause of morbidity (e.g., hospitalization) and mortality – GI complications or cardiovascular events?

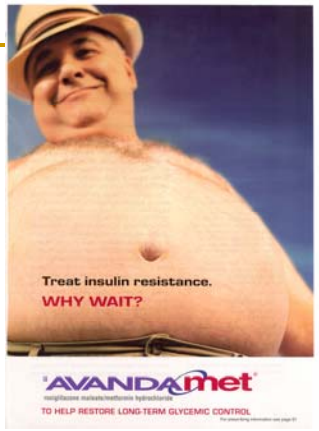
Potential Impact of Lumiracoxib

- Based on TARGET trial effects, CIHI, CCORT data
  - GI bleeds assume 65% RRR
    - Decrease GI bleed hospitalization by ? 7800
    - Decrease mortality by ? 420
  - Cardiovascular harm assume 48% RRI (compared to naproxen)
    - Increase cardiovascular hospitalizations by approx ? 200,000
  - Increase mortality by ? 69,000
  - Additional concern re: hepatotoxicity
    - Increased liver enzymes in 2.6%, reversible

COX-2 NSAID Summary

- Lum turned down for reimbursement May and July 2007
  - Withdrawn from market October 2007
  - Due to hepatotoxicity
- Still paying for celecoxib and meloxicam
  - And approx. 17 other NSAIDs
- Still not forcing first line acetaminophen then naproxen
- High quality literature on pain treatments remains very scant

Glitazones: Clinical Outcomes



- Very few trials
  - Restricted formulary access based on surrogate outcomes*
- Pioglitazone
  - Large RCT - Type 2 DM known vascular disease
  - No difference in vascular event composite at 3 yr
  - For every vascular event prevented, 2 cases CHF caused
- Rosiglitazone
  - Large RCT in Type 2 DM comparing first line monotherapies
  - A1C slightly lower but rate of vascular events was higher than glyburide (3.4% vs 1.8%) – mainly CHF and non-fatal MI – at 5 yr
  - Weight gain 9 kg more than metformin

PROACTIVE. Lancet 2005;366:1279

Kahn SE et al. ADOPT.NEJM 2006;355:2427

Rosiglitazone: New Safety Issues

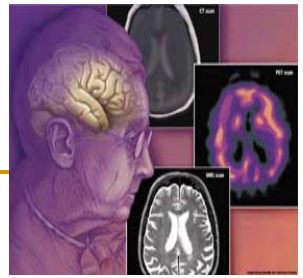
- Increased fracture rate in ADOPT
  - NNH approx. 16 – 24 compared to metformin and glyburide
    - Health Canada warning Feb07
- Cardiovascular risk
  - Several meta-analyses
    - > 40 trials, > 27,000 patients
    - Suggest increased odds cardiovascular events and death by about 50%
  - CHF rates consistently doubled

Glitazone Summary

- 8 years on market
  - Still poor data on real clinical benefit and harm
    - Still need large RCT on cardiovascular and microvascular outcomes
  - No good data to refute class effect but are rosi and pio similar?
  - Increased CHF events is consistent across studies, CHF is dangerous, so…?
    - Nov 2007 Health Canada Dear Doctor letter
      - Rosi contraindicated in any patient with any stage CHF, not to be used as monotherapy or second-line drug or third-line drug, not to be used with insulin….

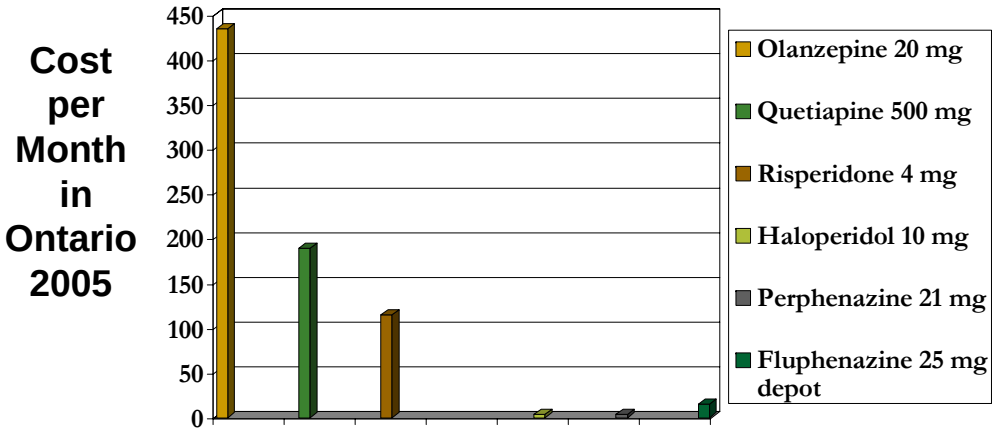
Antipsychotic Drugs in Dementia

- Prevalence of dementia up to 50% > 85 yr
- Neuropsychiatric behaviours
  - Occur in most patients, mostly later stages
    - Agitation, aggression, wandering, delusions
  - Main cause of institutionalization
- Use of Antipsychotic Drugs
  - Off – label use for several*
  - 24% patients newly admitted to LTC are prescribed antipsychotic drug within 12 months of admission
- Do antipsychotic drugs help these symptoms? Are the new drugs better than old drugs?



Antipsychotic Drugs

- Likely $200 million in Canada yearly
  - 99.5% cost in Ont due to atypical agents olanzepine, risperidone, quetiapine
    - Approx 66% cost due to olanzepine
  - Assumed to be primarily (? > 75%) for dementia/delirium
  - Are they cost-effective?



Antipsychotic Drugs in Dementia

- Several recent systematic reviews
  - Elderly, institutionalized, mean MMSE ~ 7/30
    - Small, inconsistent improvement in some scales/sub-scales compared to placebo with olanzepine and risperidone
    - No difference overall compared to haloperidol
  - Overall increase in mortality of 1-2% for olanzepine, risperidone, quetiapine compared to placebo
- CATIE-AD
  - Practical RCT in community-dwelling dementia with NPB
  - No difference vs placebo, 4X rate of discontinuations for adverse events

Schneider LS. NEJM 2006;355:1525

Drugs for Dementia Summary

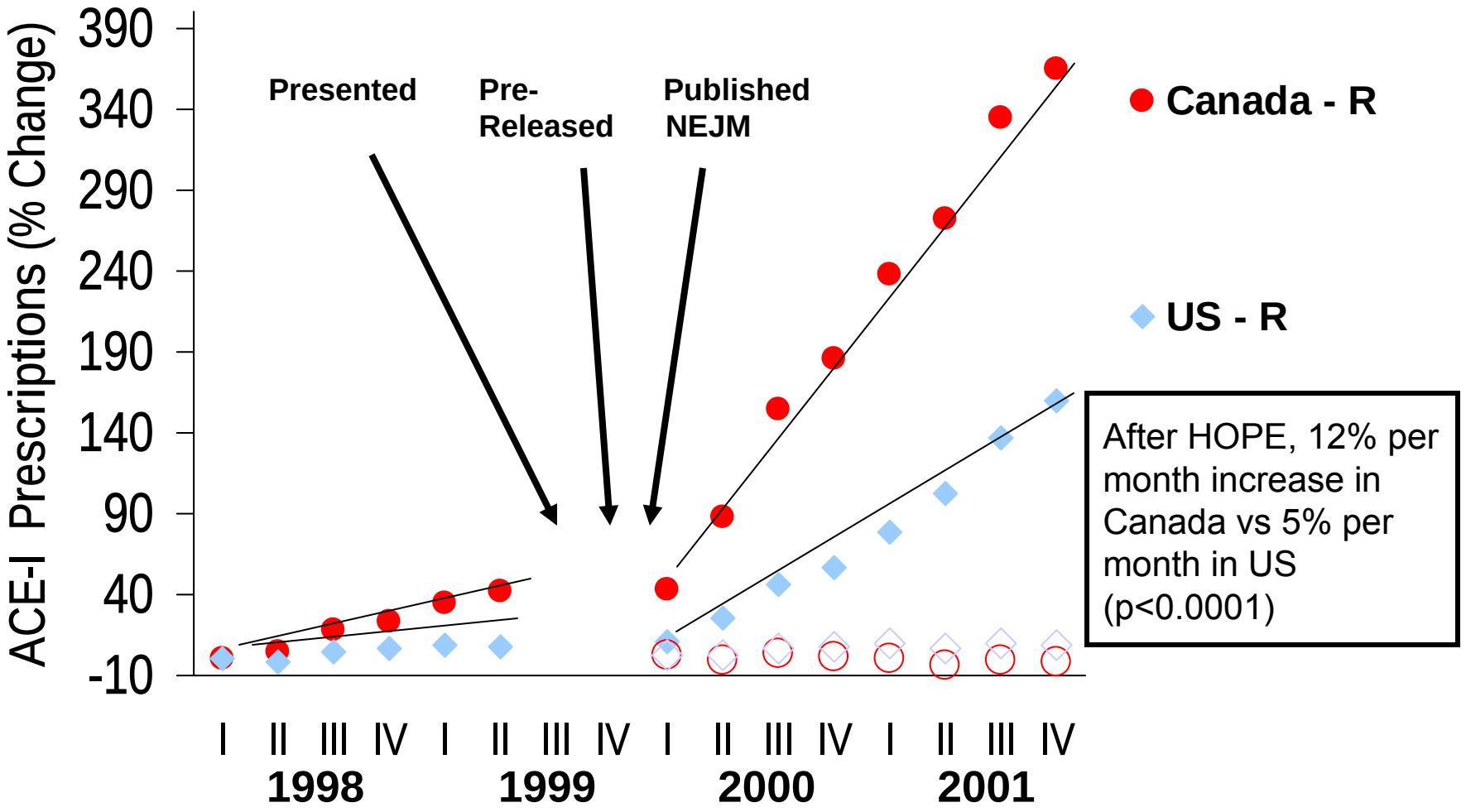
- Major burden of illness
  - NP behaviours stress caregivers
    - Family and long-term care
    - Insufficient community or institutional resources
- No effective, safe drug treatment
  - Cholinesterase inhibitors negative
  - Futility of therapy hard to admit
- Virtually no studies of non-pharmacologic management

Why so Many Problems with Drugs?

- Long development pipeline
  - Manufacturers desperate for profits
    - Push for short trials, non-inferiority, surrogate markers
- NOC oriented to efficacy vs placebo
  - Incomplete portfolio
- Aggressive marketing new drugs
- No ongoing extension or surveillance of benefits or harms
- Inadequate consultation with public re: threshold values for $$$
- Nobody weighing value of new drug vs new family physician or new MRI

Ramipril Use Before and After HOPE:

Canada vs US



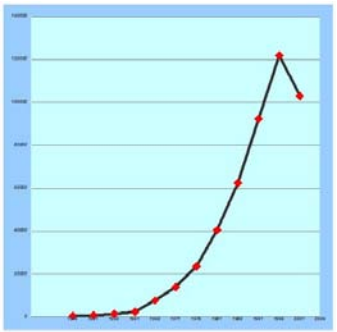
Majumdar et al. Am J Med. 2003;115:467

General Solutions

- More useful RCTs
- Better targeting of drugs to patients
- Better use of knowledge at hand
  - Understand utilization
    - Facilitators and barriers of desired
  - Interventions that can change practice
    - Without the marketing budget of pharma
- Better policy

How Many Studies are Useful in Practice?

- 2000 RCTs per month worldwide
  - Only 12-15 abstracted per 2 months in ACPJC
    - Methods good
    - *Relevant to IM clinicians*
  - *Far fewer directed at policy*
- Observational studies useful to examine utilization, trends, signals especially for harms
  - not sufficiently robust to prove causation
    - Can never be sure that confounding is completely controlled



Gluud C. Trials 2007;8:7

What is a Practical RCT?
(aka Effectiveness vs Efficacy Trial)

1. Population based in usual care setting
2. Less stringent eligibility criteria
3. Interventions include current standard of care
4. Outcomes are health outcomes – real outcomes that matter to patients
5. Longer duration
6. Adverse events are rigorously reported
7. Sample size is sufficient for MCID
8. Intention to treat (ITT) analysis

Gartlehner G. J Clin Epi 2006;59:1040

Targeting Drugs to Patients

- Warfarin
  - Prevents stroke in atrial fibrillation but potentially 2900 extra ER visits for bleeding per year in Canada
  - Is there a way to tailor therapy to only those who will have more benefit than harm?

	Warfarin Harm (+)	**No Warfarin Harm (-)**
Warfarin Benefit (+)	(1) No Stroke/Bleed (+ / +)	(2) No Stroke/No Bleed (+ / -)
No Warfarin Benefit (-)	(3) Stroke/Bleed (- / +)	(4) Stroke/No Bleed (- / -)

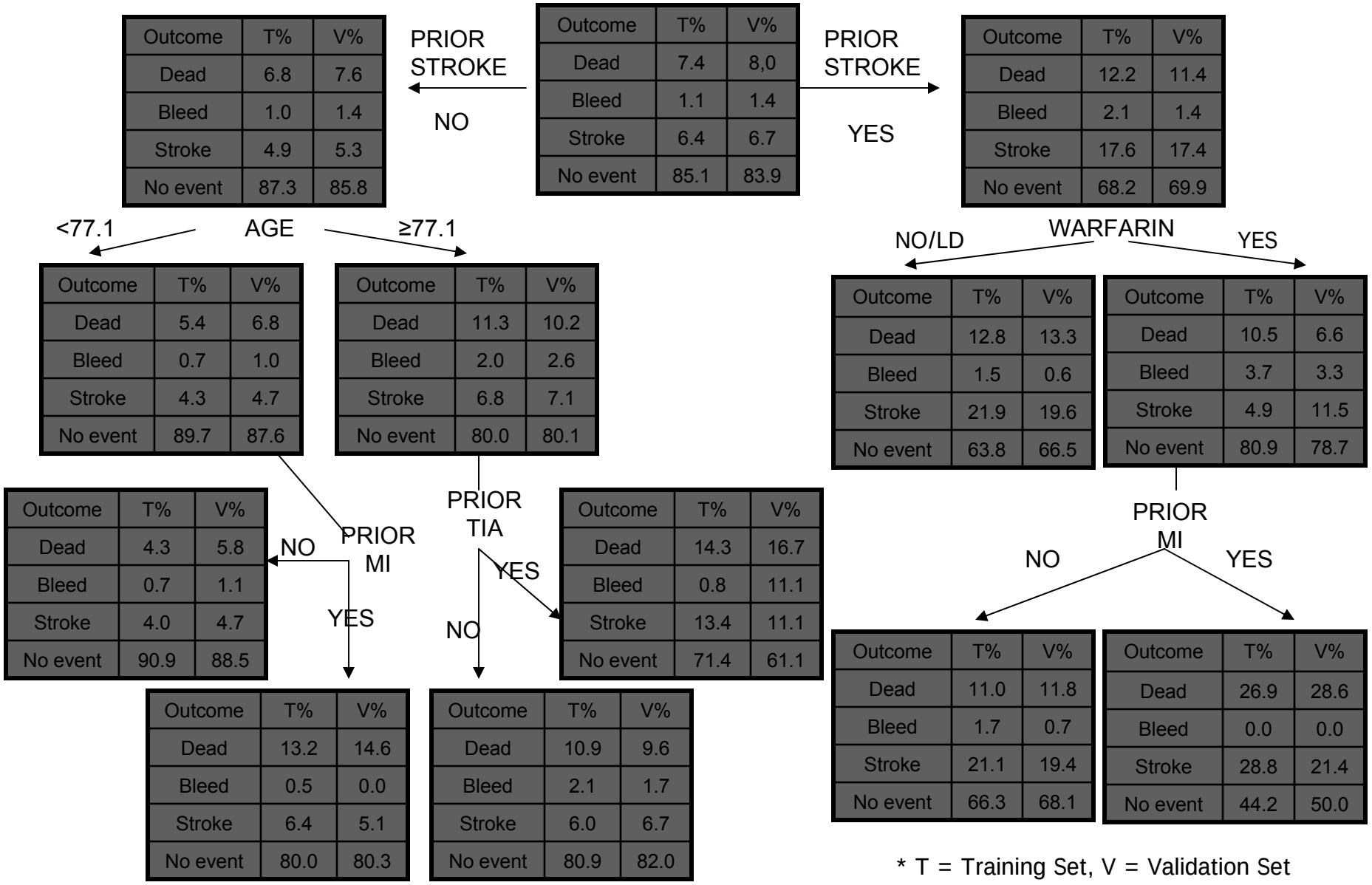
Gage B. Thromb Res 2005;117:55

Potential Warfarin Benefit and Harm

- $CHADS_2$ score
  - **C**HF, **H**TN, **A**ge ≥ 75, **D**M, Previous **S**troke or TIA
  - Stroke risk 1.9%/yr to 18.2%/yr
- HEMORRHAGES score
  - 12 factors
  - Bleeding risk 1.9%/yr to 12.3%/yr

Gage BF et al. JAMA 2001;285:2864. Gage BF et al. Am Heart J 2006;151:713

Warfarin: Predictors of Death vs Bleed/no stroke vs Stroke/no bleed vs No Event: AFI CART Modeling



* T = Training Set, V = Validation Set

Pereira J. PhD in Progress 2007

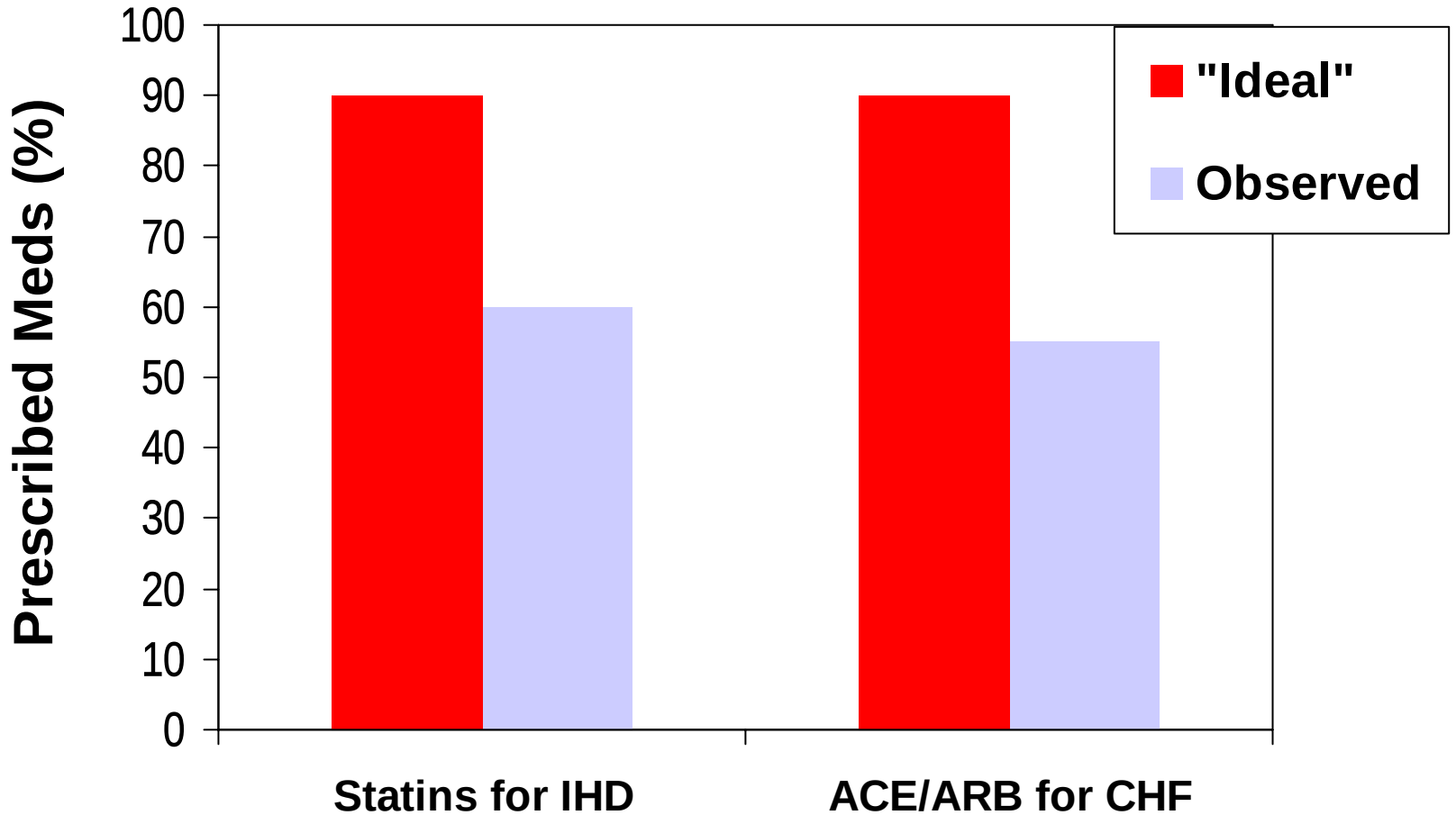
Better Use of Knowledge Available

- In God We Trust
  - All others need data…
    - Relatively recent phenomenon
  - Does this drug work? is much simpler than If this drug is to be cost-effective, which people at which dose and which time at what price should receive it?

Top10 Drugs by Cost Ontario 05/06

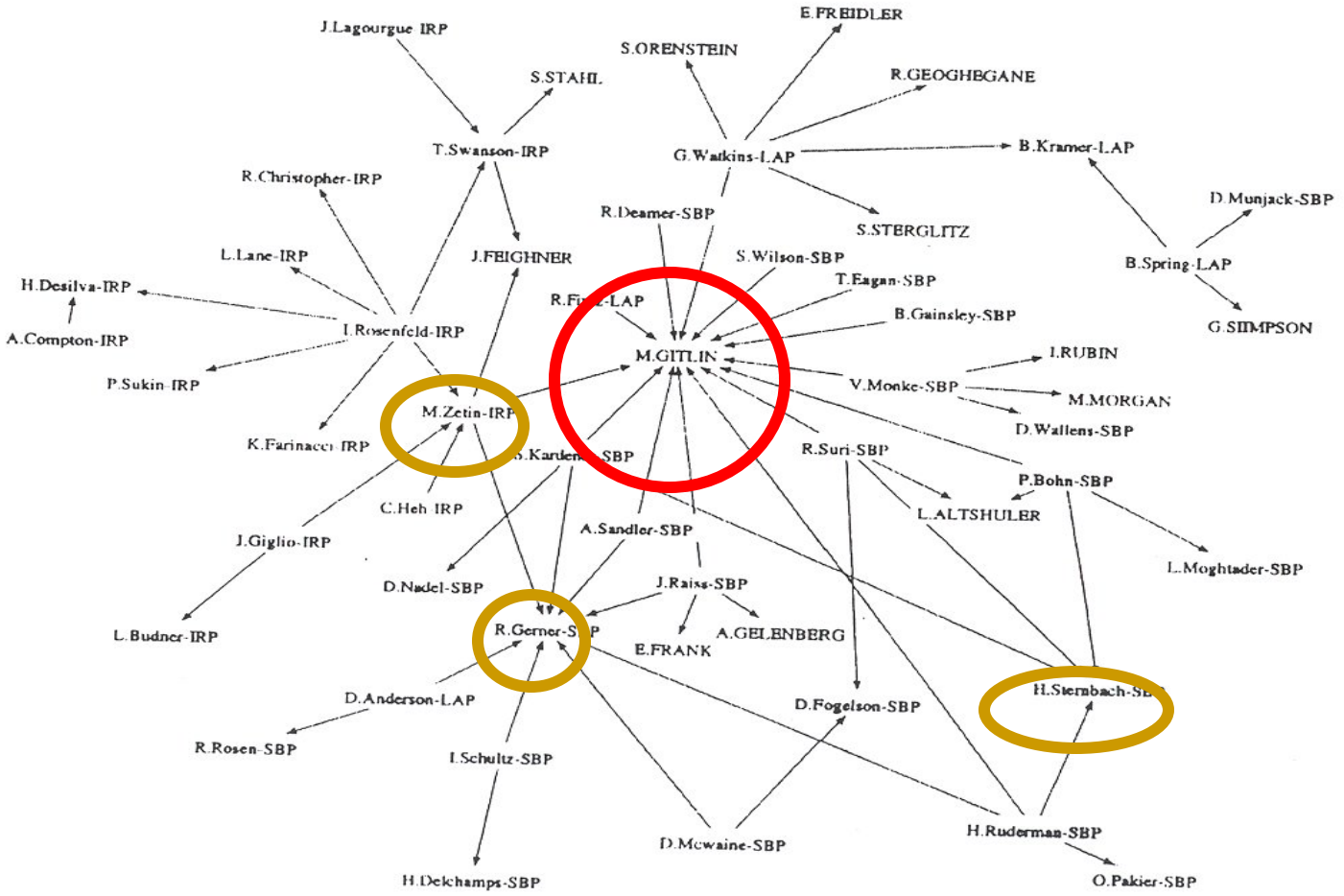
Rk	Drug Name	Class	Drug Cost	% Total Drug Cost
1	Atorvastatin (Lipitor)	Cardiovascular	$230M	7.9%
2	Amlodipine Besylate (Norvasc)	Cardiovascular	$107M	3.7%
3	Ramipril (Altace)	Cardiovascular	$97M	3.3%
4	Diagnostic Agents (Diabetes)	Diagnostic Agents	$90M	3.1%
5	Omeprazole Magnesium (Losec) - LU	Gastrointestinal	$85M	2.9%
6	Olanzapine (Zyprexa)	Central Nervous System	$79M	2.7%
7	Simvastatin (Zocor)	Cardiovascular	$55M	1.9%
8	Pantoprazole (Pantoloc) - LU	Gastrointestinal	$48M	1.7%
9	Donepezil HCl (Aricept) – LU	Autonomic Agents	$46M	1.6%
10	Rabeprazole Sodium (Pariet)	Gastrointestinal	$43M	1.5%
TOTAL Top-10			$881M	30.4%

Gap Between Evidence and Practice:
Outpatients with Chronic Heart Disease



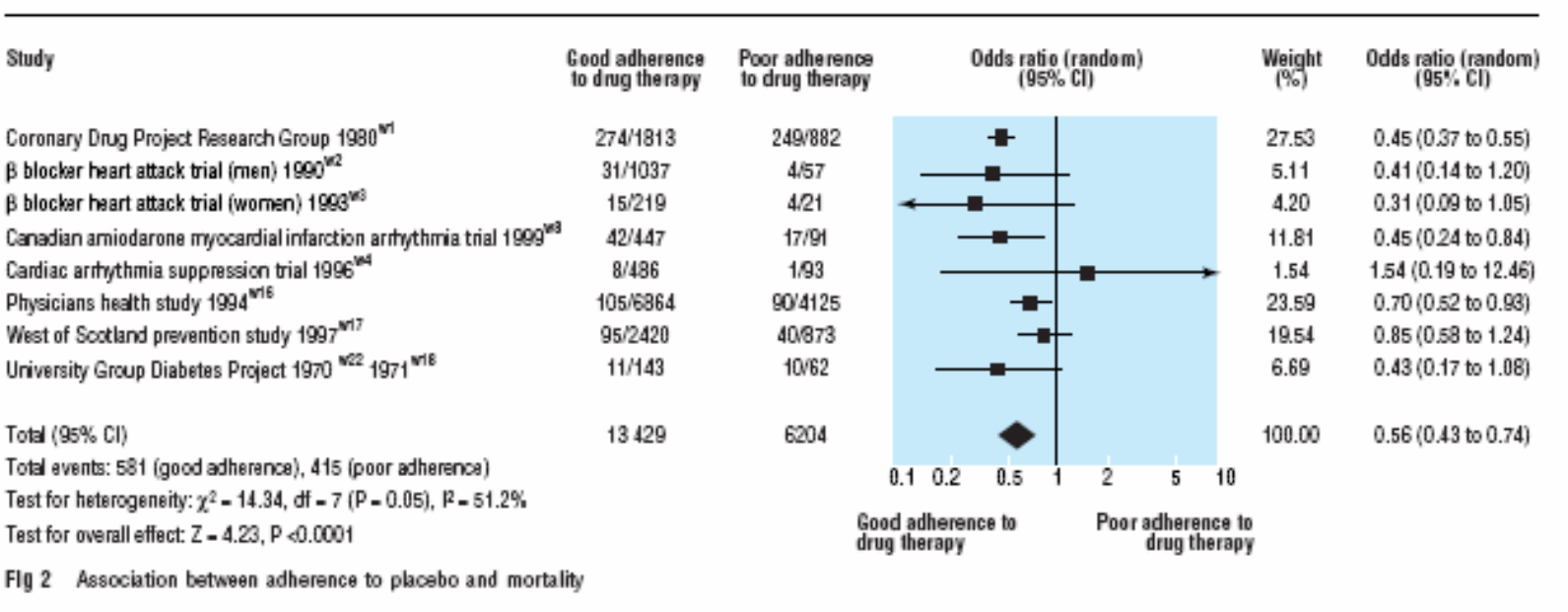
Majumdar et al. Am Heart J. 2007;153:22

Opinion Leader Influence: BP Medications



Majumdar S. unpublished 2007

Adherence and Mortality



Study	Good adherence to drug therapy	Poor adherence to drug therapy	Weight (%)	Odds ratio (random) (95% CI)
Coronary Drug Project Research Group 1980[w1]	274/1813	249/882	27.53	0.45 (0.37 to 0.55)
β blocker heart attack trial (men) 1990[w2]	31/1037	4/57	5.11	0.41 (0.14 to 1.20)
β blocker heart attack trial (women) 1993[w3]	15/219	4/21	4.20	0.31 (0.09 to 1.05)
Canadian amiodarone myocardial infarction arrhythmia trial 1999[w3]	42/447	17/91	11.81	0.45 (0.24 to 0.84)
Cardiac arrhythmia suppression trial 1996[w4]	8/486	1/93	1.54	1.54 (0.19 to 12.46)
Physicians health study 1994[w16]	105/6864	90/4125	23.59	0.70 (0.52 to 0.93)
West of Scotland prevention study 1997[w17]	95/2420	40/873	19.54	0.85 (0.58 to 1.24)
University Group Diabetes Project 1970[w22] 1971[w18]	11/143	10/62	6.69	0.43 (0.17 to 1.08)
Total (95% CI)	13 429	6204	100.00	0.56 (0.43 to 0.74)

Total events: 581 (good adherence), 415 (poor adherence)
Test for heterogeneity: $\chi^2 = 14.34$, df = 7 (P = 0.05), $I^2 = 51.2\%$
Test for overall effect: Z = 4.23, P <0.0001

Fig 2 Association between adherence to placebo and mortality

NNT = 26

Simpson S, BMJ 2006;333:15

Other Unexpected Influences on Medication-taking

- RCT patient preferences for anticoagulation for atrial fibrillation
  - Presented data to patients first blinded to drug names, then repeated unblinded
    - Data on benefits and risks exactly the same
  - Main factor changing decision was drug name
    - 46% warfarin and 78% no treatment change

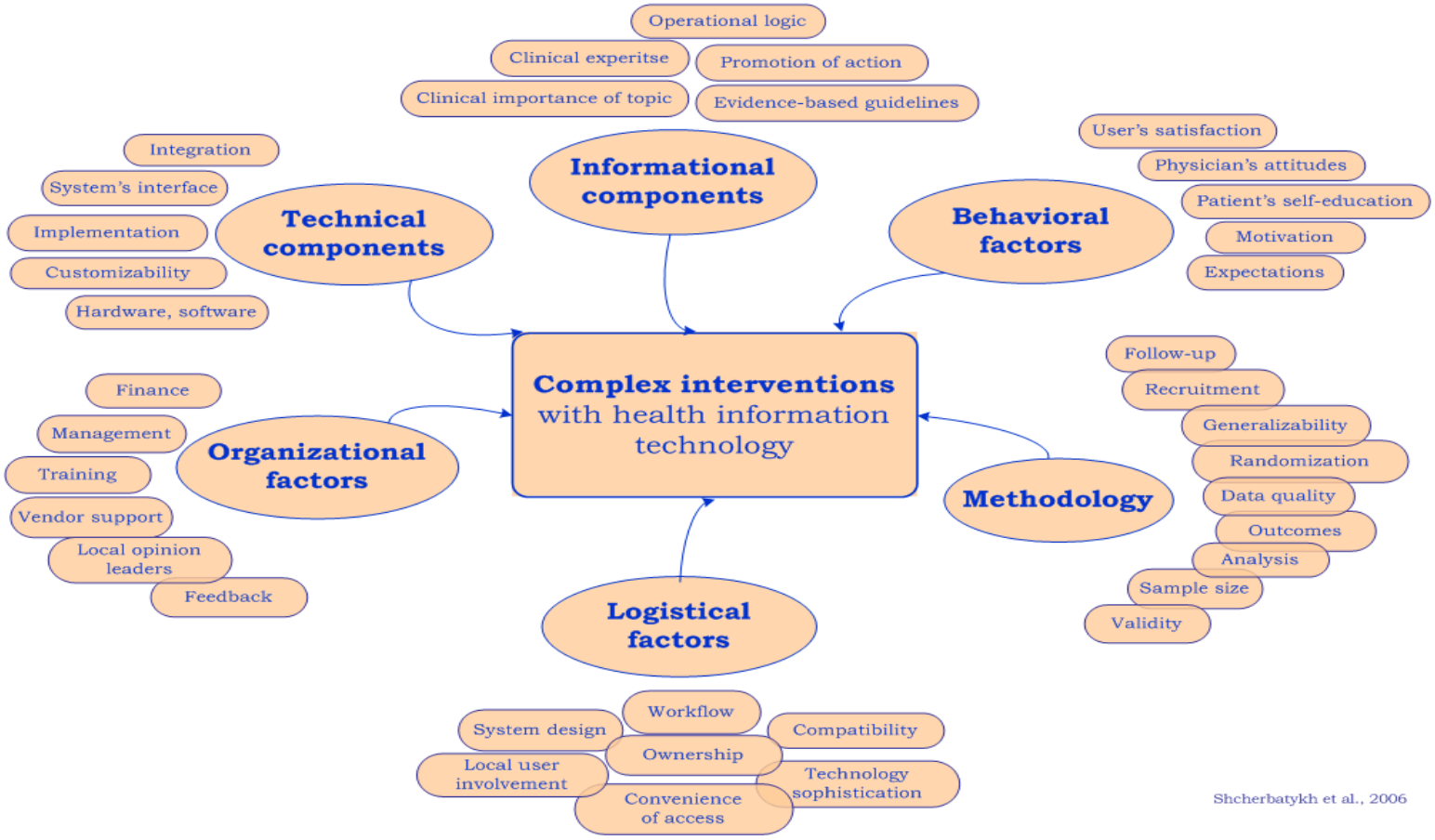
Holbrook AM et al. CMAJ 2007;176:1583

Knowledge Implementation is Key

- Educational
  - CDSS, audit and feedback, peer influential, academic detailing
- Policy intervention
  - Reference Pricing, Restrictive listings, Price negotiation, shared drug assessments

KT Studies are Complex

Complex intervention components…



Shcherbatykh et al., 2006

COMPETE

Future Policy Directions

- Intelligent policy is vital
- Federal/provincial/territorial
  - Require PMS studies and ensure completion
  - Enforce restricted listings
  - Run ongoing signal detection service
    - However methods are immature, methods of bias adjustment/prevention are imperfect
  - Mandate registration of early phase trials and access to results
  - Better risk communication
    - Transparency, safety communication, disagreements
  - Direct communication of evidence summaries to clinicians
  - Monitor utilization
  - Tender on prices
  - Test “CED” – coverage for evidence development