

Unbiased Prescribing Information



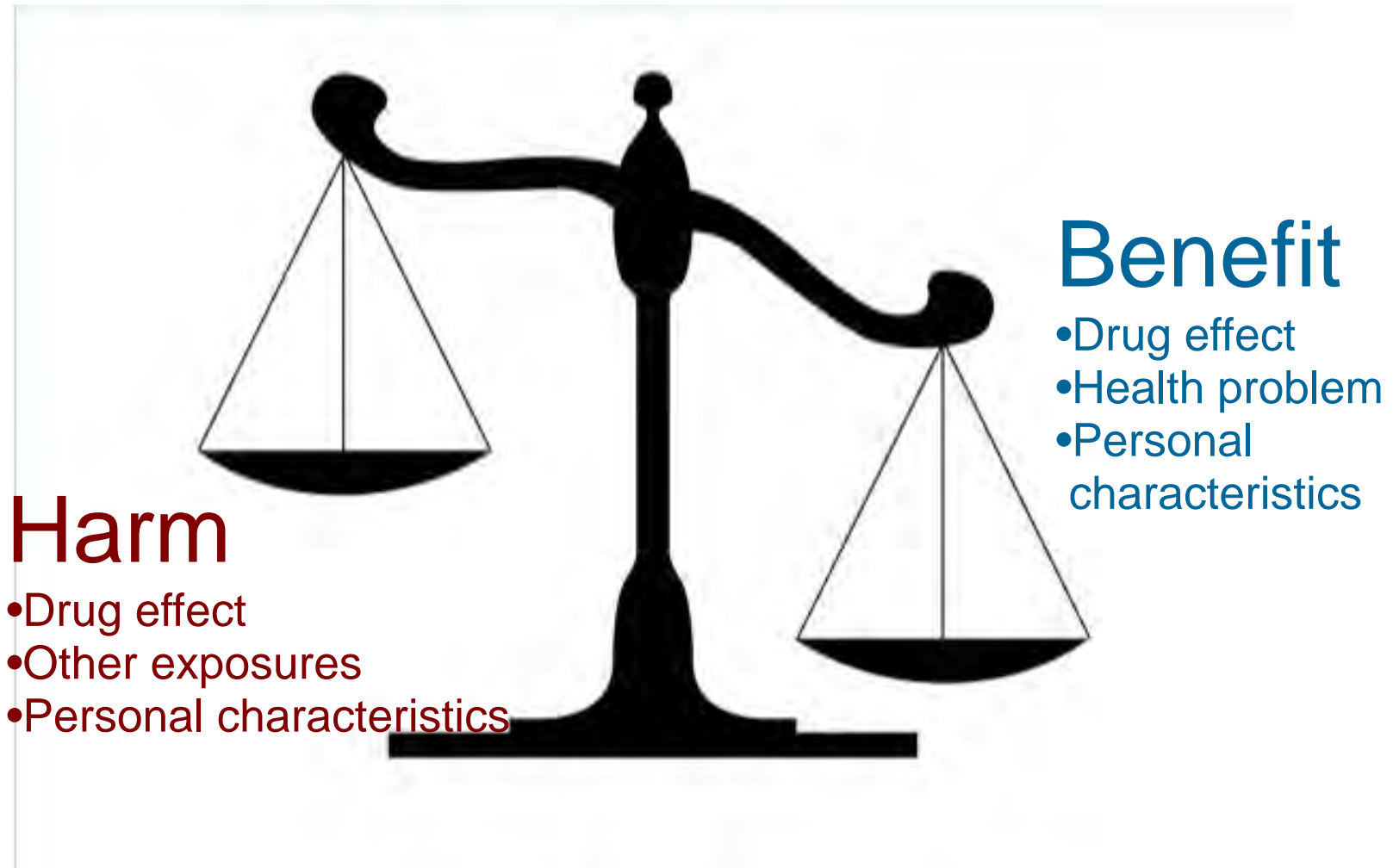
Barbara Mintzes, Therapeutics Initiative
University of British Columbia, Vancouver BC Canada
Health Action International (HAI Europe)

Summer School on drug promotion,
Ventspils, July 1-4, 2014, Barbara.mintzes@ti.ubc.ca

What this presentation covers

- Background to advertising analysis
- What type of evidence is needed to guide prescribing decisions?
- A few useful measures: NNT, ARR, etc.
- Critical appraisal – judging research quality

All medicine use is a balance





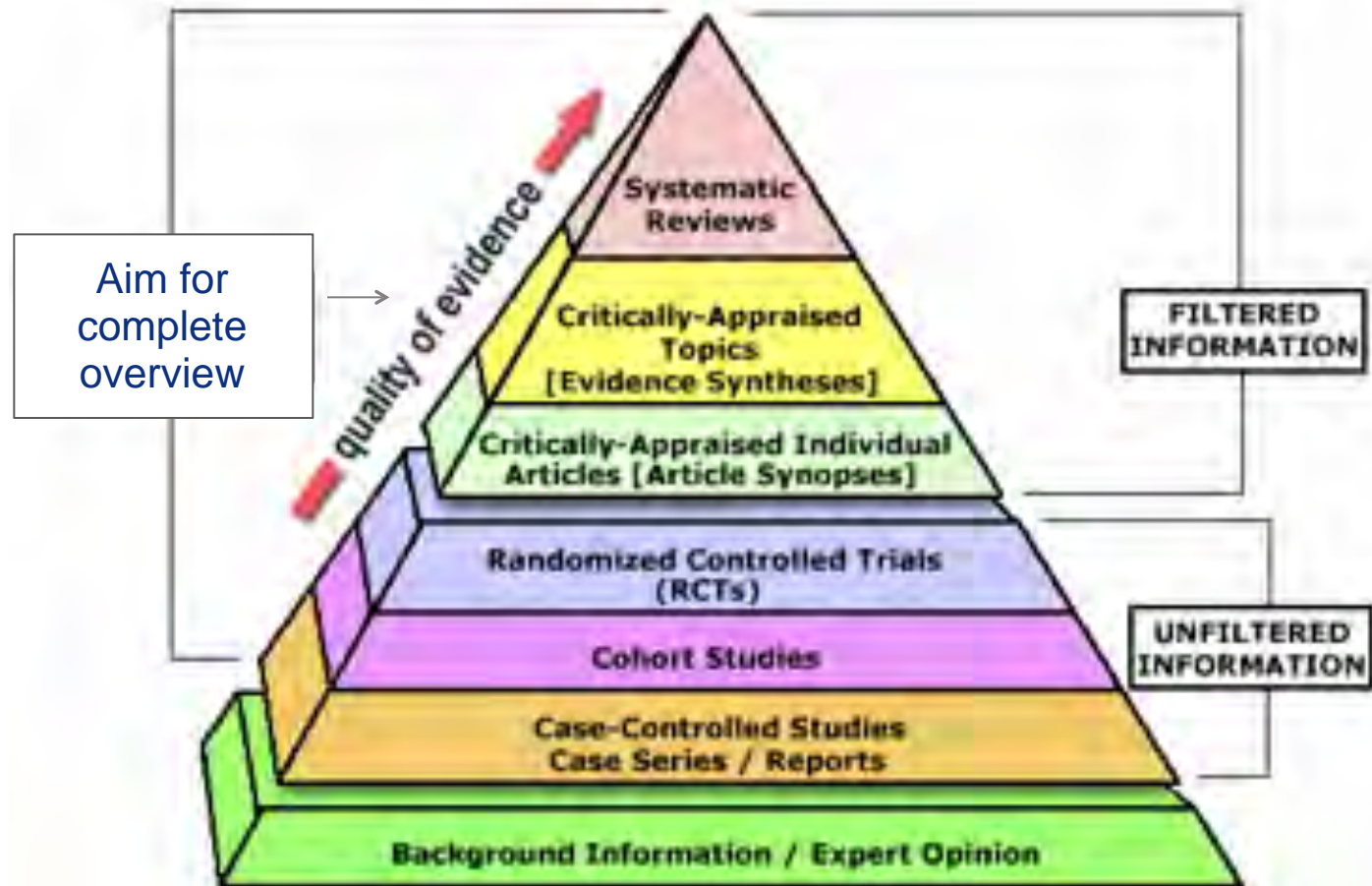
“Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.”

- *Sackett D. BMJ 1996; 312:71-72*

What defines best evidence'?

- **Completeness:** full body of scientific research
- **Strength of evidence:** design and quality of studies, results replicated
- **Magnitude of effect:** is there enough of a difference to make a difference?
- **Health impact:** effects important to patient health
- **Balance:** benefits clearly outweigh harm

Hierarchy of evidence



What is a systematic review?

“A concise summary of the best available evidence that addresses a sharply defined clinical question and attempts to answer it using explicit and rigorous methods to identify, critically appraise and synthesize all relevant studies.”



An example – systematic review results versus advertising messages



Are your OAB patients on the verge of experiencing an accident?

TURN TO

P^r Toviaz™

Demonstrated superiority in treating UUI episodes/24 hours with TOVIAZ 8 mg vs. tolterodine ER 4 mg in 2 head-to-head trials^{1,2‡§}

Demonstrated excellent safety and tolerability profile⁴

• Winsorized mean changes from baseline:

Study 1: -1.5 placebo, -1.6 tolterodine ER, and -1.7 TOVIAZ (p=0.017 TOVIAZ vs. tolterodine ER)

Study 2: -1.6 placebo, -1.7 tolterodine ER, and -2.0 TOVIAZ (p=0.0072 TOVIAZ vs. tolterodine ER)

- Most common adverse events ≥5%: dry mouth (18.8% 4 mg and 34.6% 8 mg) and constipation (4.2% 4 mg and 6.0% 8 mg)
- Discontinuation rates due to dry mouth were 0.4%, 0.4% and 0.8% in patients receiving placebo, TOVIAZ 4 mg and 8 mg, respectively

Indication and Clinical Use:

TOVIAZ is indicated for the treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.

Safety and efficacy in pediatric populations have not been established.

Contraindications:

- Urinary retention
- Gastric retention
- Uncontrolled narrow-angle glaucoma
- Hypersensitivity to tolterodine L-tartrate, soya, peanuts, lactose

Relevant warnings and precautions:

- increase in heart rate
- interaction with potent CYP3A4 inhibitors (i.e., max of 4 mg)
- patients at risk of gastric retention
- patients at risk of urinary retention
- patients with impaired hepatic function
- angioedema
- patients with myasthenia gravis
- patients with controlled narrow-angle glaucoma
- patients with impaired renal function (i.e., max of 4 mg for severe impairment)
- contraception in women of childbearing potential
- not recommended during breastfeeding

For more information:

Please consult the product monograph at http://www.pfizer.ca/en/our_products/products/monograph/317 for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

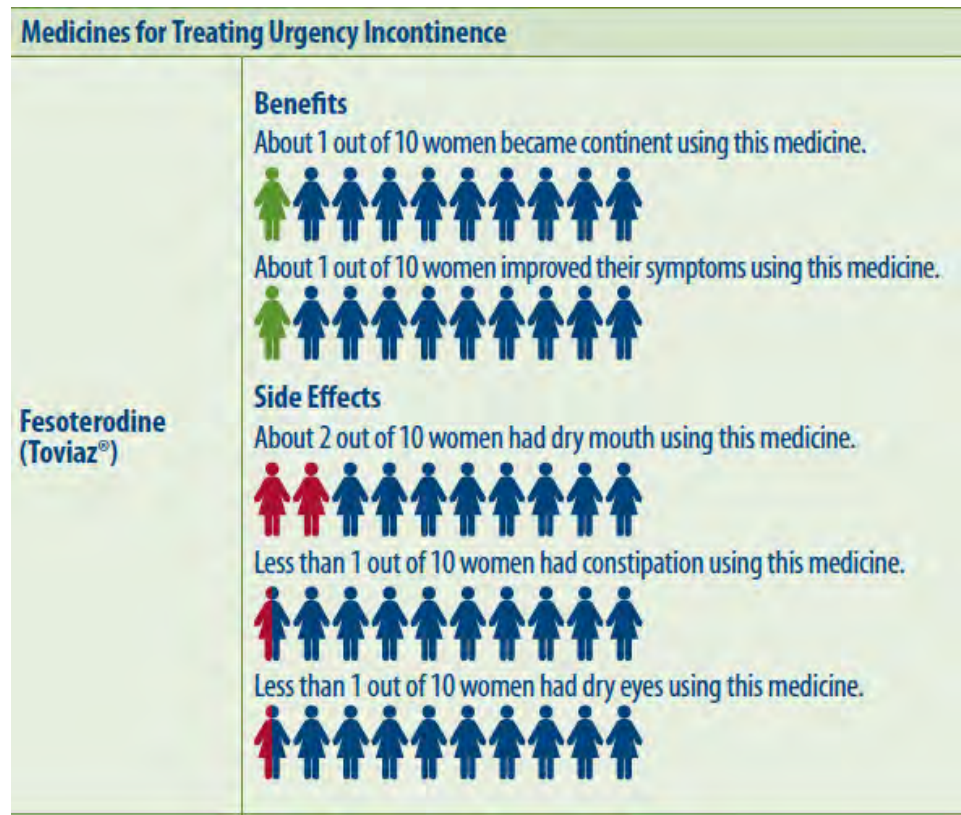
The product monograph is also available by calling 1-800-463-6001.

¹ TOVIAZ is covered on formulary with special authorization in Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland and Labrador.

² 12-week, double-blind, double-dummy, placebo-controlled, parallel-group, randomized clinical trial of patients with OAB (≥8 voids and ≥1 UUI episodes/24 hrs on a 3-day bladder diary). Patients were randomized to placebo (n=334), maximum dose of tolterodine ER 4 mg (n=684), or maximum dose of TOVIAZ (4 mg for 1 week then 8 mg for 11 weeks, n=675). Number of patients evaluated for UUI episodes/24 hrs was 347, 625, and 519, respectively. Baseline means for UUI episodes/24 hrs were 2.6, 2.5, and 2.4, respectively.

³ 12-week, double-blind, double-dummy, placebo-controlled, parallel-


Do benefits outweigh harm?



Agency for Healthcare Research and Quality (AHRQ). Non-surgical treatments for urinary incontinence. Consumer Summary 2012. www.ahrq.gov

* The project benefits from a grant from Iceland, Liechtenstein and Norway through the EEA Grants.

How does it compare to non-drug options?

Options for Treating Urgency Incontinence	
Non-drug Treatments: Lifestyle Changes	
Bladder training	<p>Benefits The number of women who became continent was not reported. 4 out of 10 women improved their symptoms using bladder-control exercises.</p>  <p>Combining PFMT with bladder training improved continence in women with urgency incontinence.</p> <p>Side Effects Not known, but most researchers think there are few if any.</p>


Agency for Healthcare Research and Quality (AHRQ). Non-surgical treatments for urinary incontinence. Consumer Summary 2012. www.ahrq.gov

* The project benefits from a grant from Iceland, Liechtenstein and Norway through the EEA Grants.

Can drug treatment lead to serious harm?

Warning: Doctors and patients have also reported some serious side effects that can occur with these medicines. Although they do not happen very often, they are more dangerous than the common side effects listed above. These side effects include rapid irregular heart rate, hallucinations, problems with thinking, and rarely death. The chance of having a serious side effect is greater for elderly patients, for patients who take many different medicines at the same time, and for patients who take some antihistamines (allergy medicines) and antibiotics along with these UI medicines. Ask your doctor about these more serious side effects.

Agency for Healthcare Research and Quality (AHRQ). Non-surgical treatments for urinary incontinence. Consumer Summary 2012. www.ahrq.gov



Are your OAB patients on the verge of experiencing an accident?

TURN TO

P Toviaz™

Demonstrated superiority in treating UUI episodes/24 hours with TOVIAZ 8 mg vs. tolterodine ER 4 mg in 2 head-to-head trials^{1,2,3,5}

- Worsened mean changes from baseline:
 - Study 1:** -1.5 placebo, -1.6 tolterodine ER, and -1.7 TOVIAZ ($p=0.017$ TOVIAZ vs. tolterodine ER)
 - Study 2:** -1.6 placebo, -1.7 tolterodine ER, and -2.0 TOVIAZ ($p=0.0072$ TOVIAZ vs. tolterodine ER)

Demonstrated excellent safety and tolerability profile⁴

- Most common adverse events $\geq 5\%$: dry mouth (18.8% 4 mg and 34.6% 8 mg) and constipation (4.2% 4 mg and 6.0% 8 mg)
- Discontinuation rates due to dry mouth were 0.4%, 0.4% and 0.8% in patients receiving placebo, TOVIAZ 4 mg and 8 mg, respectively

Indication and Clinical Use:
TOVIAZ is indicated for the treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.
Safety and efficacy in pediatric populations have not been established.

Contraindications:

- Urinary retention
- Gastric retention
- Uncontrolled narrow-angle glaucoma
- Hypersensitivity to tolterodine L-tartrate, soya, peanuts, lactose

Relevant warnings and precautions:

- increase in heart rate
- interaction with potent CYP3A4 inhibitors (i.e., max of 4 mg)
- patients at risk of gastric retention
- patients at risk of urinary retention
- patients with impaired hepatic function
- angioedema
- patients with myasthenia gravis
- patients with controlled narrow-angle glaucoma
- patients with impaired renal function (i.e., max of 4 mg for severe impairment)
- contraception in women of childbearing potential
- not recommended during breastfeeding

For more information:
Please consult the product monograph at http://www.pfizer.ca/en/our_products/products/monograph/317 for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.
The product monograph is also available by calling 1-800-463-6001.

¹ TOVIAZ is covered on formulary with special authorization in Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland and Labrador.
² 12-week, double-blind, double-dummy placebo-controlled, parallel-group, randomized clinical trial of patients with OAB (≥ 3 voids and ≥ 1 UUI episodes/24 hrs on a 3-day bladder diary). Patients were randomized to placebo ($n=334$), maximum dose of tolterodine ER 4 mg ($n=684$), or maximum dose of TOVIAZ (4 mg for 1 week then 8 mg for 11 weeks, $n=678$). Number of patients evaluated for UUI episodes/24 hrs was 367, 625, and 619, respectively. Baseline mean for UUI episodes/24 hrs were 2.5, 2.5, and 2.4, respectively.
³ 12-week, double-blind, double-dummy placebo-controlled, parallel-

Communicating treatment outcomes

Have I got a deal for you!



- Special offer: 50% off
- Any takers?

Relative or absolute risk difference

- 1 in 100 patients improve on placebo
- 2 in 100 patients improve on drug

- Relative risk reduction = $(1/100) \div (2/100)$
- Absolute risk reduction (ARR) = $0.02 - 0.01$

- Number needed to treat for 1 to benefit = $\text{NNT } 1 \div \text{absolute risk reduction}$



Statins Given for 5 Years for Heart Disease Prevention (With Known Heart Disease)



83 for mortality

In Summary, for those who took the statin for 5 years:

Benefits in Percentage

- 96% saw no benefit
- 1.2% were helped by being saved from death
- 2.6% were helped by preventing a repeat heart attack
- 0.8% were helped by preventing a stroke

Harms in Percentage

- 2% were harmed by developing diabetes**
- 10% were harmed by muscle damage

RELATED REVIEWS

Cardiac Interventions That *Do* Work

Cardiac Interventions That *Don't* Work

Cardiac Interventions That Need More Study

INTERACT

Share on Facebook

www.thennt.com/nnt/statins-for-heart-disease-prevention-with-known-heart-disease/

* The project benefits from a grant from Iceland, Liechtenstein and Norway through the EEA Grants.



Statin Drugs Given for 5 Years for Heart Disease Prevention (Without Known Heart Disease)



60 for non-fatal heart attack

In Summary, for those who took the statin for 5 years:

Benefits in Percentage

- 98% saw no benefit
- 0% were helped by being saved from death
- 1.6% were helped by preventing a heart attack
- 0.4% were helped by preventing a stroke

Harms in Percentage

- 2% were harmed by developing diabetes**
- 10% were harmed by muscle damage

RELATED REVIEWS

[Cardiac Interventions That *Do* Work](#)

[Cardiac Interventions That *Don't* Work](#)

[Cardiac Interventions That Need More Study](#)

INTERACT

[Customize This NNT](#)

* The project benefits from a grant from Iceland, Liechtenstein and Norway through the EEA Grants.

EVISTA ES EFICAZ EN TODO TIPO

REDUCE EL RIESGO DE
FRACTURAS VERTEBRALES

En el estudio NORA, el 50% de las fracturas osteoporóticas
ocurrieron en pacientes con osteopenia*

EN MUJERES
CON OSTEOPENIA*

↓ 47%

EVISTA reduce el riesgo de fractura vertebral radiológica
a los 3 añosTM

EN MUJERES
CON OSTEOPENIA*

↓ 75%

EVISTA reduce el riesgo de fractura vertebral sintomática
a los 3 añosTM

EN MUJERES
CON OSTEOPOROSIS

SIN FRACTURA
VERTEBRAL PREVIA:

EVISTA reduce el riesgo de
a los 3 añosTM

EN MUJERES
CON OSTEOPOROSIS

CON FRACTURA
VERTEBRAL PREVIA:

EVISTA reduce el riesgo de
a los 3 añosTM

FRACTURAS

EN MUJERES
CON OSTEOPOROSIS

CON FRACTURA
VERTEBRAL PREVIA:

EVISTA reduce el riesgo de
a los 3 añosTM

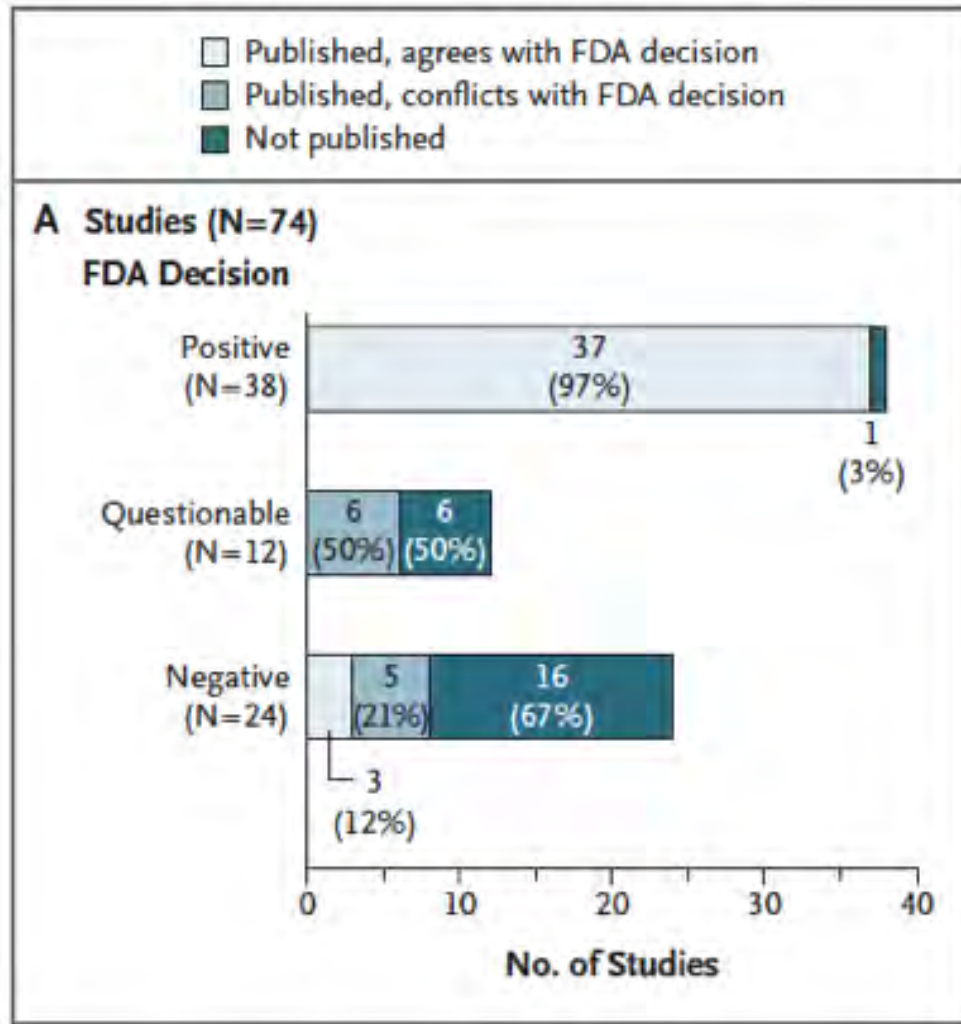
* Osteopenia es el primer tipo (MAYNES 10)

* The project benefits from a grant from Iceland, Liechtenstein and Norway through the EEA Grants.

An imperfect evidence base



Antidepressant effectiveness



- Turner et al. *N Engl J Med* 2008;358:252-60

* The project benefits from a grant from Iceland, Liechtenstein and Norway through the EEA Grants.

TAMIFLU

A Cochrane group's attempt to reproduce an analysis underpinning the use of oseltamivir in pandemic influenza hit a brick wall. **Deborah Cohen** retraces its steps



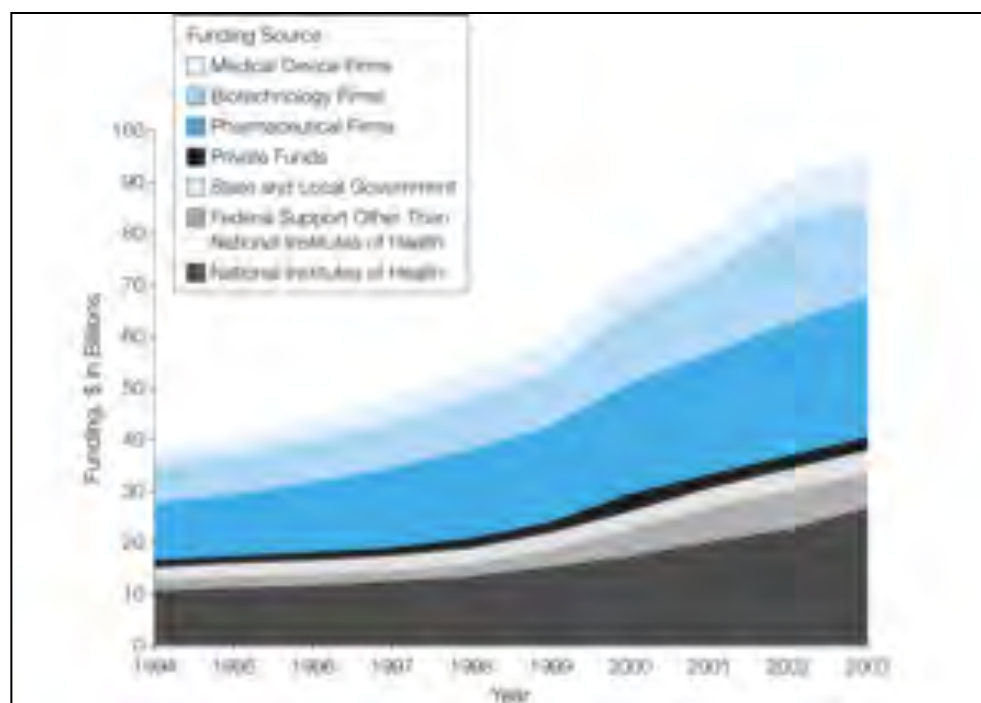
COMPLICATIONS

Tracking down the data on oseltamivir

Industry research sponsorship

- twice the odds of favourable results
 - Odds ratio = 2.15 (95% CI 1.7-2.7)

Lundh et al. Cochrane library 2012



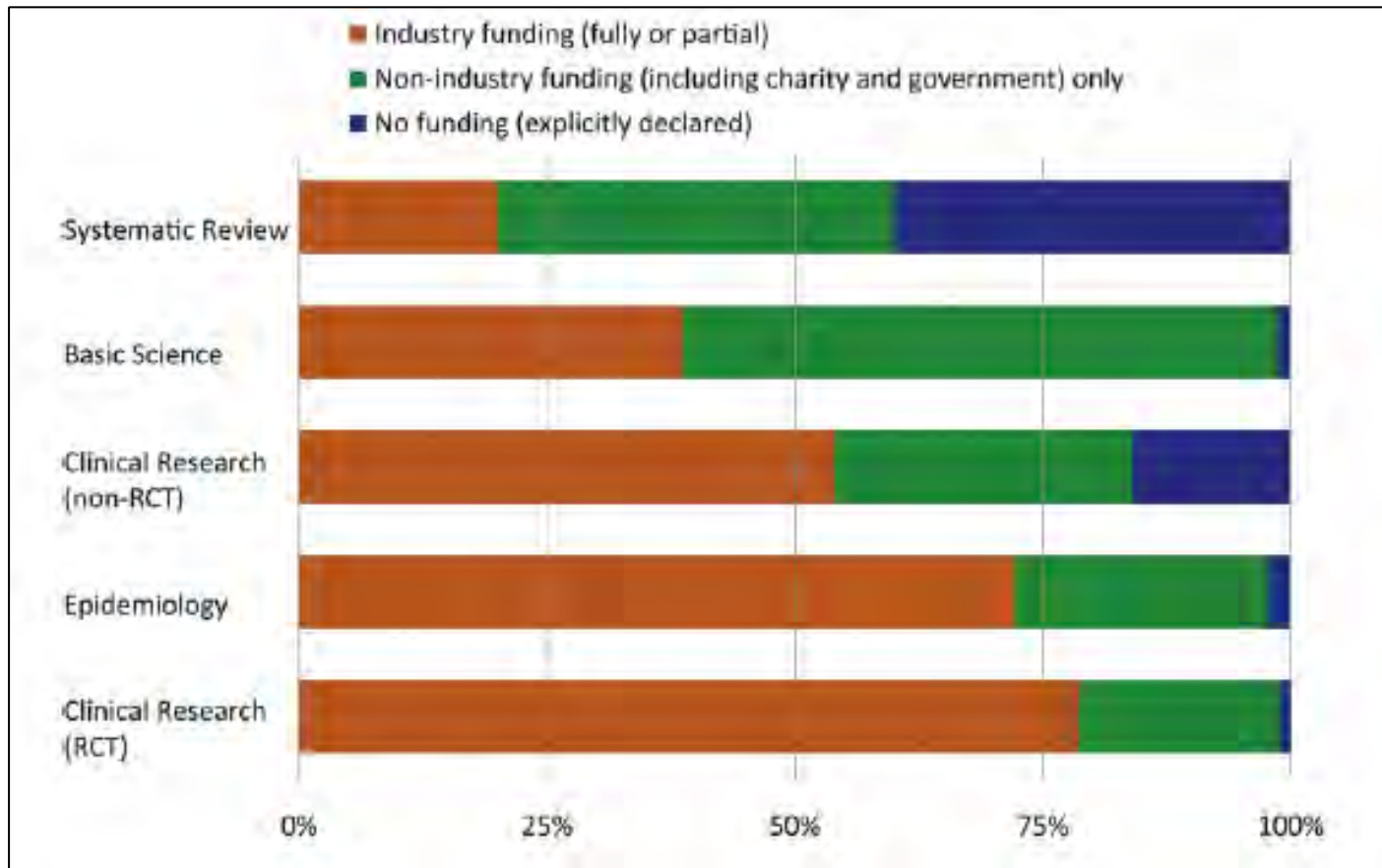
Moses et al. JAMA. 2005;294(11):1333-42

Trials comparing 2 or more cholesterol-lowering drugs

- Bero et al. *PLoS Med* 2007; 4(6):e184

- Systematic review; n=192 studies
- 95 (50%) industry-sponsored
- Sponsor strong predictor of which drug did best
 - OR=20 (95% CI 4 - 93) – results favour sponsor's drug
 - OR=35 (95% CI 7 – 168) – conclusions favour

Body of research literature on overactive bladder



Tikkinen et al. Europ Urol 2012; 61: 746-8

* The project benefits from a grant from Iceland, Liechtenstein and Norway through the EEA Grants.

Reshaping disease diagnoses

1 in 3 adults 40 years of age and older report OAB symptoms of urgency, frequency, and leakage.



Learn more now >

013E-057-8026



health topics ▾ healthy living ▾ pregnancy & parenting ▾ midlife & beyond ▾ womentalk ▾ community **for professionals**

RSS Feed sign up for free newsletters Print

oab center

featured article

Health Center - Overactive Bladder

OAB affects up to 43% of women and has life-altering symptoms. The good news is that you do not have to just cope. OAB is a treatable medical condition. Here, you will find tips to help manage OAB symptoms, learn about new treatment options and get help starting the conversation about OAB with your health care provider.



Critical appraisal – evaluating study quality and risk of bias

Critical appraisal “in a nutshell”

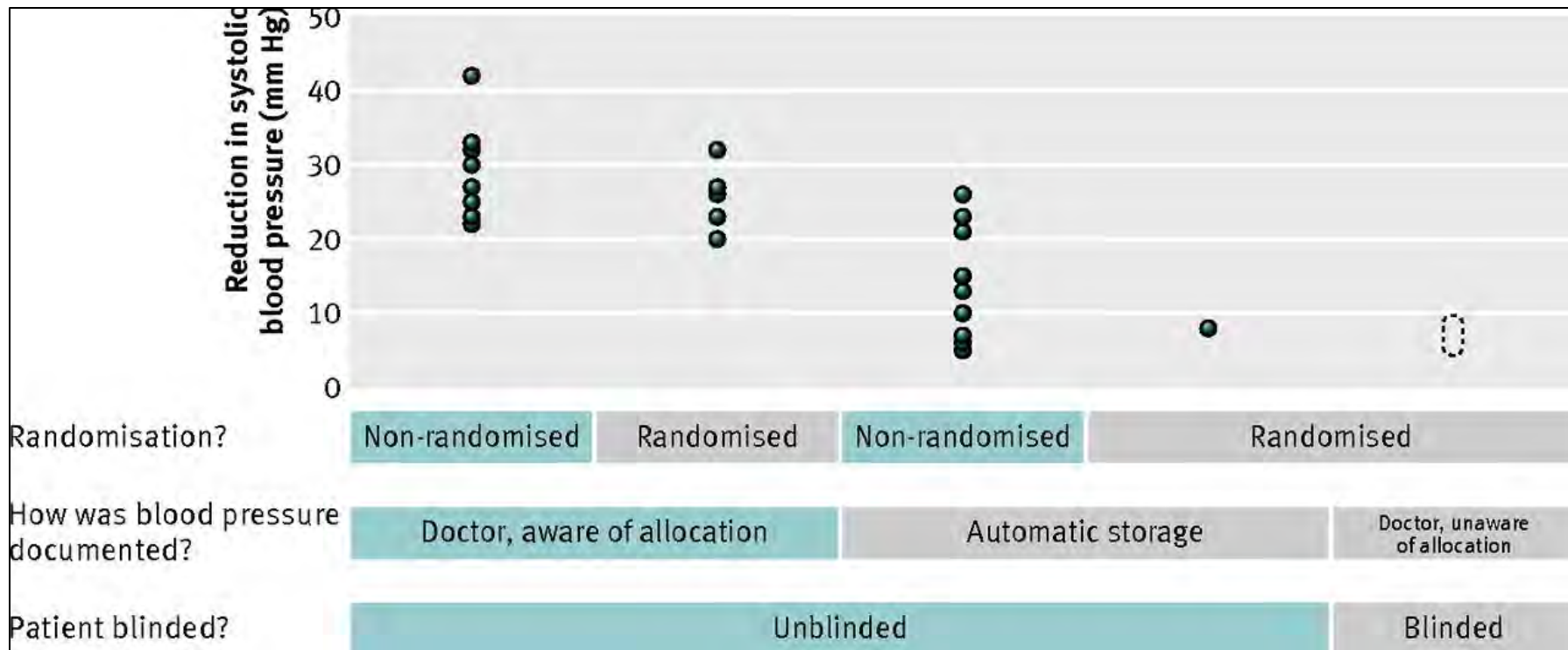
- How strong is the study design?
- How well was it carried out?
- Can you trust the results?
- Can you apply them to ‘real life’ patients?

Cochrane Risk of Bias Tool

(biases known to exaggerate estimated effects)

Type of bias	
<i>Selection bias</i>	<i>Randomization, allocation</i>
Performance bias	Blinding of participants and caregivers
<i>Detection bias</i>	<i>Blinding of outcome assessment</i>
Attrition bias	Incomplete outcome assessment
<i>Reporting bias</i>	<i>Selective outcome reporting</i>

<http://handbook.cochrane.org/>



“Measurement of a noisy variable by unblinded optimistic staff is a known recipe for calamitous exaggeration.”

Shun-Shin et al. Removing the hype from hypertension. BMJ 2014;348:bmj.g1937



Counting and accounting for all study participants



* The project benefits from a grant from Iceland, Liechtenstein and Norway through the EEA Grants.

Post hoc subgroup analyses ...there are many ways to cut a pie



How to get the results you want

- Compare to an inferior treatment
 - Compare to too low or too high a dose
 - Use too small a sample
 - Report only the most favourable results (endpoints; trial centres; subgroups)
 - Present results for strongest impact
- *Smith R. PLoS Med 2005; 2(5) e138*

Critical appraisal of advertisements

Hitchhiker's guide to drug ads

1. Beauty is only skin deep- seductive images
2. What's the point? – main message
3. Examine the claims – check the evidence
4. The great picture show (graphs & data)
5. “Lies, damned lies, and statistics”
6. Non sequiturs – irrelevant information
7. References – listed and obtainable?

www.healthyskepticism.org

A few sources of independent drug information

- Cochrane Database of Systematic Reviews
 - www.cochrane.org
- Therapeutics Letter
 - www.ti.ubc.ca
- Drug & Therapeutics Bulletin of Navarre
 - www.navarra.es
- US “Worst Pills, Best Pills” - \$20/ year subscription
 - www.worstpills.org
- Prescrire International
 - <http://english.prescrire.org/en/>
- UK Drugs & Therapeutics Bulletin – subscription
 - <http://www.dtb.org.uk/>
- NPS Radar – Australia
 - www.nps.org.au
- US Agency for Health Research and Quality (AHRQ)
 - www.ahrq.gov
- UK National Institute of Clinical Excellence (NICE)
 - www.nice.org.uk
- The number needed to treat
 - www.nnt.com



Comments?