# NIHR CRSU

Complex Reviews Support Unit

# Constructing the right question in the face of complexity

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# Reviews should help us to make decisions

Fundamental Questions

- What is the most appropriate treatment/strategy for this patient?
- What further studies should be commissioned?

# An example review



## Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

*Andrea Cipriani, Toshi A Furukawa*, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*

### Summary

**Background** Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.

*Lancet* 2018; 391: 1357–66

Published Online February 21, 2018 http://dx.doi.org/10.1016/S0140-6736(17)32802-7

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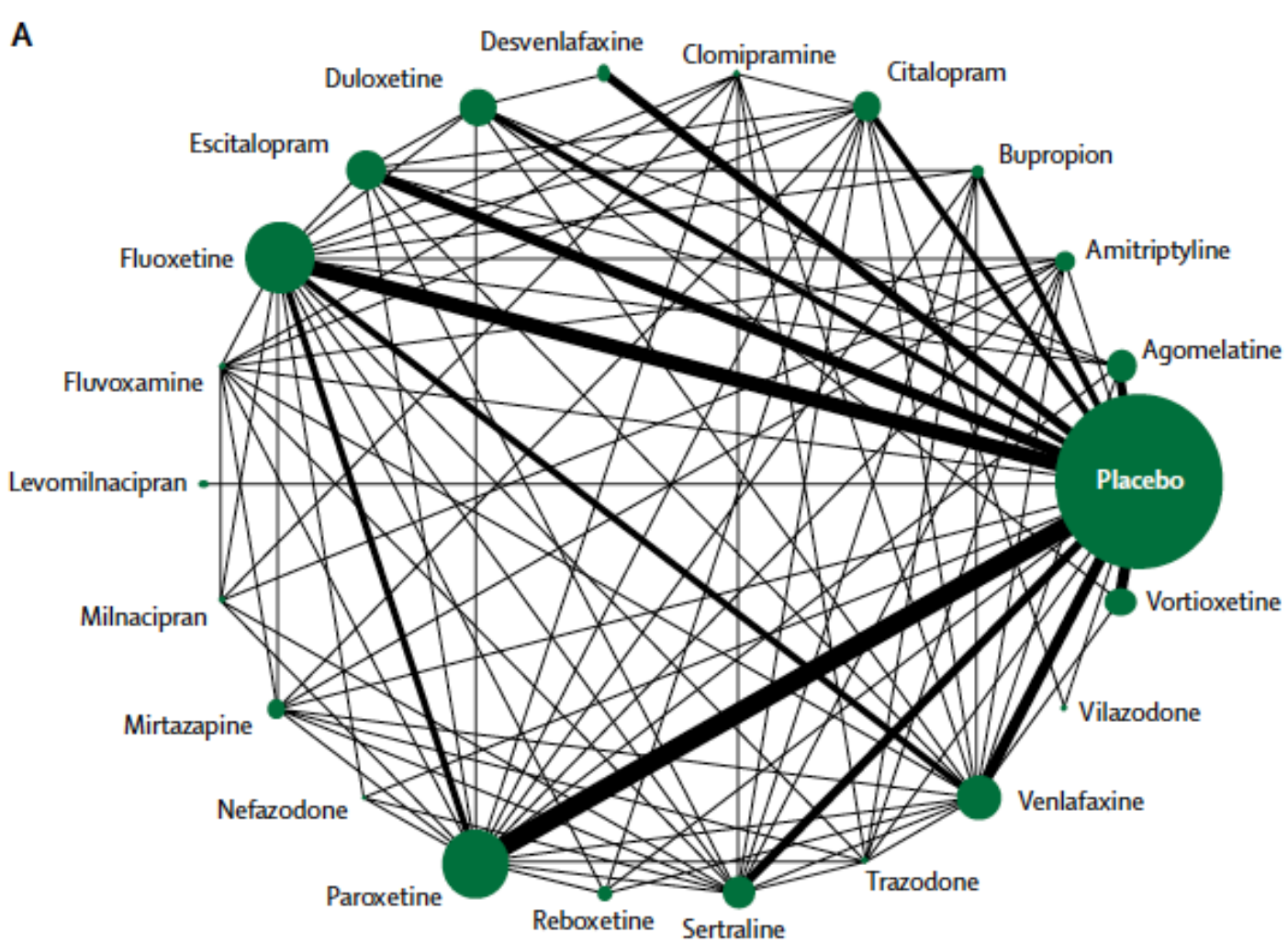
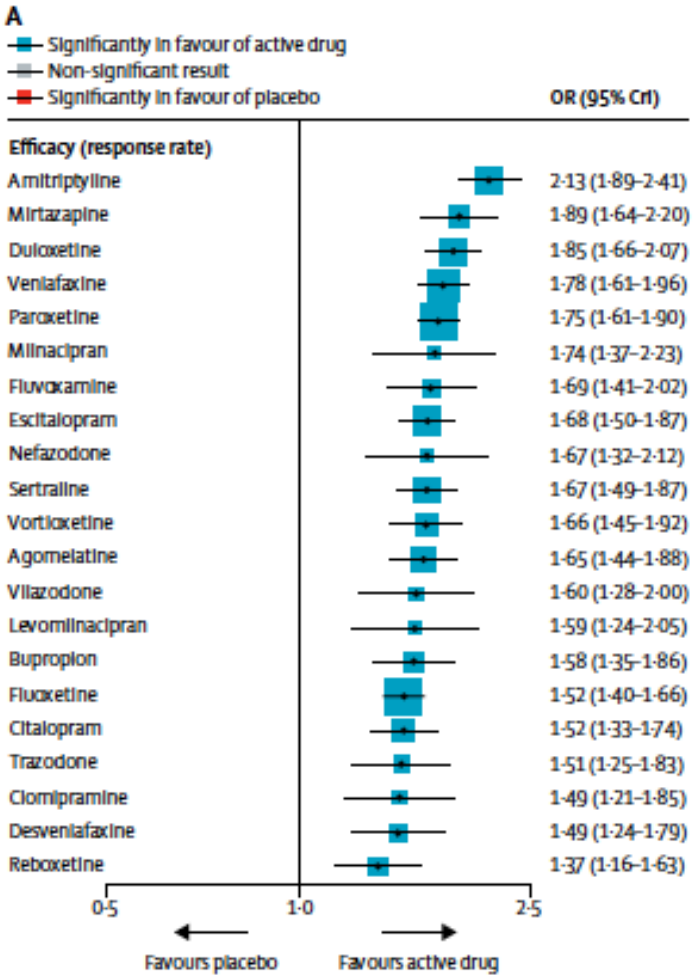
# Included an extensive network of trials and comparators

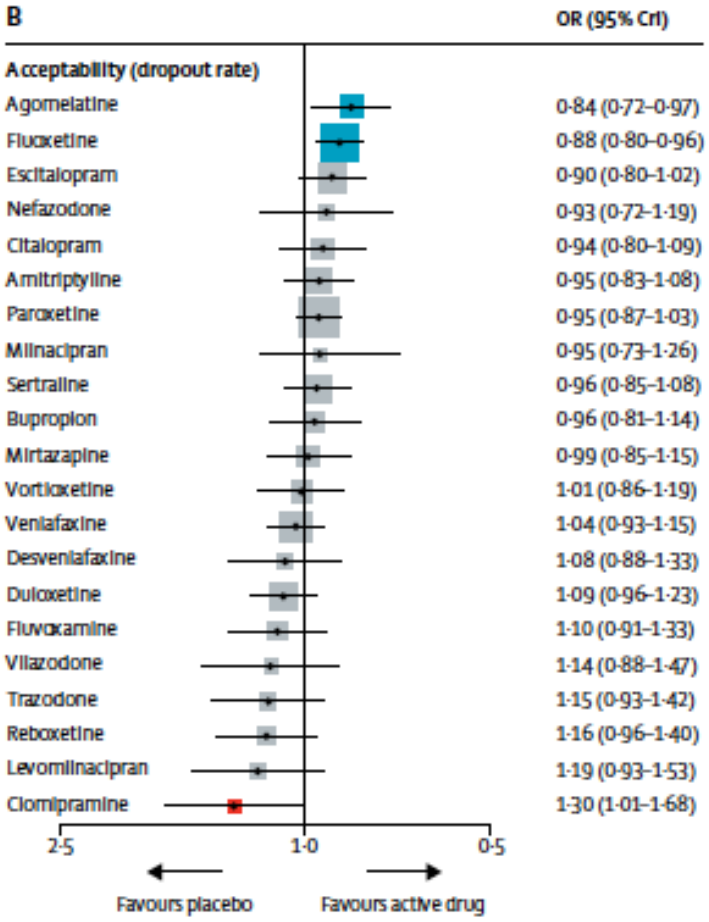


# Analysed short term outcomes

50% reduction  in Hamilton depression score at 8 weeks




All cause dropout rates at 8 weeks



# Reaction

- Lancet: “A direct clinical implication is that the three net efficacious antidepressants might be considered first choice, whereas the three less efficacious antidepressants might be avoided initially.”

- BMJ: ”Antidepressants are more effective than placebo for short term treatment of acute depression in adults, a large meta-analysis has found”

thebmj

*BMJ* 2018;360:k847 doi: 10.1136/bmj.k847 (Published 22 February 2018)



RESEARCH NEWS

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## Large meta-analysis ends doubts about efficacy of antidepressants

Abi Rimmer

The BMJ

Antidepressants are more effective than placebo for short term treatment of acute depression in adults, a large meta-analysis has found.[1] others. Our findings are relevant for adults experiencing a first or second episode of depression—the typical population seen in general practice.”

Comment

## More data, more answers: picking the optimal antidepressant

In an era of increasingly large datasets for health and emphasis on so-called big data analyses, key clinical questions remain unpretentiously simple. For example, do some antidepressants work better than others for depression? And are some more tolerable than others, at least as measured in dropout rates? A quick PubMed search of antidepressant meta-analyses yields more than 2000 hits, but the complexity of understanding which antidepressants are better or more tolerable than others is made particularly daunting by the fact that more than 40 antidepressants are available.

Andrea Cipriani and colleagues[1] provided a novel answer this latest paper, Cipriani and colleagues[2] carefully follow recommended procedures to optimise methodological rigour and identify potential sources of bias and error.[3-7] They also sought to maximise clinical relevance by focusing not only on modern antidepressants but also including the two WHO recommended essential antidepressants, amitriptyline and clomipramine.[8] Special effort to minimise bias was achieved by obtaining additional unpublished data for more than half of the studies, and also by separate analyses to look for various potential contributors to bias including pharmaceutical sponsorship. Finally, for clinical relevance and face validity,

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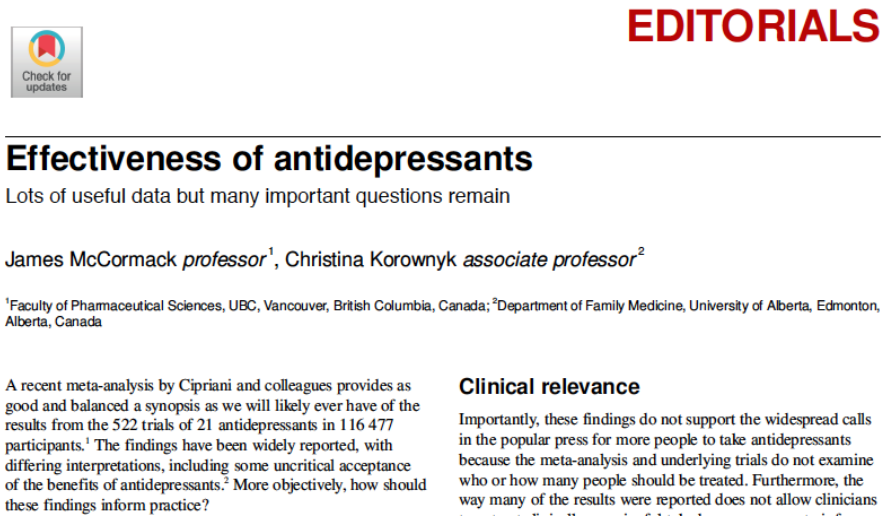
# However…

- “Authors noted novelty effect, whereby a medication looked significantly better when evaluated as the novel comparator in a trial than when as the older or control comparator”
- “patient population in this meta-analysis was limited to adults with moderate to severe depression”
- “didn’t report data on specific adverse effects such as sedation, dry mouth, sexual dysfunction, and weight gain—vital information for patients”
- “an odds ratio of about 1.6 [average across treatments] means about 10-12% more people in the treatment group would benefit compared with the placebo group [30 to 40%]”



EDITORIALS

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**Effectiveness of antidepressants**

Lots of useful data but many important questions remain

James McCormack *professor*[1], Christina Korownyk *associate professor*[2]

[1]Faculty of Pharmaceutical Sciences, UBC, Vancouver, British Columbia, Canada; [2]Department of Family Medicine, University of Alberta, Edmonton, Alberta, Canada

A recent meta-analysis by Cipriani and colleagues provides as good and balanced a synopsis as we will likely ever have of the results from the 522 trials of 21 antidepressants in 116 477 participants.[1] The findings have been widely reported, with differing interpretations, including some uncritical acceptance of the benefits of antidepressants.[2] More objectively, how should these findings inform practice?

**Clinical relevance**

Importantly, these findings do not support the widespread calls in the popular press for more people to take antidepressants because the meta-analysis and underlying trials do not examine who or how many people should be treated. Furthermore, the way many of the results were reported does not allow clinicians

Trial efficacy may not be the only, or indeed main, driver of treatment choice. Safety, patient preference, treatment and disease history, cost, may be important

# Study questions

Trial efficacy may not be the only, or indeed main, driver of treatment choice. Safety, patient preference, treatment, disease history, and cost, may be important drivers.

Consequently there are a wide range of potential study questions:

- Is this drug efficacious? Can it is do something to somebody
- Is this drug effective? What will it do something to a particular person
- What is its comparative effectiveness? How does it effects compare to alternatives
- What is the optimal duration of treatment? What is the duration of therapeutic effect
- What are its adverse effects?
- What is the effect of missing doses?
- What is its comparative effectiveness and safety in diabetic patients?, in renally impaired patients, in pregnant patients, in frail patients, in patients who have primary failure to a drug from the same class, in patients who have secondary failure,
- How does the drug interact with other drugs?
- …

# There is not a trial [or network meta-analysis] for every decision problem, or a decision problem for every trial

- Decisions are informed by a synthesis of a wide range of different types of evidence
  - May be informal and qualitative or formal and quantitative.
    - Decision aids
    - Risk benefit models
    - Cost-effectiveness models
- What is the role of systematic review and meta-analysis in this process?

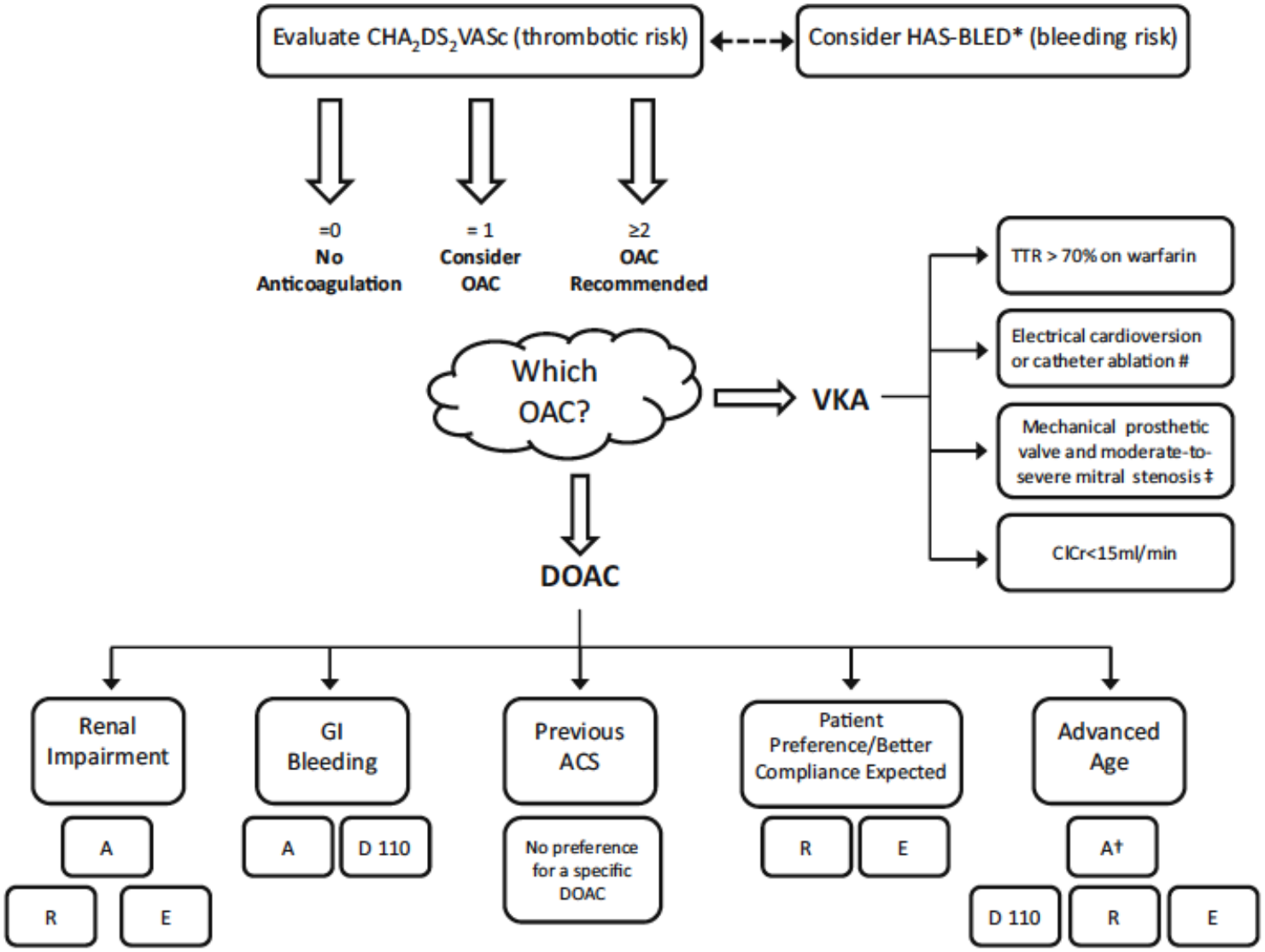
# Trisha Greenhalgh's criticisms of EBM and some suggestions

- "…stripping away all but the bare bones of a focused experimental question removes what practitioners and policymakers most need to engage with: the messy context in which people get ill, seek health care (or not), receive and take treatment (or not), and change their behaviour (or not)"
- "…refocusing on providing useable evidence that can be combined with context and professional expertise so that individual patients get optimal treatment"
- "Tools that contain quantitative estimates of risk and benefit are needed, but they must be designed to support conversations not climb probability trees."

# Practical suggestions

1. Be clear which remaining uncertainties our reviews are addressing
2. Recognise that trials may provide “parameter estimates” that are used in models (explicit or implicit) of the decision problem rather than directly addressing the decision problem
3. When considering network meta-analysis, we should be compare treatments that are likely to be comparable for identifiable set(s) of patients
   - Subgroups may be key
4. Consider non-RCT studies and other methods of synthesis (prognostic reviews, realist synthesis, decision-analytic modelling)

# Where are the remaining uncertainties in OAC use?




1. Raschi E, Bianchin M, Ageno W, De Ponti R, De Ponti F. Risk–Benefit Profile of Direct-Acting Oral Anticoagulants in Established Therapeutic Indications: An Overview of Systematic Reviews and Observational Studies. Drug Saf.; 2016;39(12):1175–87.

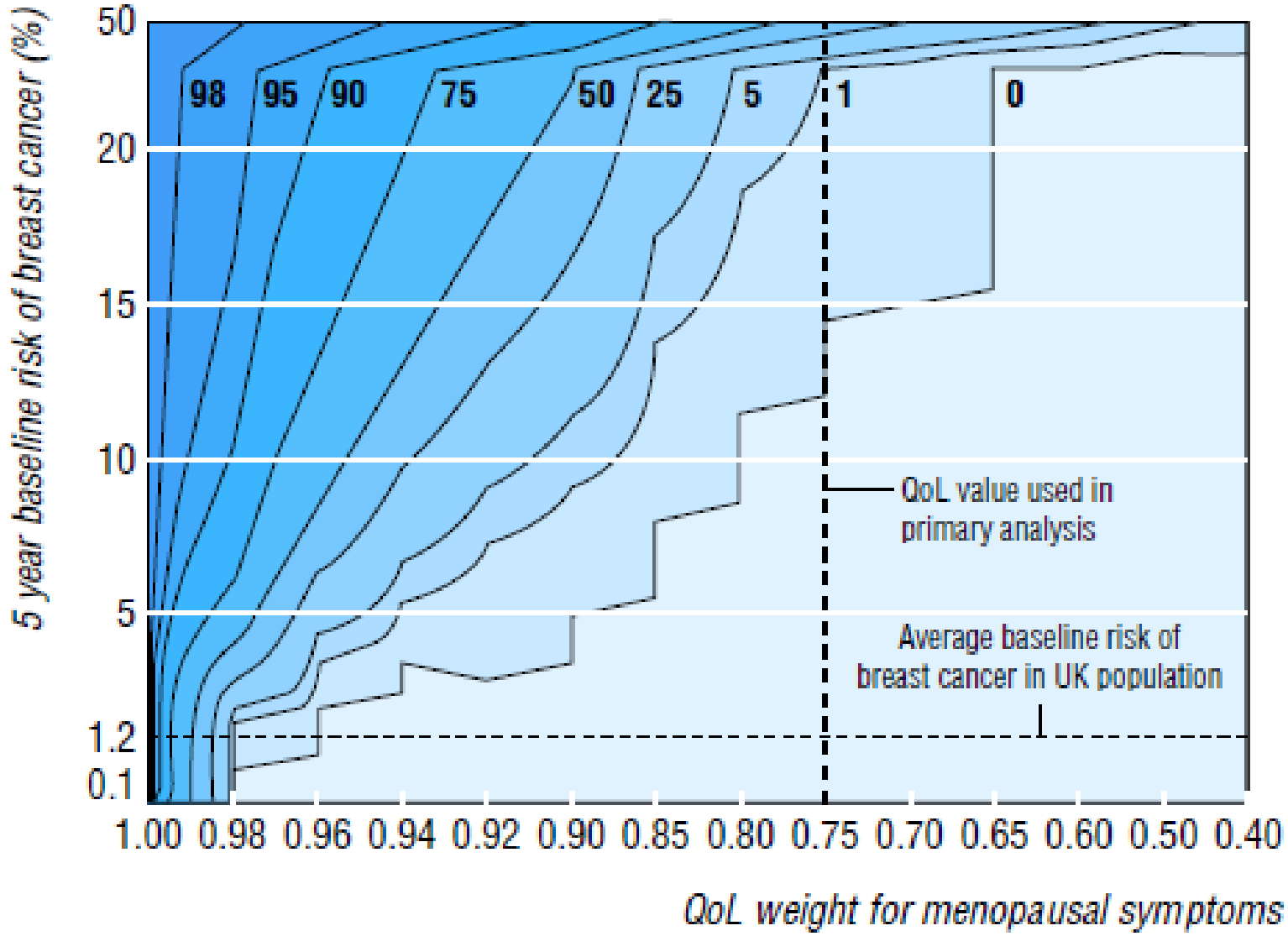
# Benefits and harms associated with hormone replacement therapy: clinical decision analysis

Data on incidence (per 10 000 population), relative risk, mortality, and quality of life used in model (see bmj.com)

| Outcome | 5 year cumulative incidence (SD) | Relative risk in 5 years* (95% CI) | Pooled relative risk (95% CrI) | 5 year cause specific mortality % (SD) | Quality of life weight (95% CI) |
|---|---|---|---|---|---|
| **Benefit:** | | | | | |
| Hip fracture | 8.8 (4.41) | HERS I and II 1.61 (0.98 to 2.66); WHI 0.66 (0.45 to 0.98) | 0.94 (0.68 to1.25) | 15.8 (5.92) | 0.92 (0.82 to 0.99) |
| Menopausal symptoms | —† | — | Cochrane Review 0.28 (0.18 to 0.44) | —‡ | 0.75 (0.66 to 0.83) |
| Colorectal cancer | 18.45 (0.45) | HERS I and II 0.81 (0.46 to 1.45); WHI 0.63 (0.43 to 0.92) | 0.69 (0.49 to 0.96) | 55.6 (0.65) | 0.80 (0.74 to 0.86) |
| Endometrial cancer | 12.25 (0.37) | HERS I and II 0.25 (0.05 to 1.18); WHI 0.83 (0.47 to 1.47) | 0.75 (0.42 to 1.24) | 17.0 (0.60) | 0.90 (0.70 to 0.98) |
| **Harm:** | | | | | |
| Breast cancer | 122.60§ (1.16) | HERS I and II 1.27 (0.84 to 1.94); WHI 1.26 (1.00 to 1.59) | 1.27 (1.03 to 1.55) | 30.0 (0.30) | 0.89 (0.86 to 0.92) |
| Coronary heart disease | 26.50 (6.80) | HERS I and II 0.99 (0.84 to 1.17); WHI 1.29 (1.02 to 1.63) | 1.08 (0.94 to 1.24) | 23.0 (0.77) | 0.86 (0.85 to 0.88) |
| Pulmonary embolism | 29.00 (10.96) | HERS I and II 2.86 (1.13 to 7.26); EVTET 2.92 (0.31 to 27.35); WHI 2.13 (1.39 to 3.25) | 2.31 (1.54 to 3.31) | 8.5 (0.56) | 0.87 (0.84 to 0.91) |
| Stroke | 40.64 (11.49) | HERS I and II 1.09 (0.88 to 1.35); WHI 1.41 (1.07 to 1.85) | 1.21 (1.02 to 1.42) | 36.7 (1.36) | 0.86 (0.85 to 0.87) |

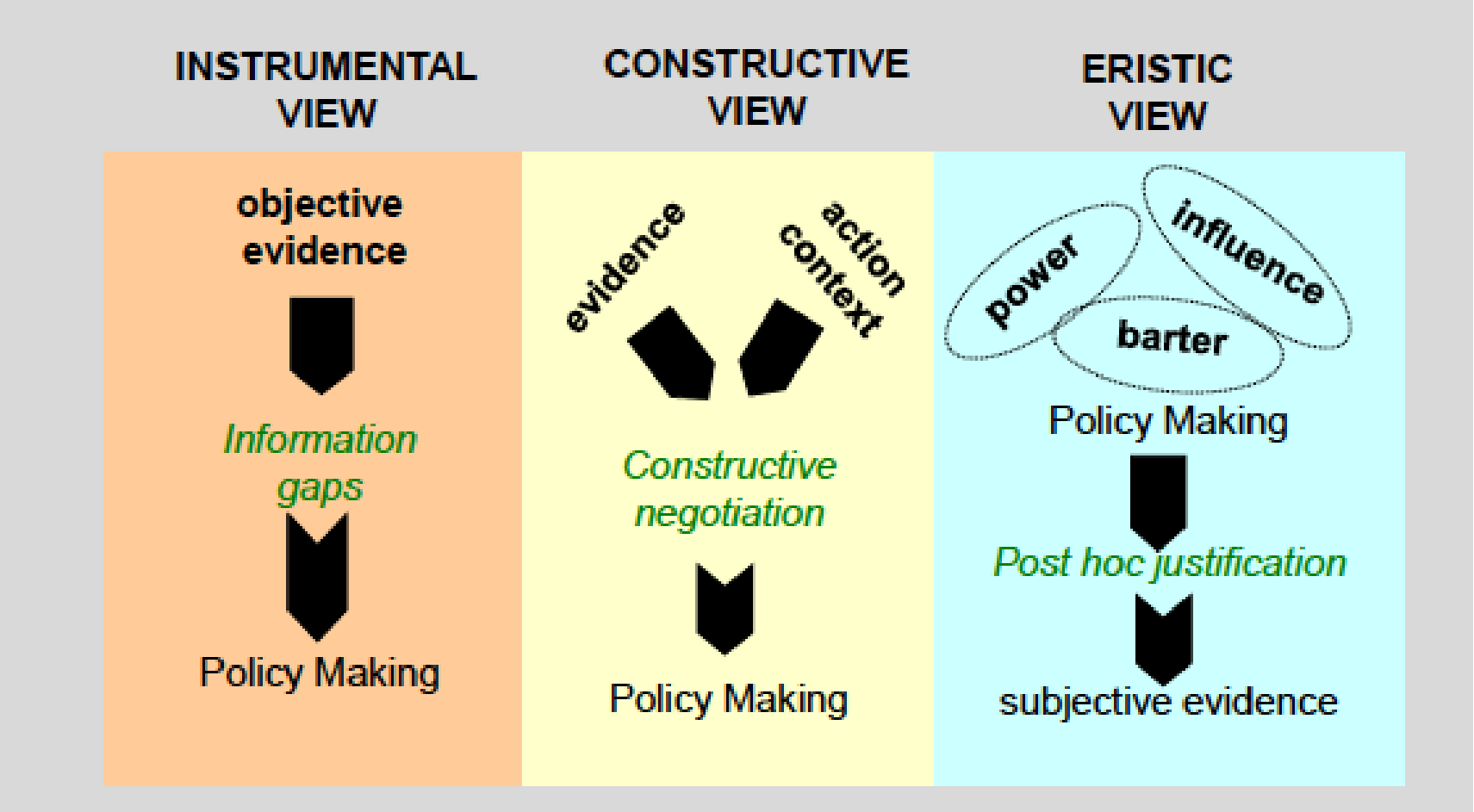
Minelli et al. *BMJ* 2004;328:371

# Implications for individual decisions



# Additional Slides

# How does evidence influence policy?




From *Royal College of Nursing International Conference*, *Oxford, 5thApril 2017*, Evidence-based policy? Really?, Professor Trish Greenhalgh