EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Monitoring the outcome of regulatory action

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Monitoring and evaluating the effect of regulatory action: some recent case studies

- Work conducted at MHRA
- Collection of 4 case studies that the epidemiology unit had wanted to carry out:
  - For scientific reasons in and of themselves
  - To test feasibility to detect impact of communications
  - To better understand CPRD use in this area
- Each perhaps too small to justify publishing by themselves
- Cover a wide variety of questions

Four Studies

- Restricting Modafanil indications
- Reminder to HCPs regarding benzodiazepines
- Introduction of risk minimisation measures for dosulepin
- Change in prescribing for piroxicam
- Will focus on the last 2 to illustrate the key points rather than run through them in depth

Operational Methodological Challenges

- Challenges in recording exposure and outcome
- Primary and secondary care prescription
- Linking to ONS mortality
- Ability to conduct meaningful sensitivity analyses

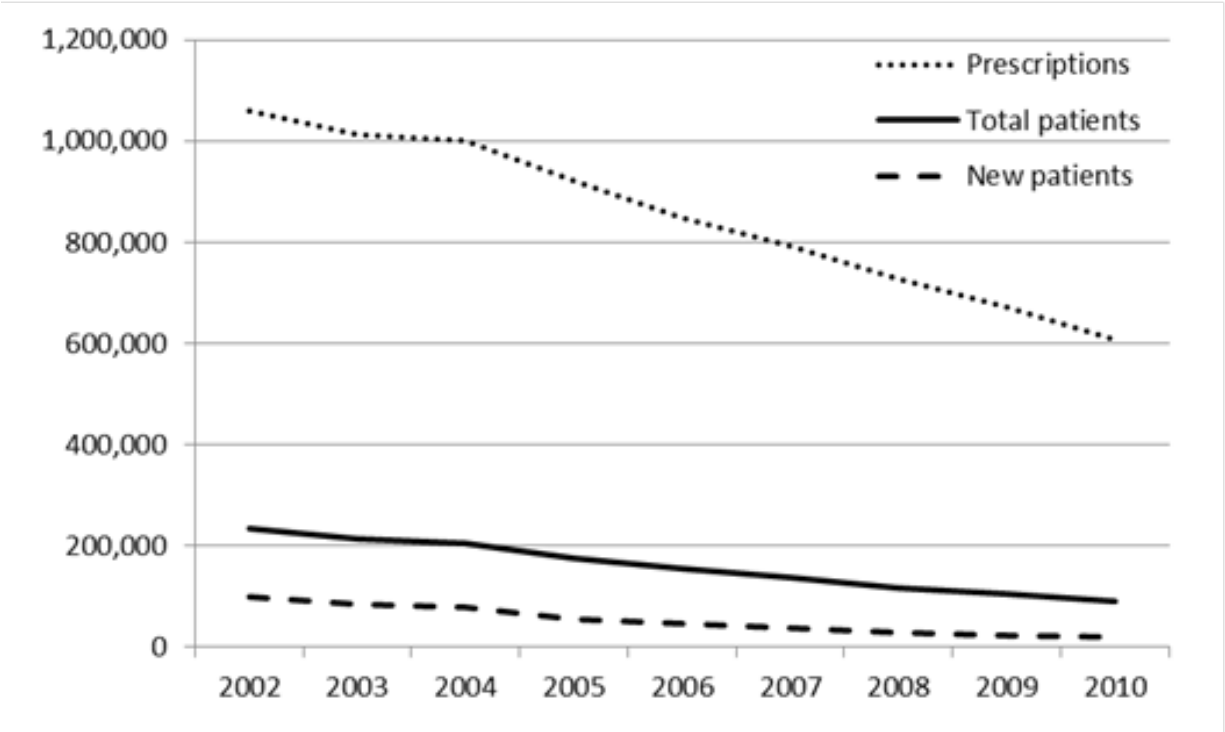
Statistical Methodological Challenges

- Selecting the right denominator
- Comparator choices
- Selecting the right ‘measure of effect’ (beyond endpoints)
- Temporal changes in patient population

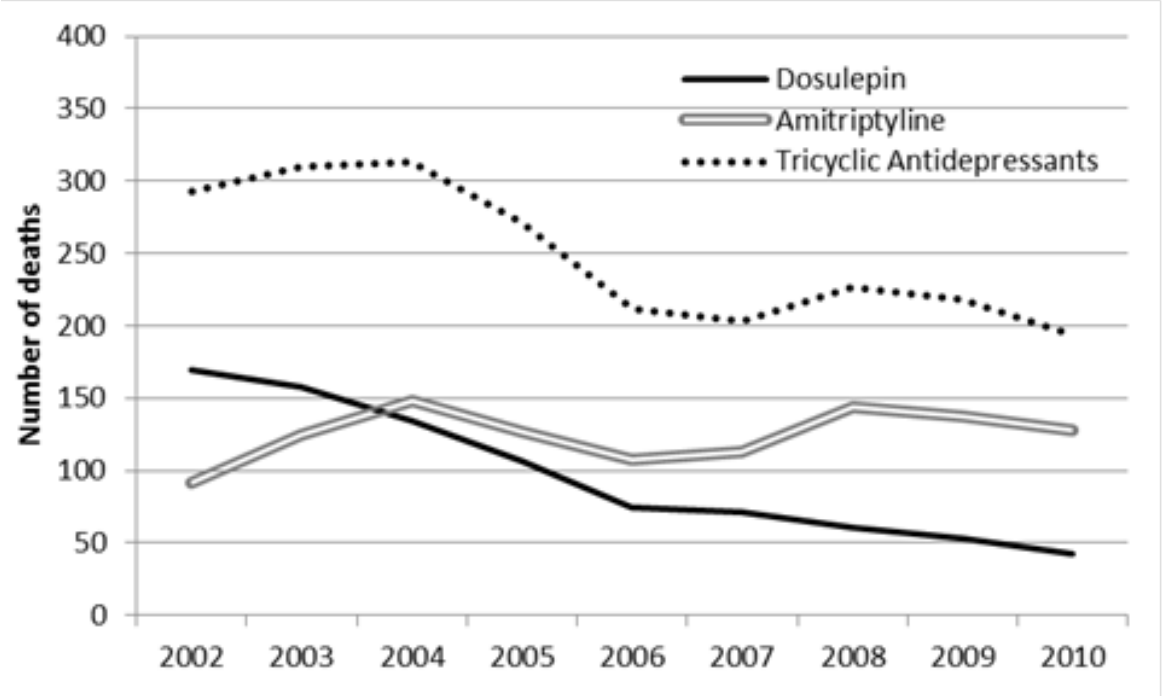
Dosulepin

- Aim to link data from CPRD to ONS data for mortality
- Pick a suitable active comparator
- See whether regulatory action had an effect on the ‘death rate’

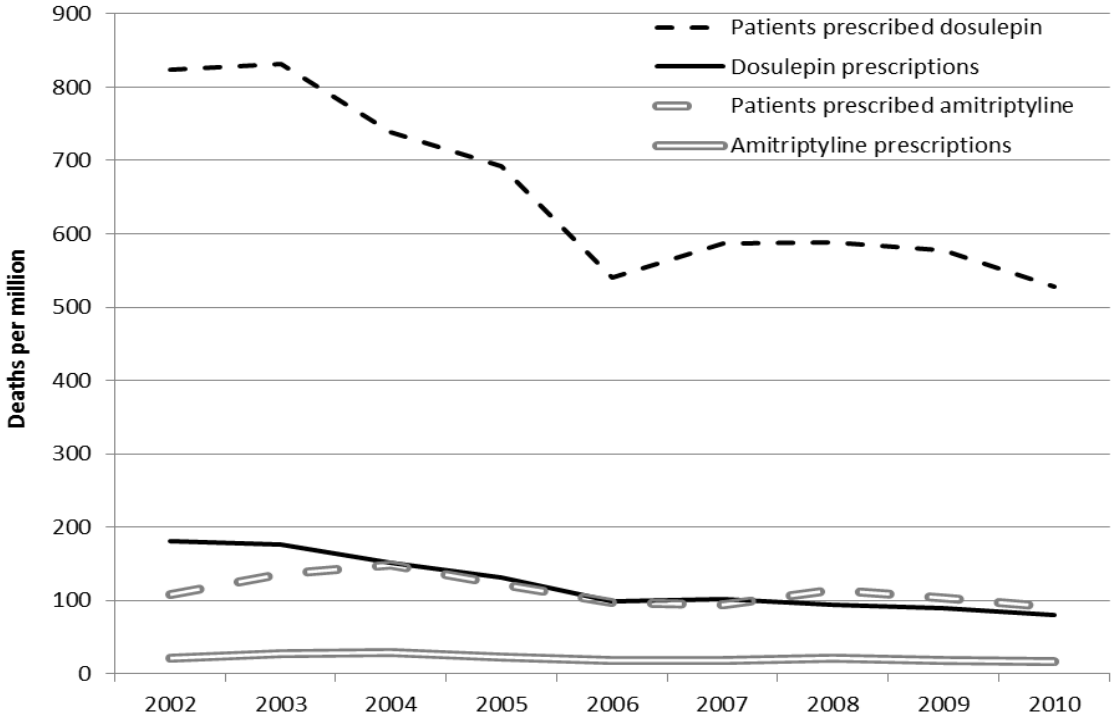
Dosulepin Prescriptions



Number of UK deaths due to poisoning from dosulepin, amitriptyline and other tricyclics



Death rate per prescription and per patient for dosulepin and amitriptyline



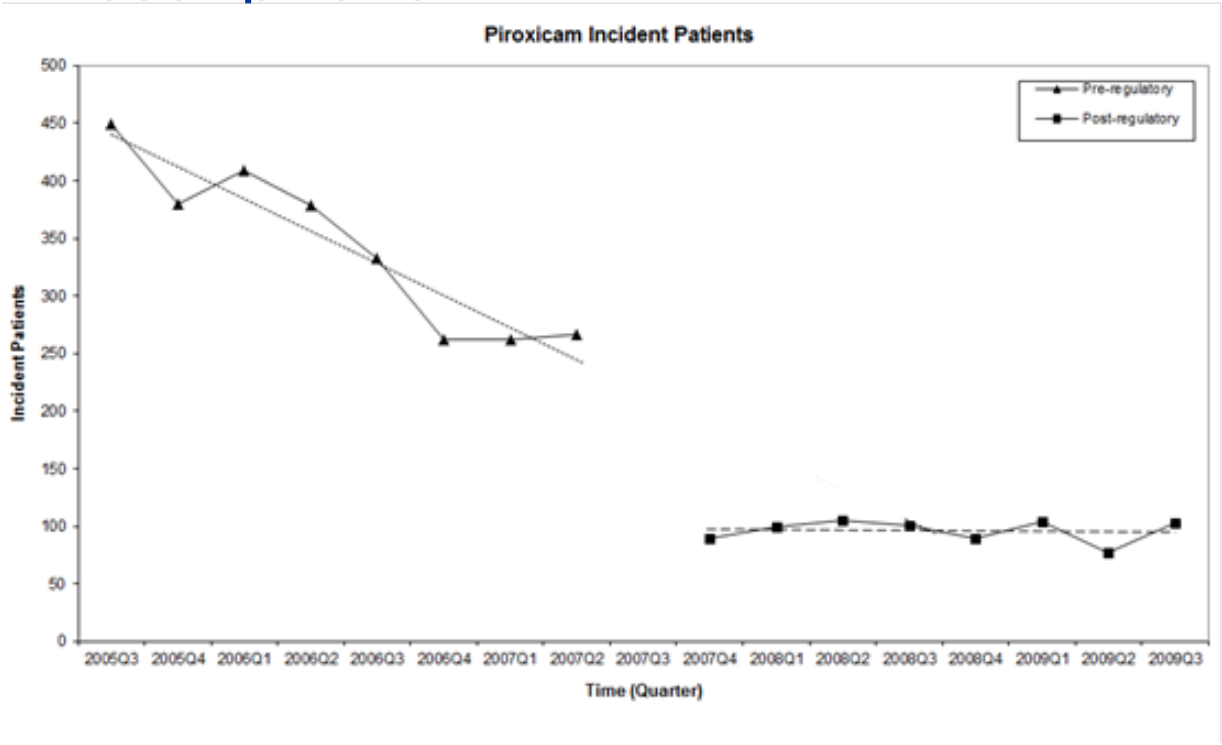
Choice of denominator

- Patients or prescriptions?
- What if average length of prescription changes?
- How much can / should you look at the denominator data before deciding on your plan of action?
- Need for pre-specification, sensitivity analyses, and the ability to report all the results, whilst acknowledging the *post hoc* nature of them
- Matter of interpretation, but clear overall differences in the amitriptyline and dosulepin experiences

Piroxicam

- Epidemiological studies were published that suggested systemic piroxicam posed a significantly greater risk of serious gastrointestinal toxicity than other NSAIDs
- Advice in June 2007:
- Restricted to 2nd line initiation by specialists
- Reducing the maximum allowable daily dose to 20mg daily

Piroxicam Prescriptions



Proportion of patients prescribed more than 20mg/day piroxicam for first prescription

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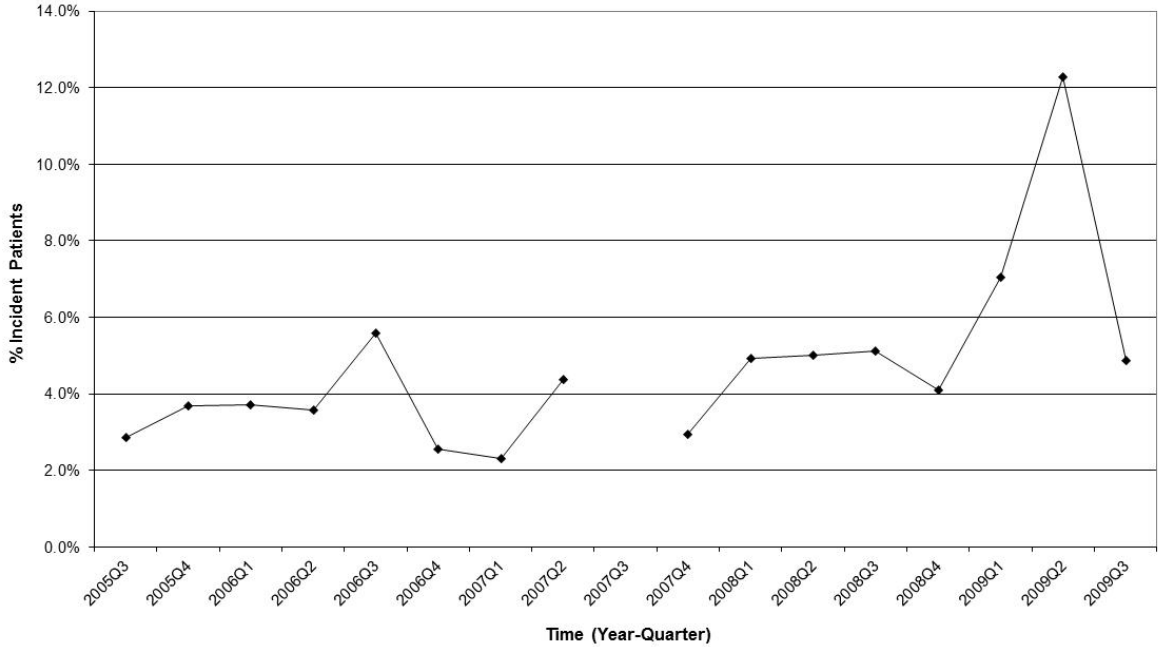

Interpreting the results

- The slope went from trending downwards to being completely flat
- Naïve slope analysis would suggest effect of action in the wrong direction
- Slope analysis would not capture the effect, due to the large discontinuity which ‘explains’ the effect
- Looking for either a discontinuity or a change in slopes
- Can we understand *a priori* what it might look like? (non-methodological question)

Interpreting the Results

- Proportion of patients being prescribed >20mg went up
- Against a background of a large drop in prescription
- Being reserved for those who *really* need it
  - Potentially more severe patient population
- Such a patient population may require a higher dose
- Change in patient population might make this a bad metric for assessing regulatory action impact
  - Clear in this example. Maybe not so much in others

Conclusions

- Examples showed the methodological and operational challenges of such approaches
- One-size-fits-all is not possible, but it *may* be possible to use such EHRs
- Careful pre-specification enhanced credibility of results
- Care needed to ensure a suitable design is chosen
- Sensitivity analyses may help with interpretation

Thank You

- Acknowledgements: Wilhelmine Meeraus, Jenny Wong, Rafe Suvarna and Katherine Donegan (all MHRA) for their input into the paper.

- Any Questions?