Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Case studies looking at regulatory action and communication – a national experience

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In this talk…

A Member State approach to communicating risk minimisation advice

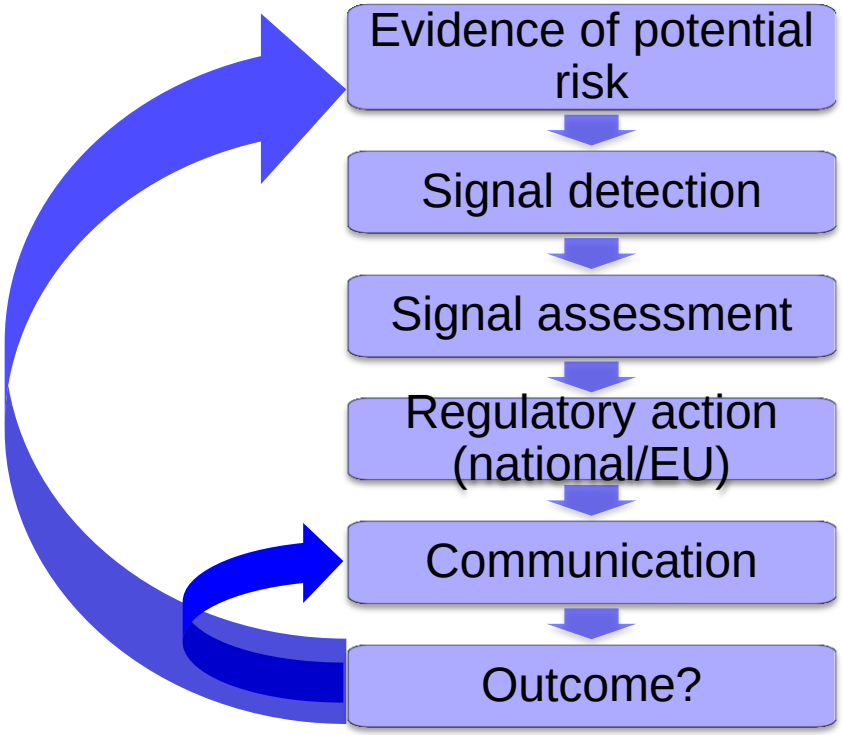
Measuring uptake of messages

- **Readership of national communications and survey results**
- **Some case studies on measuring prescribing changes and outcomes**

Factors that affect level of uptake and implementation of risk minimisation

Conclusions on this experience

Pharmacovigilance as an audit cycle



How do we communicate risk minimisation?

EU regulatory action CHMP/PRAC/CMD(h):

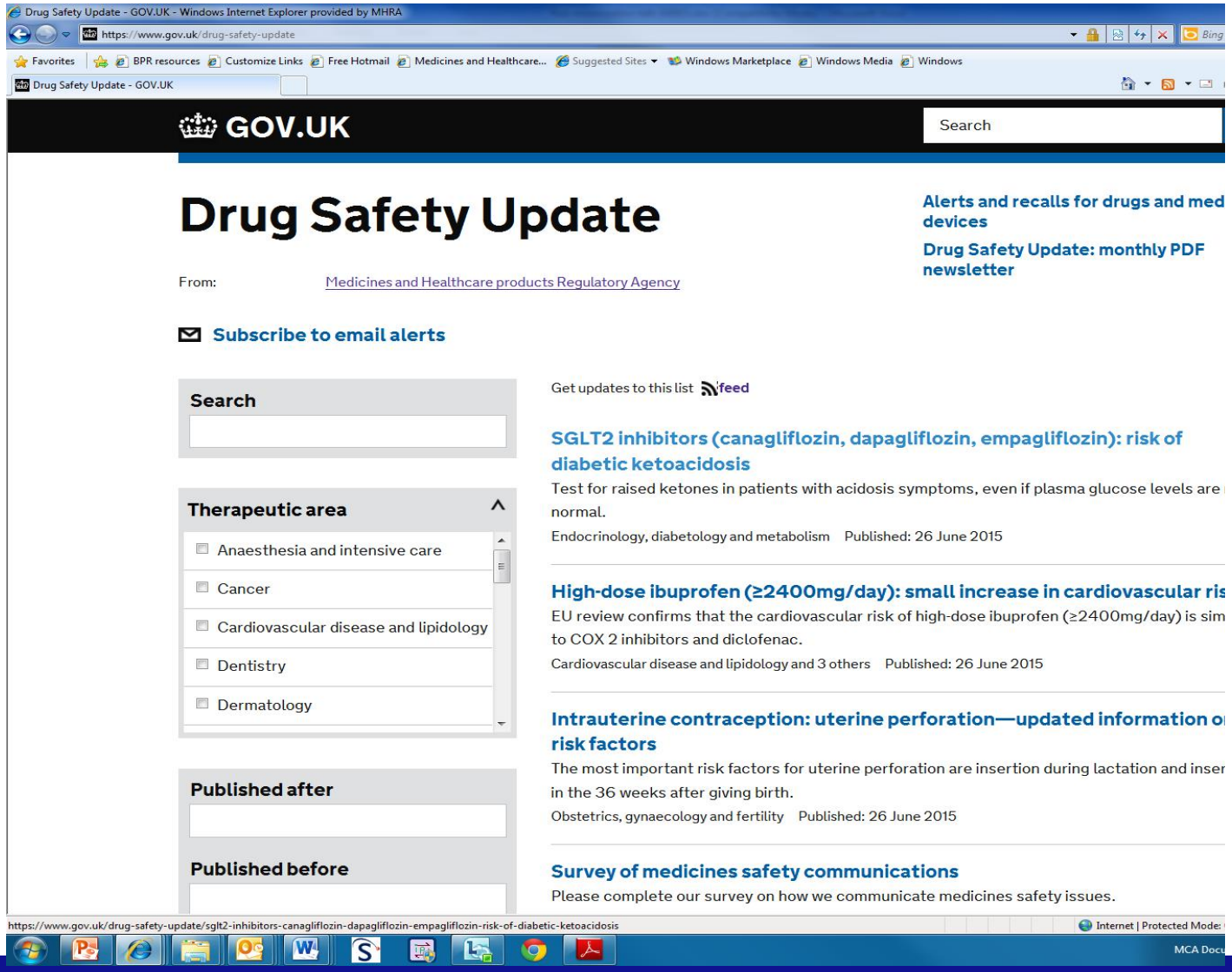
Product information (SPC/PIL)

Primary comms: DHPC; **Drug Safety Update;** Urgent message cascade, MHRA website

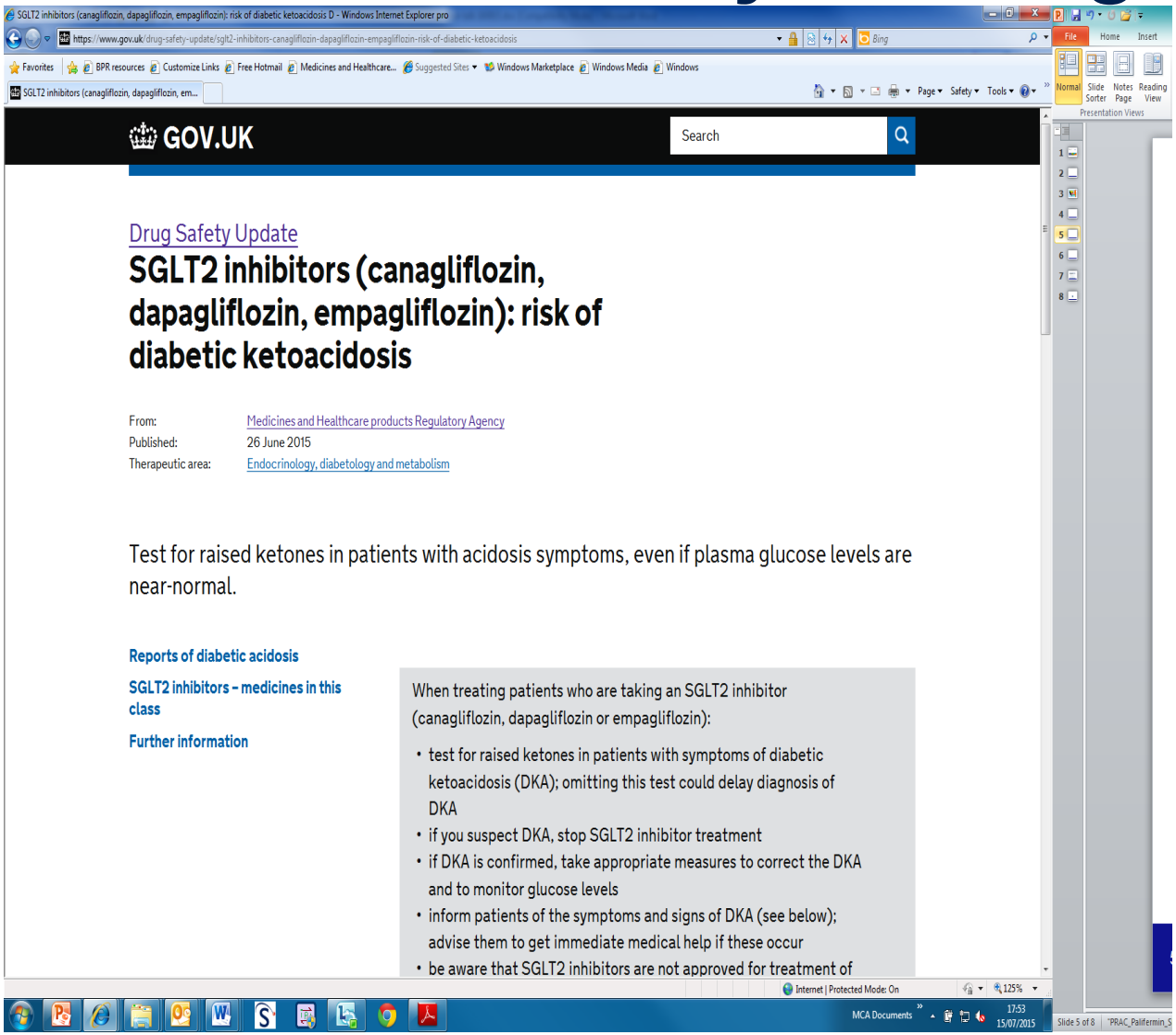
Secondary comms: Publication and networks: **BNF**; **NICE**; BMJ Public Assessment reports; Others

Impact assessment? Range of measurements/studies…

DRUG SAFETY UPDATE



Short articles with key messages



GOV.UK

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Drug Safety Update

SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin): risk of diabetic ketoacidosis

From: Medicines and Healthcare products Regulatory Agency
Published: 26 June 2015
Therapeutic area: Endocrinology, diabetology and metabolism

Test for raised ketones in patients with acidosis symptoms, even if plasma glucose levels are near-normal.

Reports of diabetic acidosis

SGLT2 inhibitors – medicines in this class

Further information

When treating patients who are taking an SGLT2 inhibitor (canagliflozin, dapagliflozin or empagliflozin):

- test for raised ketones in patients with symptoms of diabetic ketoacidosis (DKA); omitting this test could delay diagnosis of DKA
- if you suspect DKA, stop SGLT2 inhibitor treatment
- if DKA is confirmed, take appropriate measures to correct the DKA and to monitor glucose levels
- inform patients of the symptoms and signs of DKA (see below); advise them to get immediate medical help if these occur
- be aware that SGLT2 inhibitors are not approved for treatment of

Secondary communications
e.g. British national Formulary

"*authoritative, independent guidance on best practice with clinically validated drug information.*

"*Information in BNF publications has been validated against emerging evidence, best-practice guidelines, and advice from a network of clinical experts*"

Updated monthly on line and 6-monthly in print: incorporates much MHRA advice

Targeted information to patients, with DSU:

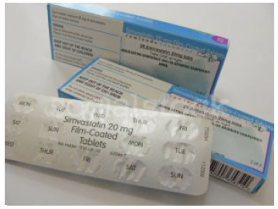
Simvastatin: why your dose or treatment may have recently changed

Article date: October 29th 2012

Key messages

Simvastatin is a medicine used to lower cholesterol and reduce the risk of heart problems and strokes.

- As with any medicine, simvastatin may cause side effects in some people. Most side effects are mild, but very rarely they can be serious
- Some medical studies have found that taking high doses of simvastatin together with the medicines amlodipine or diltiazem may increase the risk of side effects such as muscle pain or cramps, and rarer serious muscle effects
- Your doctor may have reduced the dose of your simvastatin treatment or changed your treatment to another statin because you are taking another medicine, such as amlodipine or diltiazem
- Stop taking simvastatin and see your doctor as soon as possible if you experience muscle pain or cramps whilst taking this medicine, whether or not you are also taking amlodipine or diltiazem



Your doctor may change your simvastatin treatment if you are taking some other medicines. If you experience muscle pain or cramps while taking simvastatin, stop taking it and see your doctor as soon as possible.

What is simvastatin and what does it do?

Simvastatin belongs to a widely used group of medicines called statins which are used in adults to lower their cholesterol levels. It is given to people with:

- high levels of cholesterol or fats in their blood
- an inherited illness called familial hypercholesterolaemia that increases cholesterol levels
- coronary heart disease (eg. heart attacks, angina), diabetes, a history of stroke, or other blood vessel diseases

Cholesterol is a chemical produced in the body and also contained in food. A certain amount is necessary for good health, but too much cholesterol in the blood can

Measuring Impact 1: DSU uptake

DSU readership – key communication tool – triggers secondary messages

Regular monitoring of viewing figures.

DSU viewing figures: 3month period before and after latest format changes:

201k unique views for pages in the DSU section Feb-Apr 14.

235k unique views for pages in the DSU section Feb-Apr 15.

... But no detailed information on who is reading or whether reading translates into action or positive outcomes

Measuring Impact 2: DSU surveys

Survey 2011

~1500 respondents – n.b. caution given low numbers

- 95% said navigation is easy/very easy
- 97% said the information is understandable
- 91% thought the length of articles is about right
- 98% said the advice is clear and easy to follow

Survey 2014

~2000 respondents – n.b. caution given low numbers

- 80% said they either act on DSU advice or refer it to colleagues
- 44% used the search tool for the DSU archive at least monthly

Limitations to interpretation but feedback is positive

Measuring impact 3: Does communication → action?

Measuring behavioural change:

Epidemiological approach

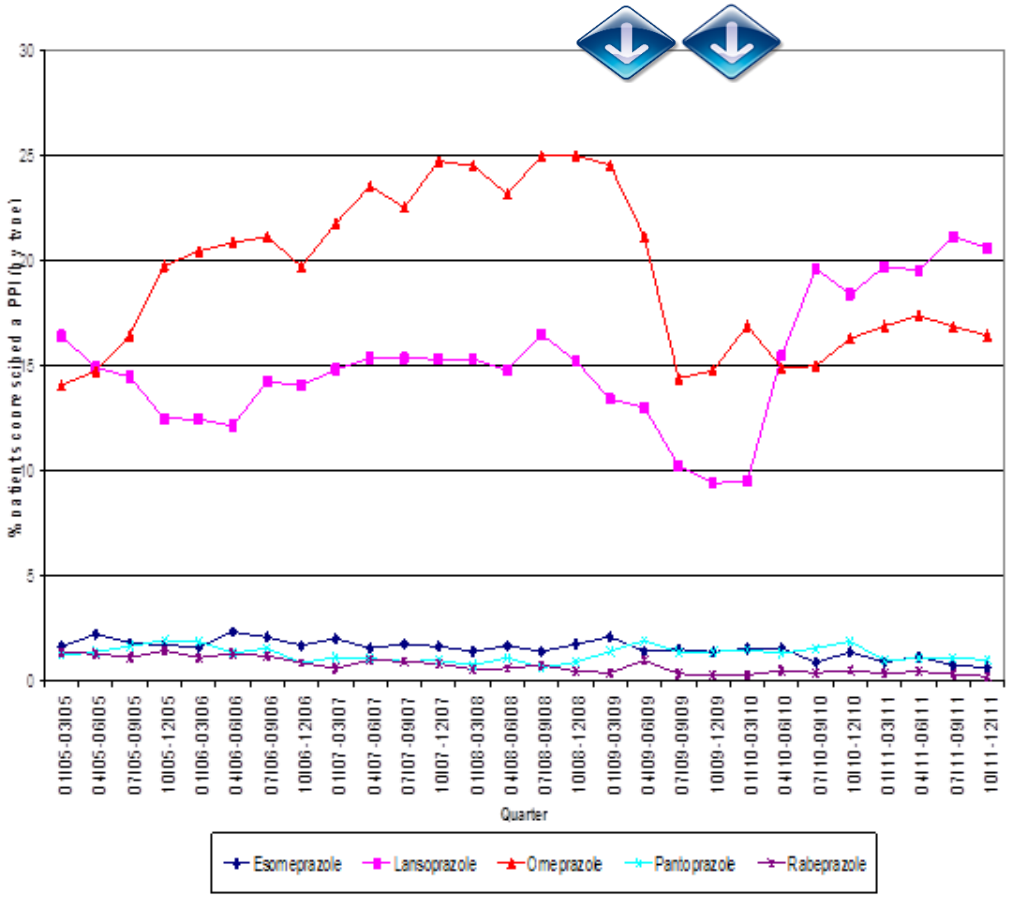
- Systematic approach
- Considered all DSU topics from launch
- Prioritisation: Public health impact and feasibility of study
- Measurable prescribing change in database e.g. CPRD,
- Selection of topics

Case studies: prescribing changes

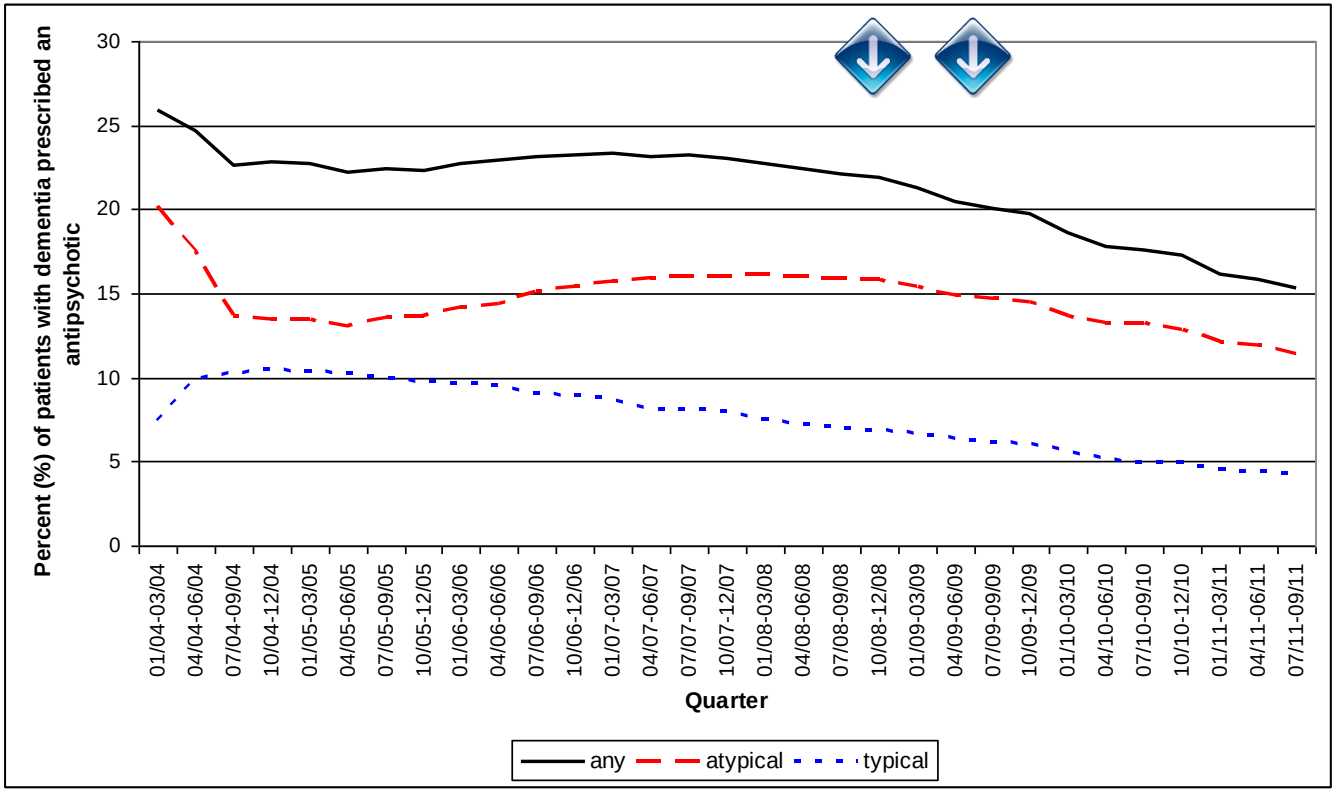
Examples:

- **Clopidogrel – interaction with PPIs**
- **Antipsychotics in dementia – risk of stroke/mortality**
- **Piroxicam – risk of GI and skin reactions**
- **Gadolinium contrast agents – Risk of NSF**

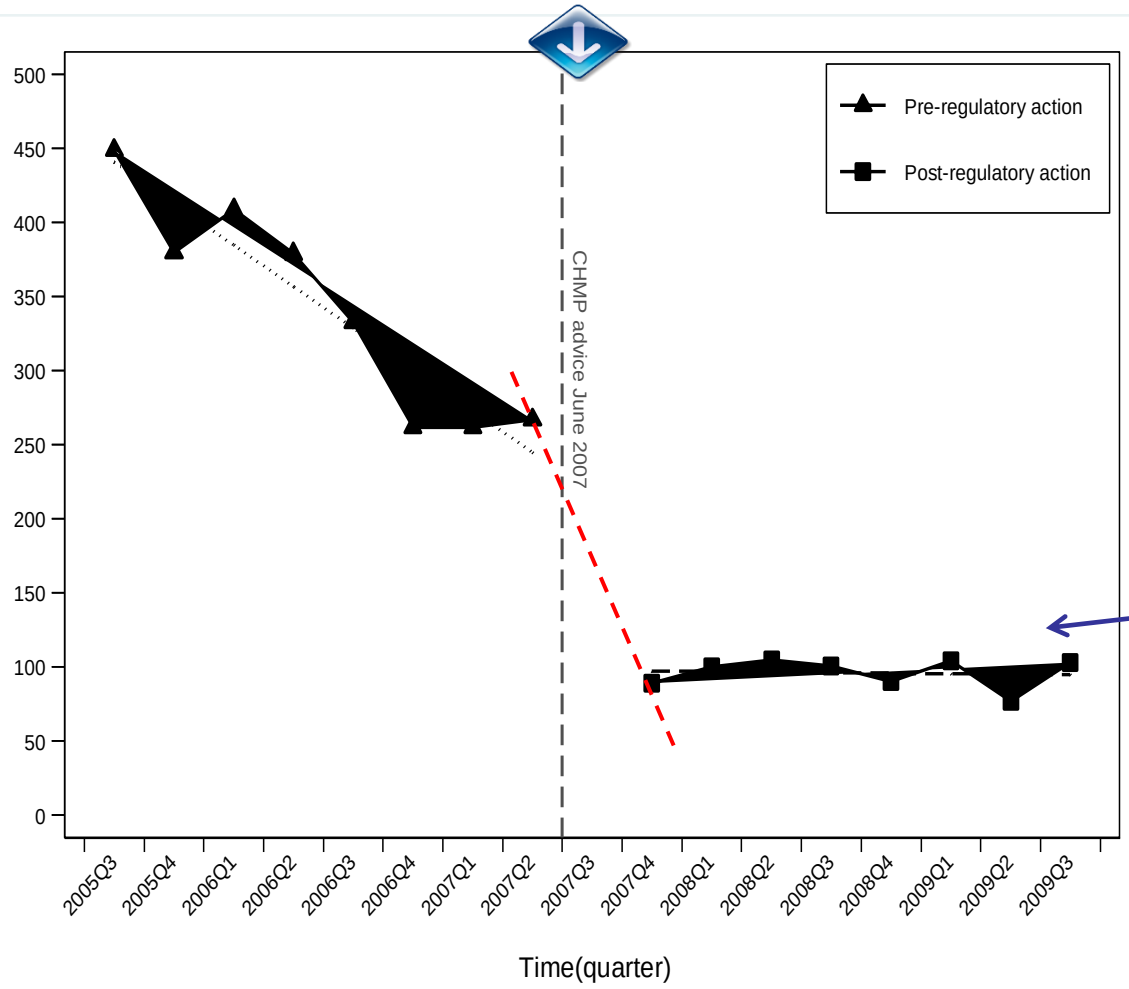
Clopidogrel/PPIs: use ‘discouraged’ CPRD 2005-2011. DSU =



Antipsychotics: advice to avoid use in dementia. DSU =

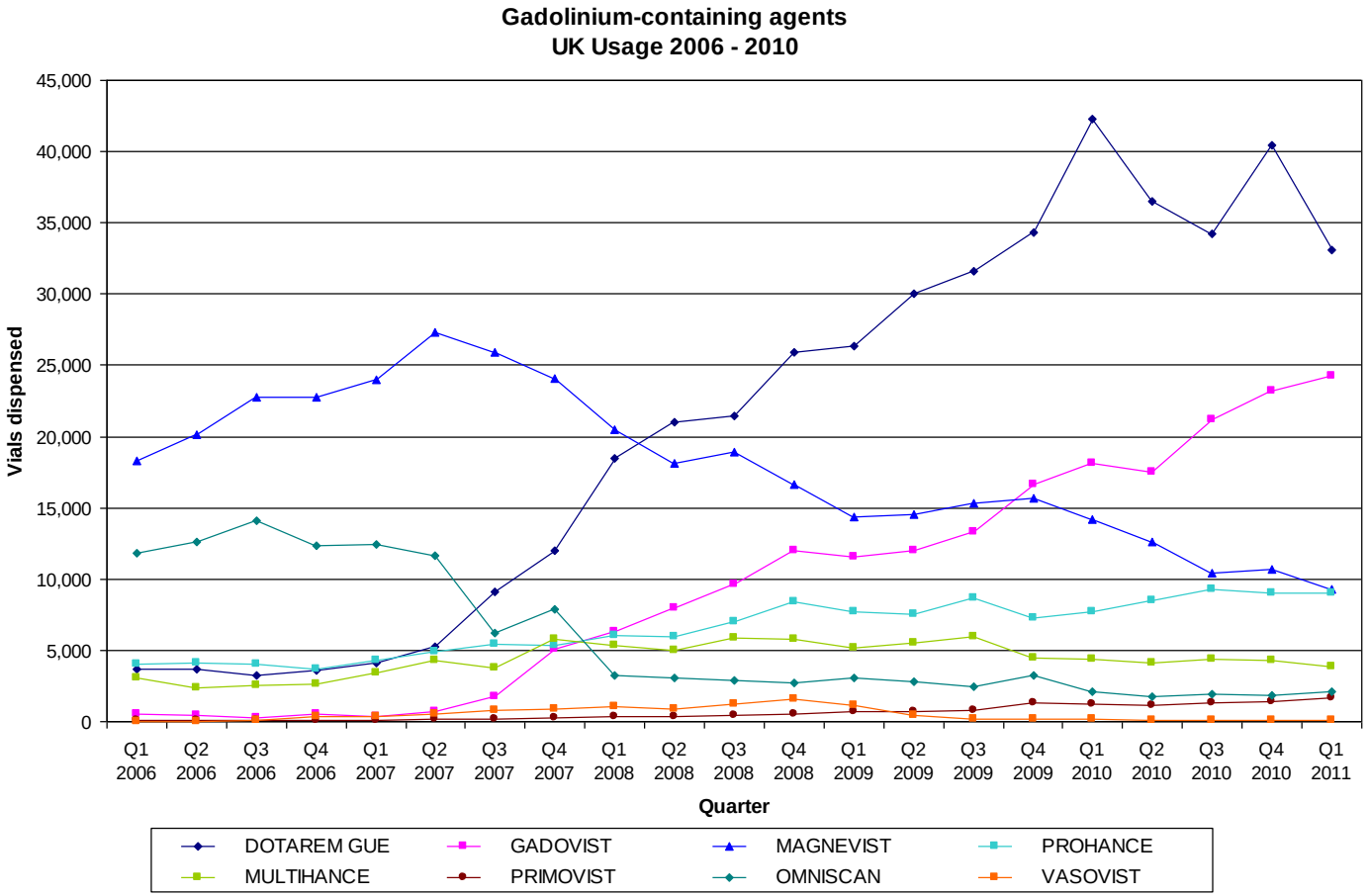


Piroxicam: second-line; restricted indications; max dose 20mg. DSU =



Higher proportion treated with > 20mg/day– patient population at greater need?

Gadolinium and NSF – High, Med, Low risk



Factors affecting uptake of RMMs?

Communication factors:

-Was the advice received?

-Was it trusted? (e.g. Industry versus Regulator versus Expert)

-Was it accessible at the time it was needed?

Message factors:

-Was it understood?

-Is the specific change in behaviour easy, or practical to execute?

-Can the message be remembered?

-How deeply ingrained is the practice that needs to change?

-What is the perceived importance of the required change?

-Is it consistent with other messages, or guidance?

Wider factors:

- What are the norms (culture) for responding to such new advice?

- What are the incentives (or disincentives) to change behaviour?

- What (local or national) support is there to assist, and remind of the need to change?

- How practical is it to keep-up with all the demands for behaviour change for various sources?

Measuring Impact 4: Prescribing change → outcome?

Challenges:

- Need registry or good database data; links to secondary care [spontaneous ADR data generally not useful].
- Case definition/validation
- May need long-term follow-up (e.g. cancers/cardiovascular)
- But it is possible to study some outcomes…

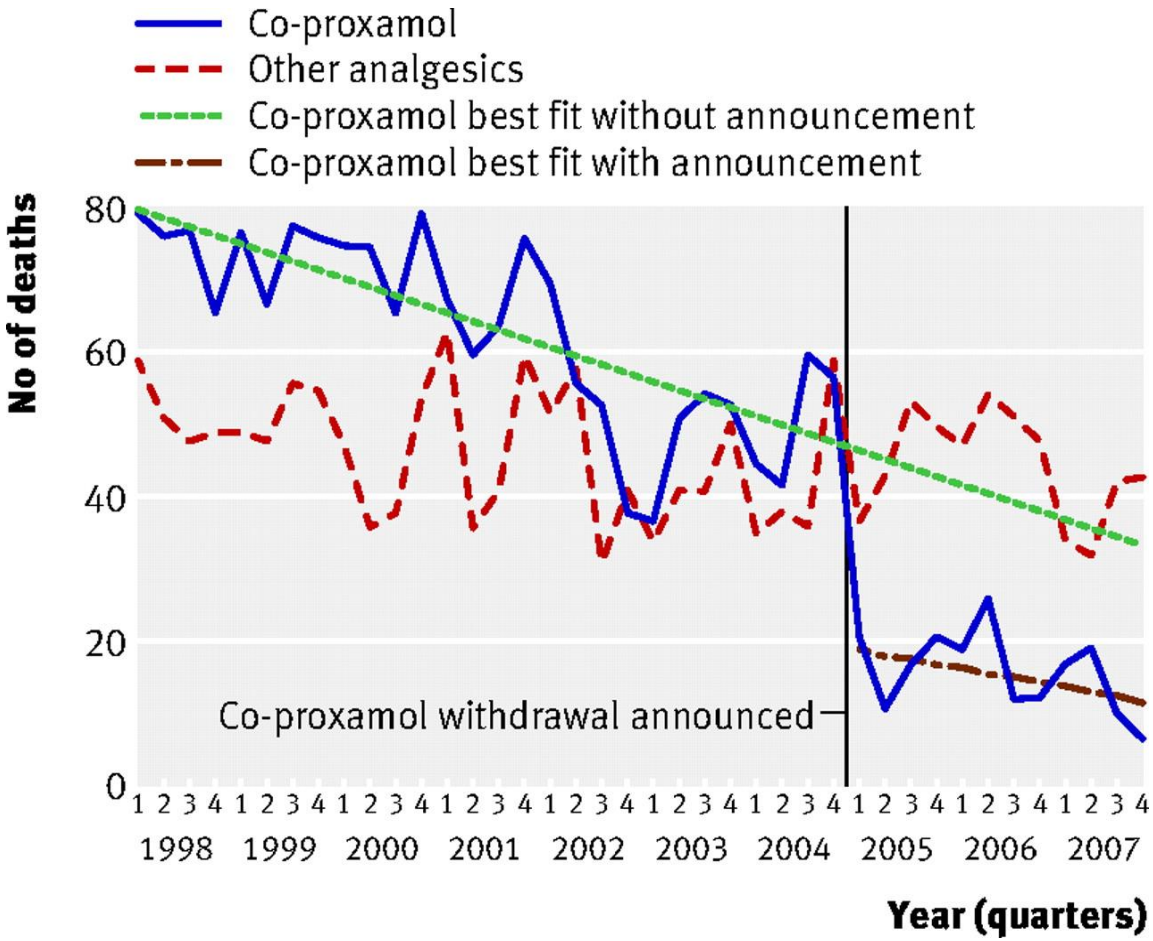
Some examples:

- **Gadolinium –** No new cases of NSF reported in EU
- **Aspirin and Reye's syndrome –** No new cases since age restriction change
- **Co-proxamol/dextropropoxyphene –** poisoning deaths

Co-proxamol/Dextropropoxyphene

Keith Hawton et al, BMJ 2009;338:b2270

“The marked reduction in suicides and accidental poisonings involving co-proxamol during this period, with no evidence of an increase in deaths involving other analgesics, suggests that the initiative has been effective”.



Reflections on national experience

- **Range of communication tools: primary; secondary**
- **Factors affecting uptake of risk minimisation measures (communications; messages; wider issues)**
- **Possible to measure 'impact' at different levels:**
- **Statistics and surveys can give *a clue* to acceptance**
- **Measuring prescribing change: possible in *some* cases**
- **Regulation: "One voice among many"**
- **Definition of "realistic" risk minimisation may vary from case to case**
- **True outcome measurement challenging – but possible**
- **Important to consider secondary effects of prescribing changes and long-term consequences**

Conclusions and future directions

Need for:

- **Communications: Variety of tools; use of networks**
- **Better use of technology; 'just in time' approach?**
- **More systematic and complete feedback from HCPs/Pts**
- **Greater use of Drug Utilisation Studies to monitor prescribing changes: shared responsibility with industry:**
  - **Have we communicated/engaged effectively?**
  - **Do we need to change or repeat the message?**
  - **Criteria for systematic measurement of impact (intended and unintended consequences)?**
- **International collaboration; maximised use of databases and registries to follow not only prescribing changes but clinical outcomes**