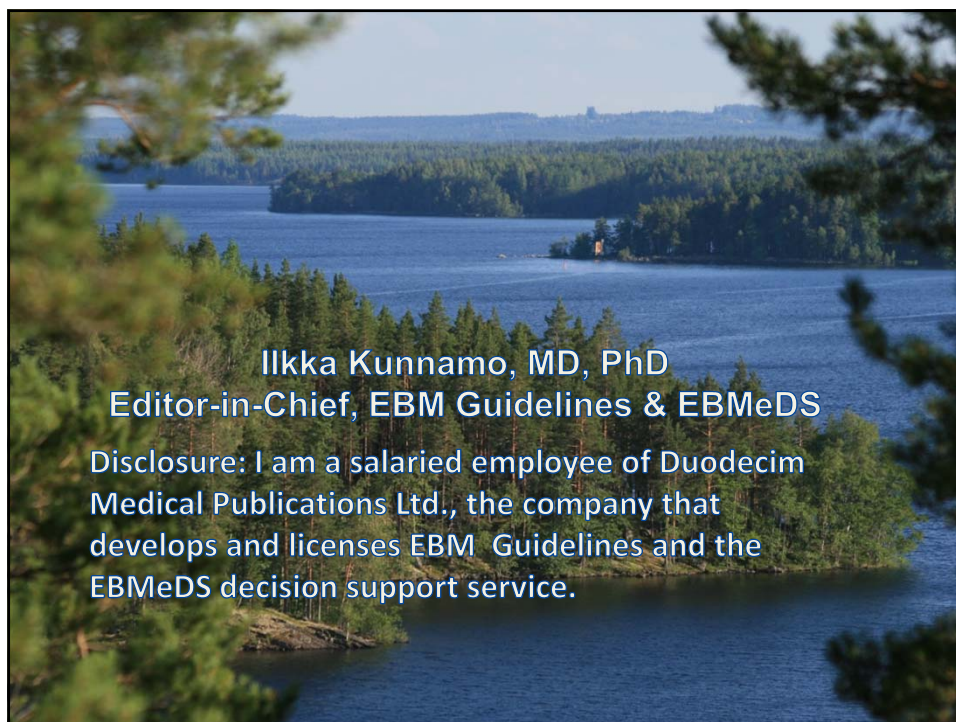




Medication and adverse drug events control with decision support systems

Ilkka Kunnamo, MD, PhD
Duodecim Medical Publications Ltd, Finland.

Nordic eHealth Exchange



Ilkka Kunnamo, MD, PhD
Editor-in-Chief, EBM Guidelines & EBMeDS

Disclosure: I am a salaried employee of Duodecim Medical Publications Ltd., the company that develops and licenses EBM Guidelines and the EBMeDS decision support service.

The PRIMA-eDS Consortium

Polypharmacy in chronic diseases: Reduction of Inappropriate Medication and Adverse drug events in elderly populations by electronic Decision Support

- Witten-Herdecke University Germany
- Rostock University Germany
- Salzburg Paracelsus University Austria
- Manchester University UK
- South Tyrolean GP Academy Italy
- Duodecim Medical Publications Finland



The problem: adverse drug events

- The median ADE incidence in ambulatory care: 14.9 per 1000 person-months.
- The preventable ADE (pADE) incidence was 5.6 per 1000 person-months.
- ADEs in ambulatory care were associated with the use of inappropriate drugs in 43%
- For pADEs requiring hospital admission, the most frequent drug therapy problem was inadequate monitoring (45%)



Thomsen LA et al, Ann Pharmacother
2007;41:1411-26



Tasks of the consortium

- Systematic literature review
- Development of an electronic decision support tool for comprehensive medication review (by Duodecim, Finland)
- Randomized trial on the effects of polypharmacy reduction in 3000 elderly outpatients



Drug adverse events preventable by robust CDS and CPOE (distribution in an analysis of 4200 paper-based electronic medical records)

	% of all
• Drug – laboratory monitoring and alerts	27
• Renal dosing	19
• Suggesting the right dose	9
• Patient age –based recommendations	9
• Reminding of guideline adherence	7
• Drug allergy warnings	4
• Dosing interval/timing	3
• Drug-drug interaction warnings	2
• Double medication alerts	1



Massachusetts Technology Collaborative and
New England Health Care Institute, 2008



Drugs most commonly associated with preventable hospitalizations

- Antiplatelet drugs 16 %
- Diuretics 16 %
- NSAIDs 11 %
- Anticoagulants 8 %
- Opioids 5 %
- Beta-blockers 5 %
- ACE/ATR 4 %
- Diabetes drugs 4 %

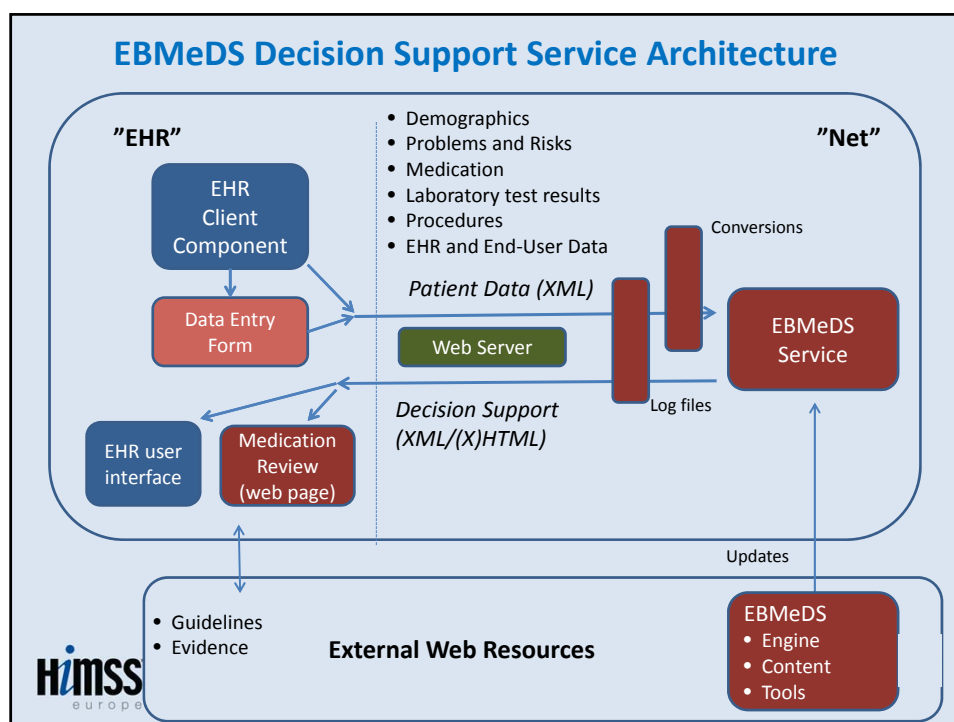
Howard RL et al. *Br J Clin Pharmacol* 2007;63:136-47



Components of comprehensive medication review

- CDS rules combining many types of data
 - Age, laboratory tests, diagnoses, vital signs, procedures...
- Indications and dosing
- Contraindications
- Drug-drug interactions
- Renal dosing
- Adverse effects
- Drugs and hepatic disease
- Cross allergies
- Drugs during pregnancy
- Drugs during lactation





Comprehensive Medication Review

- List of recorded indications (diagnoses) and drugs used by the patient for each indication
- Weight, BMI, blood pressure, eGFR, selected test results
- Laboratory monitoring for safe drug therapy
- Renal dosing, interactions, contraindications
- Drugs unsuitable for the elderly and better alternatives
- Adverse effects (cumulative across all drugs used by the patient)
- **Reminders and recommendations (stop, change, start)**

Example of a reminder

- Patient has recurrent urate tests and she/he is using thiazide diuretics medication. If the tests were taken because of gout attacks, consider switching into losartan, which has also a slight uricosuric action [i](#).

[Link to guideline](#)

D Evidence-Based Medicine Guidelines

EBMG HOME N

Lowering serum uric acid concentration

- Withdrawal of diuretic therapy and its replacement with, for example, an ACE inhibitor or angiotensin receptor blocker should be considered (**losartan** is uricosuric, i.e. it increases the excretion of uric acid).
- Diet therapy is essential and dietary advice should be given to every patient. Give written dietary instructions.
- Medication aims either to prevent the formation of urate (allopurinol and febuxostat) or increase the excretion of urate (probenecid and benzbromarone). Medication should not be prescribed based only on a raised urate concentration, unless the concentration is significantly high.
- If the patient has recurrent episodes of inflammatory arthritis or chronic gout, allopurinol should be prescribed. Allopurinol is also indicated if the patient has had renal stones. Allopurinol inhibits the formation of oxalate and urate renal stones.
 - To avoid exacerbation of symptoms, allopurinol should not be started until an acute attack has subsided. Treatment is started with a low initial dose (100–150 mg per day), which is increased to the therapeutic dose (300 mg per day) within two weeks.
 - If the plasma urate concentration does not reduce, the dose may be increased to 600 mg per day.
 - In renal failure (plasma creatinine 160–560 µmol/l) the dose is halved. In severe renal failure the maximum dose is 50–100 mg per day.

warfarin - metronidazole

- Consequences
- Recommendation
- Mechanism
- Background
- References

The evidence base for each recommendation is available

warfarin	metronidazole
Formulation	Formulation
Enteral or Parenteral	Enteral or Parenteral

Consequences

A marked increase in the effect of warfarin and bleeding may occur due to concomitant systemic metronidazole. Topical anticoagulation, but to a lesser extent.

Recommendation

Avoid combination of warfarin and systemic metronidazole treatment. If unavoidable, a dose reduction of warfarin by one half is recommended. Short-term topical (e.g. vaginal) use of metronidazole can probably be used safely during warfarin treatment.

Mechanism

Inhibition of CYP2C9 catalysed warfarin metabolism by metronidazole.

Background

The interaction between warfarin and metronidazole was recognised more than 20 years ago (1), and the clinical consequences have been studied in several patients. A study found a strong association between concomitant use of warfarin and metronidazole and overanticoagulation. The maximum effect was observed 7 - 8 days after the co-administration was initiated. While the INR was above the therapeutic range of 2.0 - 4.0 in 14 of 32 patients during the 12-day period after concomitant warfarin and metronidazole was started. However, the dose adjustment of warfarin prior adding metronidazole to the regimen in order to master the interaction was found to be difficult. The potentiation of anticoagulation remained for several days, even after the administration of warfarin was stopped (4).

Concomitant use of warfarin and metronidazole has been shown to increase the risk of acute bleeding in several studies (5,6).

Example: Merged diagnosis and medication lists according to guideline-based indications

Crohn's disease (K50)
- Methotrexate (ATC:L01BA01)

Rheumatoid arthritis (M06)
- Methotrexate (ATC:L01BA01)

Congestive heart failure (I50)
- Enalapril(ATC:C09AA)
- Furosemide (ATC:C03CA01)

Type 2 diabetes (E11)
- Aspirin (ATC:B01AC06)
- Metformin (ATC:A10BA02)
- Insulin Protaphane (ATC:A10AC01)

Coronary heart disease (I20)
- Aspirin (ATC:B01AC06)
- Isosorbide mononitrate (ATC:C01DA08)

Deep vein thrombosis (I80)
- Warfarin (ATC:B01AA03)

No recorded indications
- Ranitidine (ATC:A02BA02)

Aspirin (ATC:B01AC06)
- Coronary heart disease (I20)
- Type 2 diabetes (E11)

Enalapril(ATC:C09AA)
- Congestive heart failure (I50)

Furosemide (ATC:C03CA01)
- Congestive heart failure (I50)

Insulin Protaphane (ATC:A10AC01)
- Type 2 diabetes (E11)

Isosorbide mononitrate (ATC:C01DA08)
- Coronary heart disease (I20)

Metformin (ATC:A10BA02)
- Type 2 diabetes (E11)

Methotrexate (ATC:L01BA01)
- Crohn's disease (K50)
- Rheumatoid arthritis (M06)

Warfarin (ATC:B01AA03)
- Deep vein thrombosis (I80)

Ranitidine (ATC:A02BA02)
- No recorded indications

Drug adverse effects: cumulative scoring

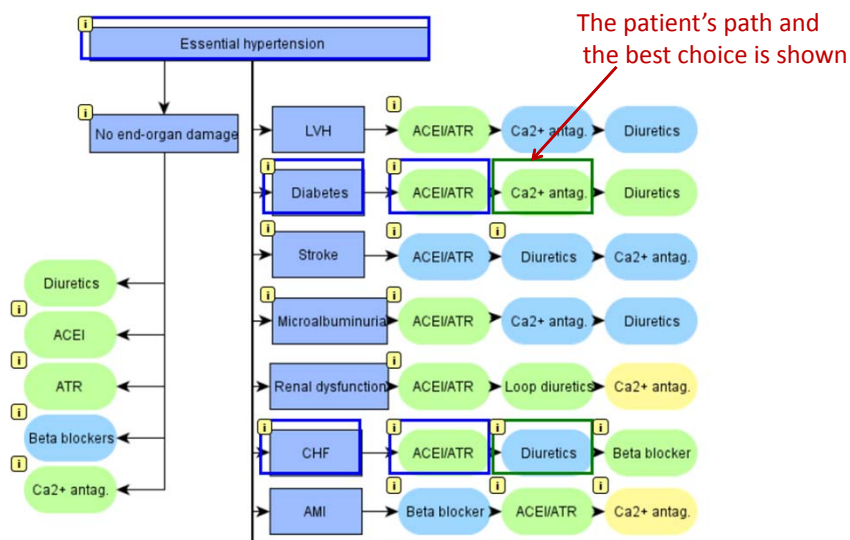
- Each drug contributes to the cumulative score for each type of adverse effect
- Example: the patient is using amitriptyline, tramadol, and clopidogrel

		amitriptyline	tramadol	clopidogrel
Anticholinergic	D	3	1	0
Bleeding risk	D	0	1	3
Constipation	D	2	2	0
Orthostatic hypotension	C	3	1	0
Prolongation of QT interval	A	1	0	0
Nephrotoxicity	A	0	0	0
Sedation	A	2	1	0
Convulsion risk	B	1	2	0
Serotonergic	C	2	3	0

The PHARAO Adverse Effects Database has been Developed by Mebase Ltd. in Swedish-Finnish collaboration



Interactive algorithms are automatically populated by patient data (diagnoses, medications, lab test results) from the EHR



The tool can be applied to patient populations ("virtual health check")

Example: renal dosing suggestions and warnings in a population of 16 000

- Check dosing 1164
- Drug not recommended/contraindicated 28



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