Adverse Drug Reactions

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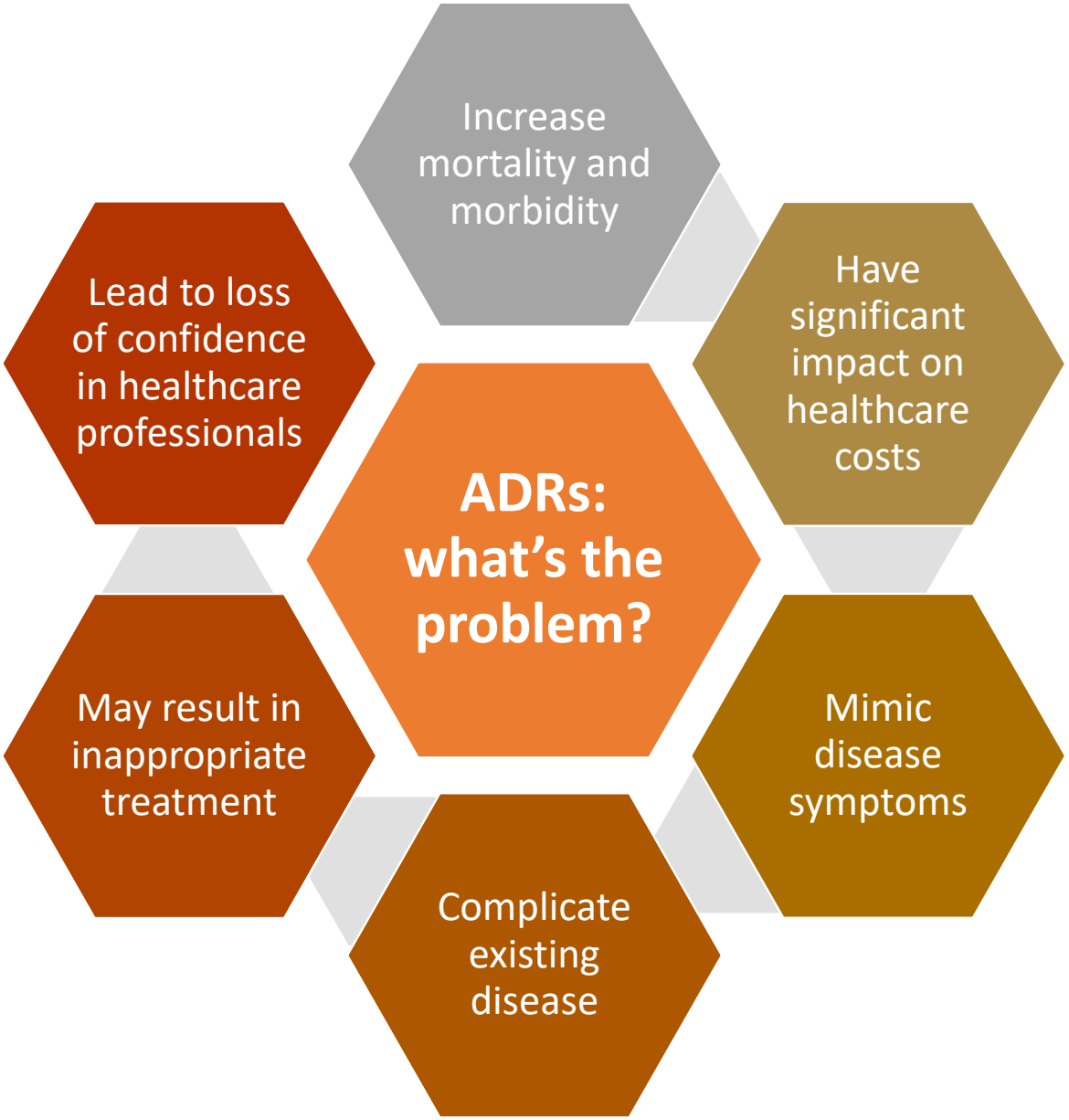
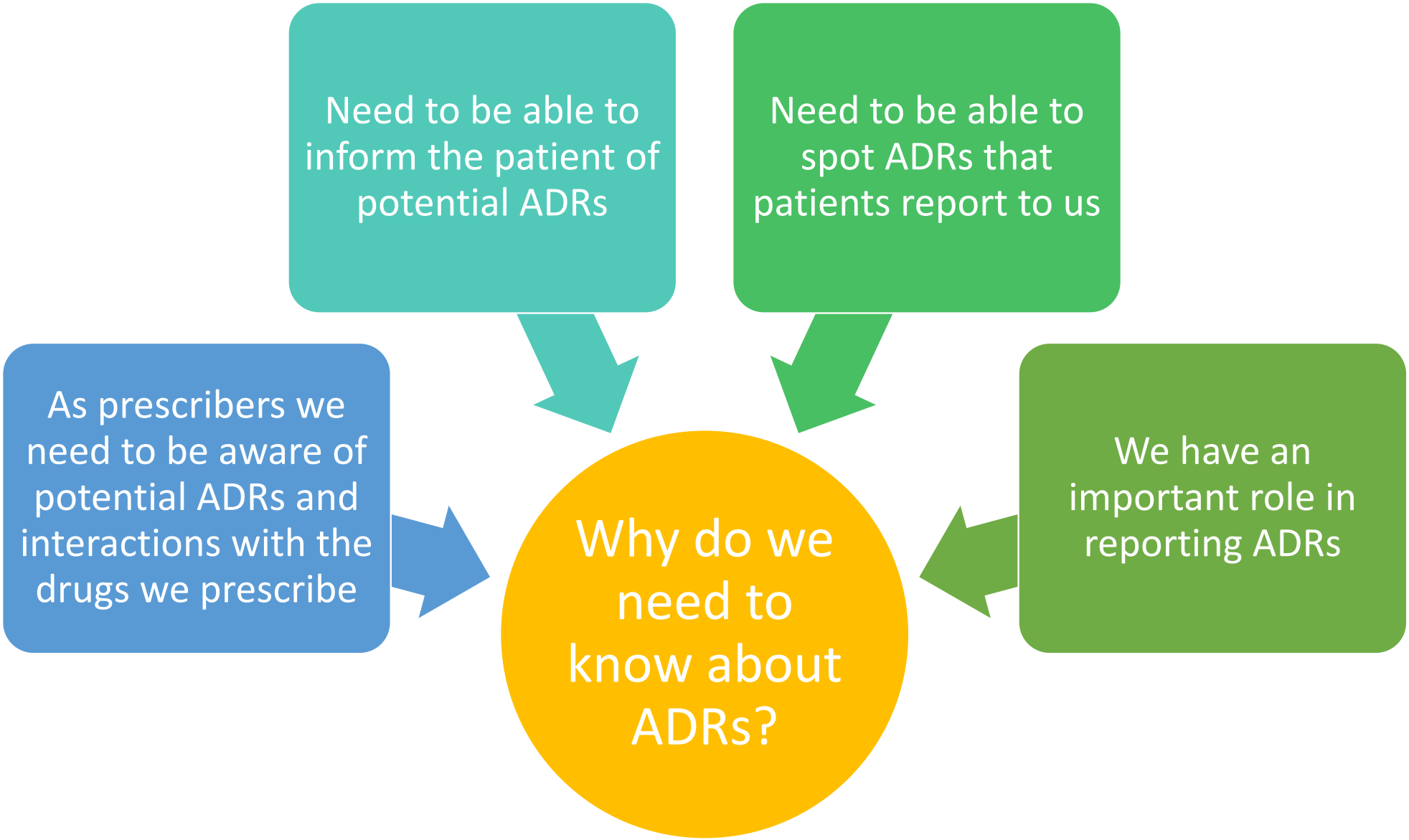
What is an Adverse Drug Reaction (ADR)?

- “An unintended and harmful reaction experienced after the administration of a drug or combination of drugs under normal conditions of use and suspected to be related to the drug”
  - The reaction may be a known side effect of the drug or it may be new and previously unrecognised

- Prevalence of ADRs varies but increases significantly:
  - when drugs are prescribed for the first time
  - following hospital discharge


Increase mortality and morbidity
Have significant impact on healthcare costs
Mimic disease symptoms
Complicate existing disease
May result in inappropriate treatment
Lead to loss of confidence in healthcare professionals
ADRs: what's the problem?


Need to be able to inform the patient of potential ADRs
Need to be able to spot ADRs that patients report to us
As prescribers we need to be aware of potential ADRs and interactions with the drugs we prescribe
Why do we need to know about ADRs?
We have an important role in reporting ADRs

Types of ADRs

Type A (Augmented)

- Exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose e.g. bleeding with anticoagulants
- Dose-dependent
- Also include reactions that are not directly related to the desired pharmacological action of the drug, e.g. dry mouth with tricyclic antidepressants

Examples

- Bradycardia with beta-blocker
- Hypoglycaemia with sulphonylurea
- Headache with GTN

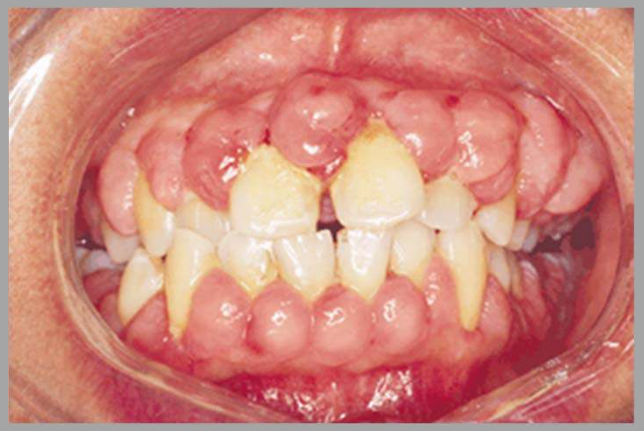
Types of ADRs

Type B (Bizarre)

- Not related to pharmacology of drug therefore unpredictable
- Often only discovered once drug is marketed
- Rare but can be fatal
- Not usually dose-dependent
- e.g. skin rash with antibiotics
- Includes allergic reactions

Examples

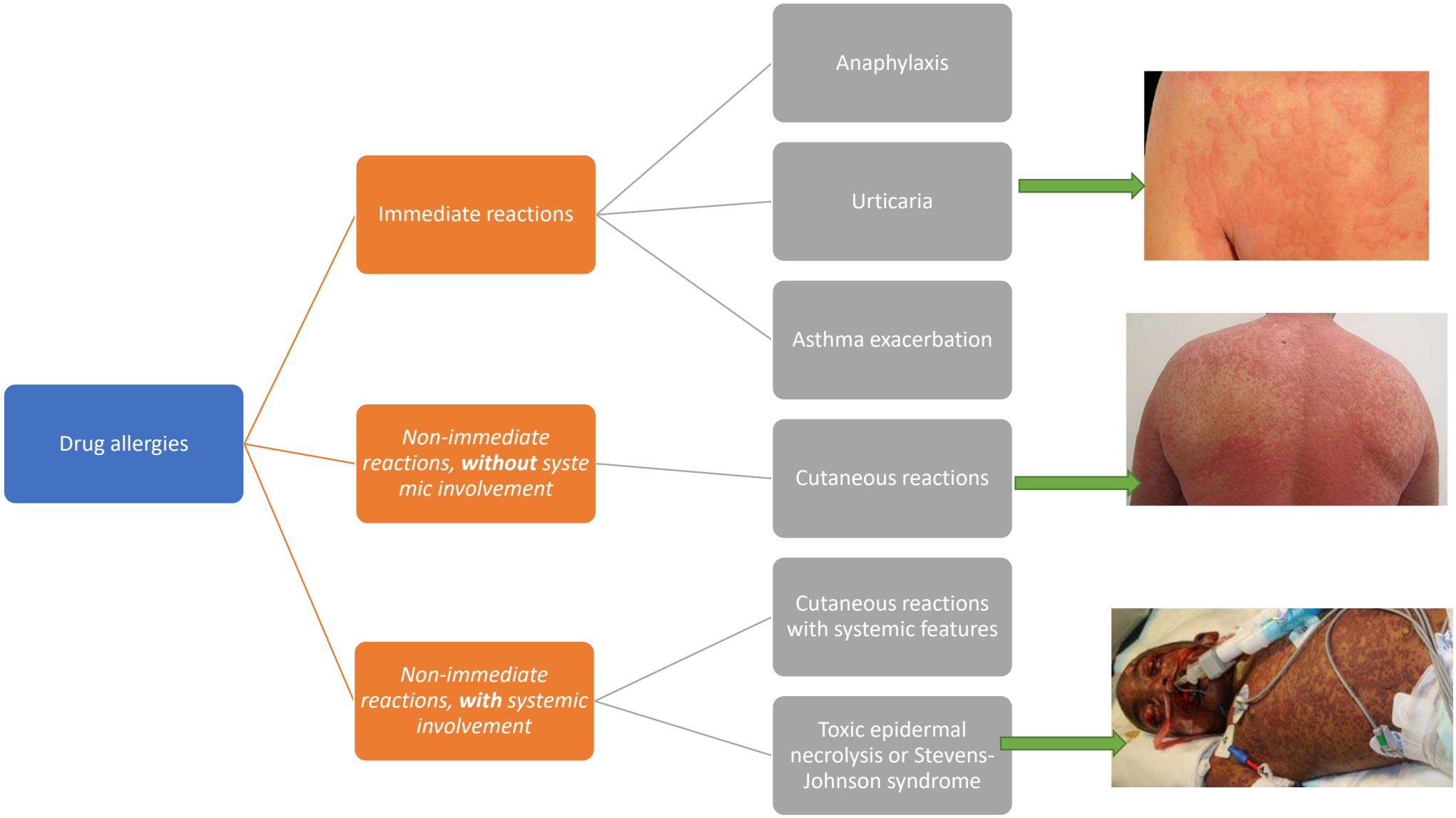
- Myopathy with statins
- Neutropenia with carbimazole
- Gingival hypertrophy with phenytoin



Allergic reactions to drugs

- Clinical features compatible with an immunological mechanism and in response to taking a drug

- As prescribers we should always:
  - Document allergies in patient's notes
  - Check allergy status before prescribing
  - Ensure patients are aware of their allergy status and encouraged to share this with relevant people


Drug allergies
Immediate reactions
Non-immediate reactions, **without** systemic involvement
Non-immediate reactions, **with** systemic involvement
Anaphylaxis
Urticaria
Asthma exacerbation
Cutaneous reactions
Cutaneous reactions with systemic features
Toxic epidermal necrolysis or Stevens-Johnson syndrome

Type B Reactions May Lead to Withdrawal of a Drug

- 2001 - Cerivastatin – rhabdomyolysis
- 2005 - Valdecoxib – serious skin reactions
- 2007 – Lumiracoxib –liver toxicity

Types of ADRs

Type C (Continuing)

- Reactions that persist for a relatively long time
- e.g. osteonecrosis of the jaw with bisphosphonates

Type D (Delayed)

- Reactions which only become apparent some time after the use of a medicine
- e.g. cholestatic jaundice with co-amoxiclav

Type E (End-of-use)

- Reactions associated with drug withdrawal, e.g. agitation and restlessness following withdrawal of opioids

Type F (Failure)

- Unexpected failure of therapy
- e.g. a herbal product reducing the efficacy of combined OCP

Type G (Genetic)

- Irreversible genetic damage
- e.g. thalidomide causing phocomelia

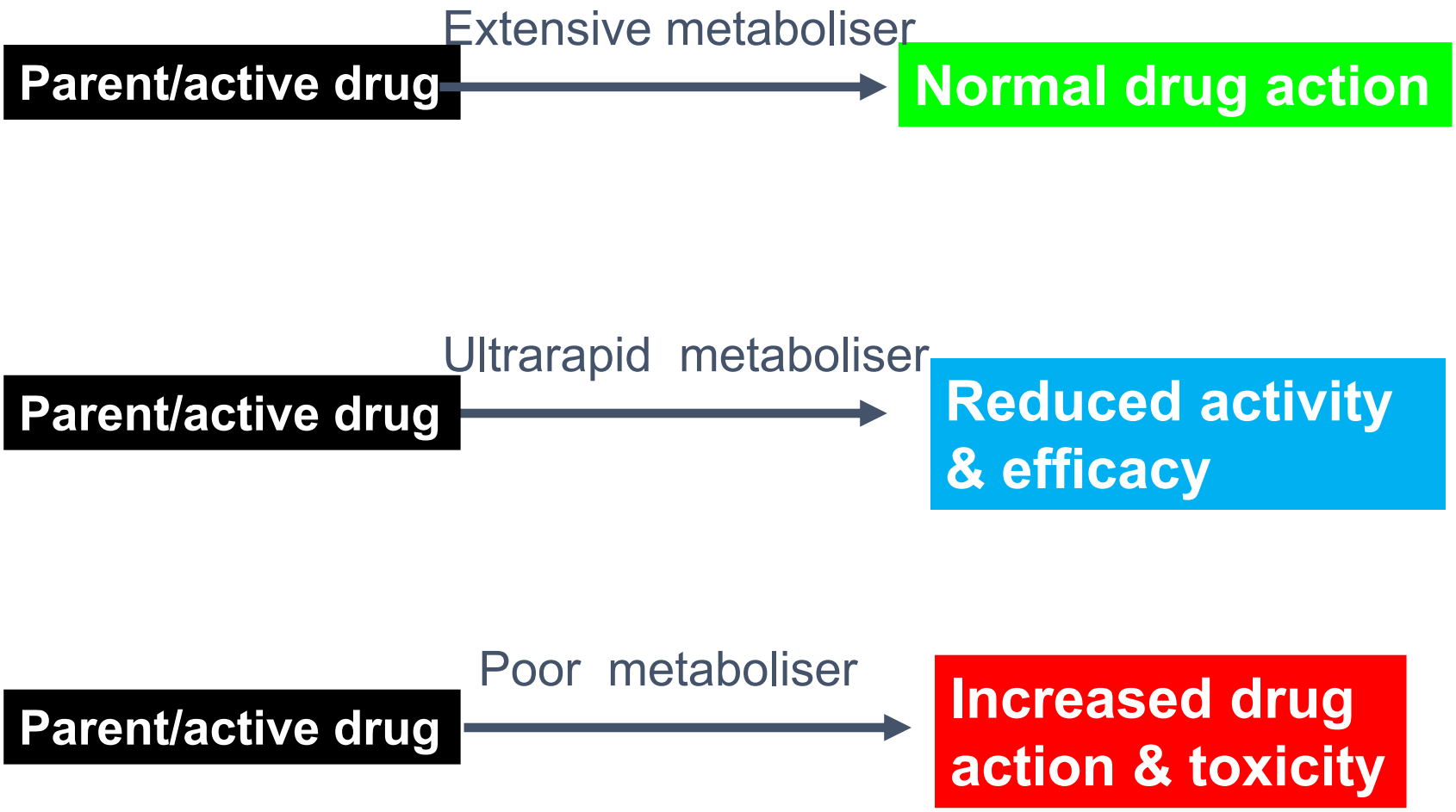
Type H (Hypersensitivity)

- Immune-mediated response to a drug
- e.g. anaphylaxis

What increases the risk of ADRs?

- Polypharmacy – exponential rise in ADRs as number of drugs increases
- Age - very old & very young more susceptible
- Gender - women generally at greater risk
- Ethnicity - genetic differences in how individuals metabolise and eliminate drugs
- Genetics – can affect e.g. rate of metabolism
- Intercurrent disease – renal, liver, allergies

Genetic polymorphisms



Clinical Examples of pharmacogenomics

Gene	Substrate drugs	ADR
CYP2C9 *VKORC1*	Warfarin	haemorrhage
CYP2D6	Tricyclic antidepressants Codeine	Dizziness, confusion Reduced consciousness, somnolence; respiratory depression; ‘pin-point’ pupils

ADRs in children

Immature kidneys, liver, more susceptible to respiratory depression

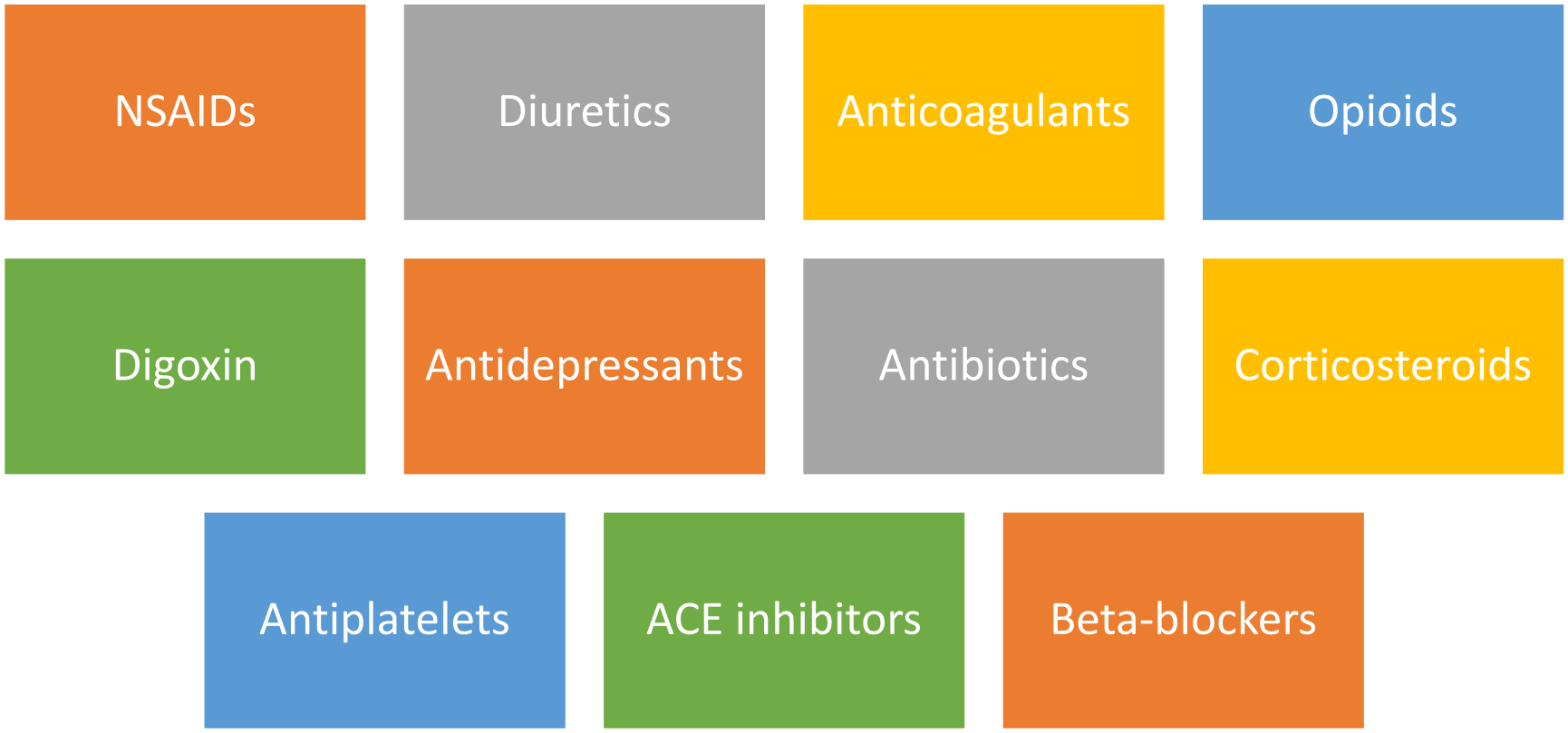
Aspirin can cause Reye's syndrome in under 16s

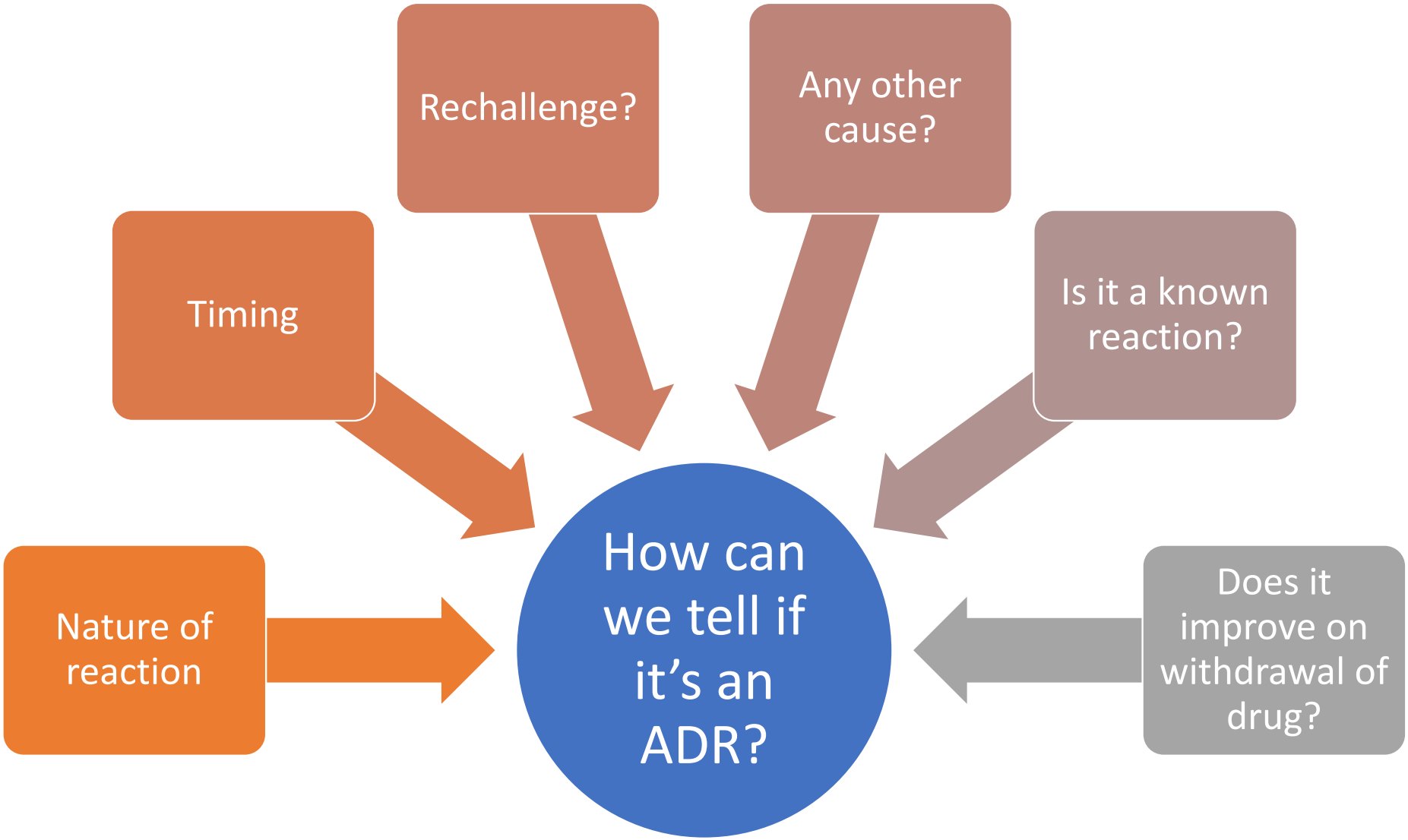
Adolescents – more susceptible to extra pyramidal side effects from e.g. metoclopramide

ADRs in the elderly

- Impaired drug metabolism and excretion
- Altered target organ sensitivity
- Polypharmacy
- Multiple pathologies
- Compliance issues
- May be taking narrow therapeutic index drugs

Drugs commonly implicated in ADRs




Rechallenge?
Any other cause?
Timing
Is it a known reaction?
Nature of reaction
How can we tell if it's an ADR?
Does it improve on withdrawal of drug?

Reducing the risk of ADRS

Don’t use drugs unnecessarily (particularly in pregnancy)	Is it the most appropriate drug to use?	Prescribe familiar drugs	Watch out for high risk drugs	Consider drug interactions
Start with low doses	Does the drug need monitoring?	Check allergy status of patient	Check what other medication the patient is taking (including self-med)	Consider age, renal or hepatic disease, genetic factors
	Does the patient have a history of ADRs	Warn patients about serious ADRs	Report ADRs	

Communicating risk to patients

Description of the frequency of side-effects

Very common
Common
Uncommon [formerly 'less commonly' in BNF publications]
Rare
Very rare
Frequency not known

1 in 10	About 1 event per family
1 in 100	About 1 event per street
1 in 1000	About 1 event per village
1 in 10000	About 1 event per small town

It’s 1956 - Guess the Drug

- ‘Outstandingly safe’
- ‘Relatively free from side effects just occasional dizziness and nausea’

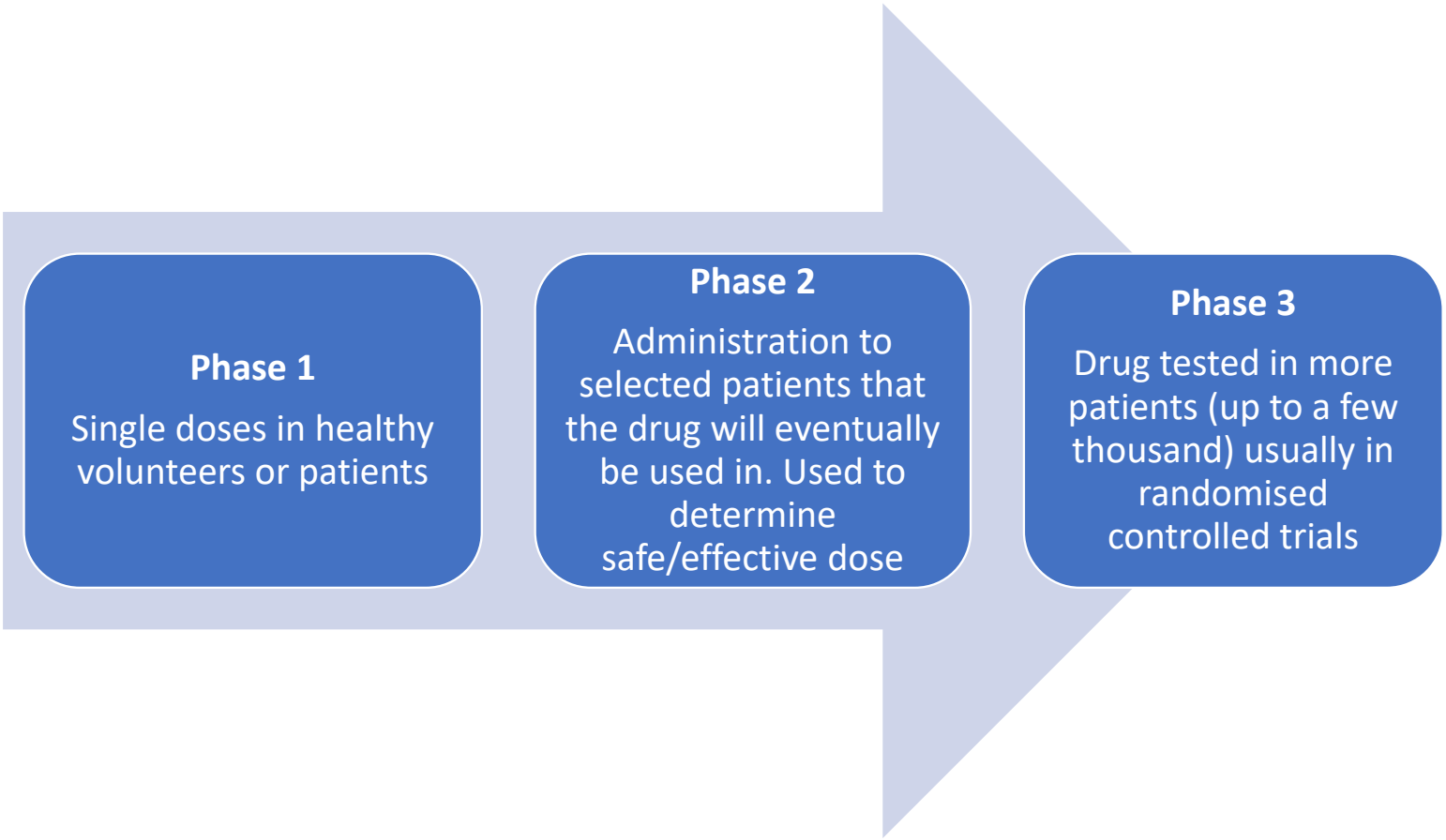
Drug monitoring agencies

Pharmacovigilance

"all methods of assessment and prevention of adverse drug reactions including pre-clinical and clinical development stages of drug development and post-marketing surveillance"

- Monitoring the use of medicines in everyday practice
- Assessing the risks and benefits of medicines to improve their safe use
- Providing information to optimise safe and effective use of medicines
- Monitoring the impact of any action taken

Evaluation of a new drug: pre-marketing

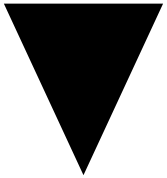


Info on ADRs in SmPC on www.medicines.org.uk

emc

Post-marketing surveillance

- A vital aspect of evaluating drug safety
- Includes post-marketing research and voluntary reporting
- Helps monitoring agencies to identify problems rapidly and take action if needed
- Provides an estimate of incidence of ADRs
- Identify risk factors for ADRs, e.g. age, disease state, treatment duration
- Supports risk-benefit assessment when making prescribing decisions



This medicinal product is subject to additional monitoring

Reporting ADRs – the Yellow Card scheme

- The UK's voluntary scheme for reporting adverse drug reactions
- Provides system for rapid detection of emerging drug safety problems
- You only need to suspect that an adverse drug reaction was caused by a medicine to report it.
- Action can be taken quickly
  - issue guidance and provide information to healthcare professionals
  - modify the existing product licence for the drug
  - Withdraw the product
- Confidential – no litigation fears

- **BUT reporting rate very low**

What should you report?

- Serious **suspected** reactions to **all** drugs
  - Fatal, life-threatening, disabling or incapacitating, or result in prolonged hospitalisation
  - Include delayed drug effects and congenital abnormalities

- **All** reactions to new drugs ▼

- The MHRA are particularly interested in reports of suspected ADRs:
  - in children
  - in patients that are over 65
  - to biological medicines and vaccines
  - associated with delayed drug effects and interactions
  - to complementary remedies such as homeopathic and herbal products

➢**You do not need to be certain of causality – you are simply reporting your suspicion**

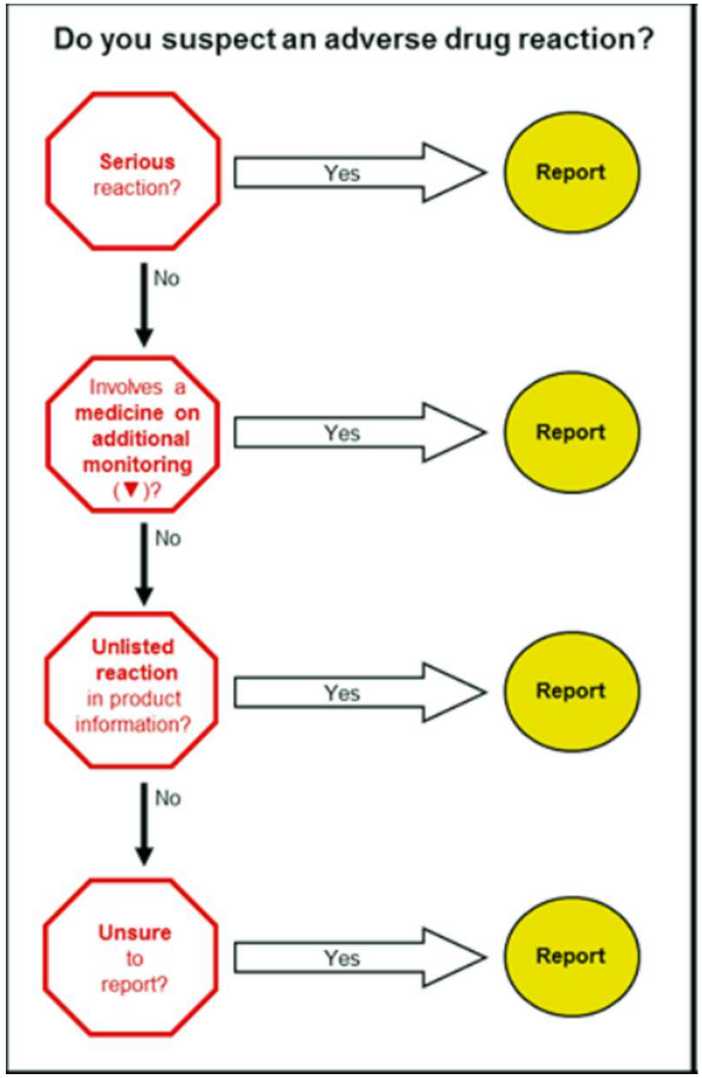
Aren't Herbs 'All Natural' and Safe?

- Short answer- NO!

Herbal product	Uses	Problems
Black cohosh	Menopausal symptoms	Liver toxicity
St John's Wort	Depression	Drug interactions – enzyme inducer Serotonin syndrome with antidepressants
Kava	Insomnia, anxiety	Liver toxicity
Feverfew	Migraine	Bleeding

How to report

- Online [Report a problem with a medicine or medical device - GOV.UK (www.gov.uk)]
- Via ‘Yellow Card’ app
- Yellow cards in back of BNF



Changes in response to yellow card reports

- Buproprion – risk of seizures
- Quinolones – risk of tendonitis
- Paroxetine warning about withdrawal reactions
- Amlodipine - grapefruit interaction
- Pregabalin – warnings relating to abuse potential strengthened
- Fentanyl patches – warnings about risk of accidental exposure to patients/carers and how to dispose of safely

MHRA

Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Volume 15 Issue 7 February 2022

Contents

COVID-19 vaccines and medicines: updates for February 2022

Recent information relating to COVID-19 vaccines and medicines that has been published since the January 2022 issue of Drug Safety Update, up to 11 February 2022.

Drug analysis prints - ramipril

Reactions by MedDRA System Organ Class, High Level Group Term, High Level Term, and Preferred Term

Term (SOC, ***HLGT***, *HLT*, PT)	Single active constituent		Multiple active constituents		Total reactions	
Expand All Collapse All	All	Fatal	All	Fatal	All	Fatal
+ Blood and lymphatic system disorders	88	2	0	0	88	2
+ Cardiac disorders	322	10	2	0	324	10
+ Congenital, familial and genetic disorders	13	0	0	0	13	0
+ Ear and labyrinth disorders	86	0	2	0	86	0
+ Endocrine disorders	5	0	0	0	5	0
+ Eye disorders	249	0	0	0	249	0
+ Gastrointestinal disorders	1539	0	10	0	1545	0

Why don’t we report more?

Healthcare professional group	Decrease in number of reports	Decrease in 2018 compared with 2017
Hospital pharmacists	–380	–11%
General practitioners (GPs)	–280	–4%
Community pharmacists	–226	–14%
Hospital doctors	–161	–7%
Physicians	–142	–46%
Nurses	–122	–5%
Healthcare professionals in hospitals	–53	–7%

Figures for 2018

Would you report?

- Hair loss with warfarin
- Withdrawal reaction with paroxetine
- Breathing difficulties with ibuprofen
- Cholestatic jaundice with flucloxacillin
- Injection site reaction with Covid vaccine
- Lower leg oedema with diltiazem

Information sources for ADRs

- British National Formulary and BNFC http://bnf.org/bnf/
- Summary of Product Characteristics (SPC) www.medicines.org.uk.
- Medicines Q&As on the Specialist Pharmacy Service website www.sps.nhs.uk
- Pharmacists / Medicines Information departments
- MHRA Yellow card website http://yellowcard.mhra.gov.uk/
- Medicines information departments of pharmaceutical companies

Case study

- Mrs Anna Thomas, aged 56, takes the following medication:
  - Atorvastatin - dose recently increased to 80mg daily
  - Bisoprolol 5mg daily – started 18 months ago
  - Ramipril – dose increased to 5mg daily 6 weeks ago
  - Aspirin 75mg daily – started 6 months ago

- During a medication review at her surgery, she reports good compliance with her medication. She does mention that she has been getting muscle aches in her arms and legs over the last 2 weeks, and she has had a tickly cough and indigestion over the past couple of months.
- Could she be experiencing an ADR? What action should the prescriber take?

Case study

- Mr Brian Smith, aged 56, has been admitted to hospital with abnormal LFTs and diagnosed with cholestasis & hepatitis. He takes the following medication:
  - Ibuprofen 400mg TDS PRN
  - Co-codamol 8/500 tablets 2 QDS PRN
  - He finished a short course of co-amoxiclav 6 weeks ago

- Could he be experiencing an ADR? What action should the prescriber take?

Any questions?