# ‘CAN YOU SELL ME SOME PAIN KILLERS?’ 2 GERIATRIC PATIENTS WHO SUFFERED FROM JOINT PAIN AND ADVERSE DRUG REACTIONS

- Inter-hospital Geriatric Meeting
- 25/10/2013
- Presenter: Dr. C P YAM
- Chairman: Dr. P P LAM

# CASE 1 MR LUK

- M/67y
- Ex-smoker, non-drinker
- No known drug allergy
- No known adverse drug reactions
- Premorbid: ADL independent, walked unaided
- Sales, part-time
- Lives with wife, no children

# PAST HISTORY

- Hypertension: follow-up a private GP previously, put on Minax (metoprolol),  Apo-amilzide (amiloride + hydrochlorthiazide), defaulted FU and self bought the 2 medications from a local pharmacy (without a doctor's prescription)
- Gout: FU the same private GP, given indomethacin, later defaulted FU, PRN use of Indomethacin capsule self bought from the same local pharmacy (without a doctor's prescription); sometimes he will also add panadol on top of indomethacin
- No HA or private FU

# HPI

- Felt dizzy and sweaty since morning  (1/8/2013)
- BP: 77/66 P: 68 at GOPD
- No chest discomfort
- No abdominal discomfort
- No loss of consciousness
- Afebrile at GOPD
- Poor appetite with weight loss 10 pounds over 3 months
- Change of bowel habit with constipation for 3 months, with normal stools, no PRB, tarry stool, or malena

# AT AED

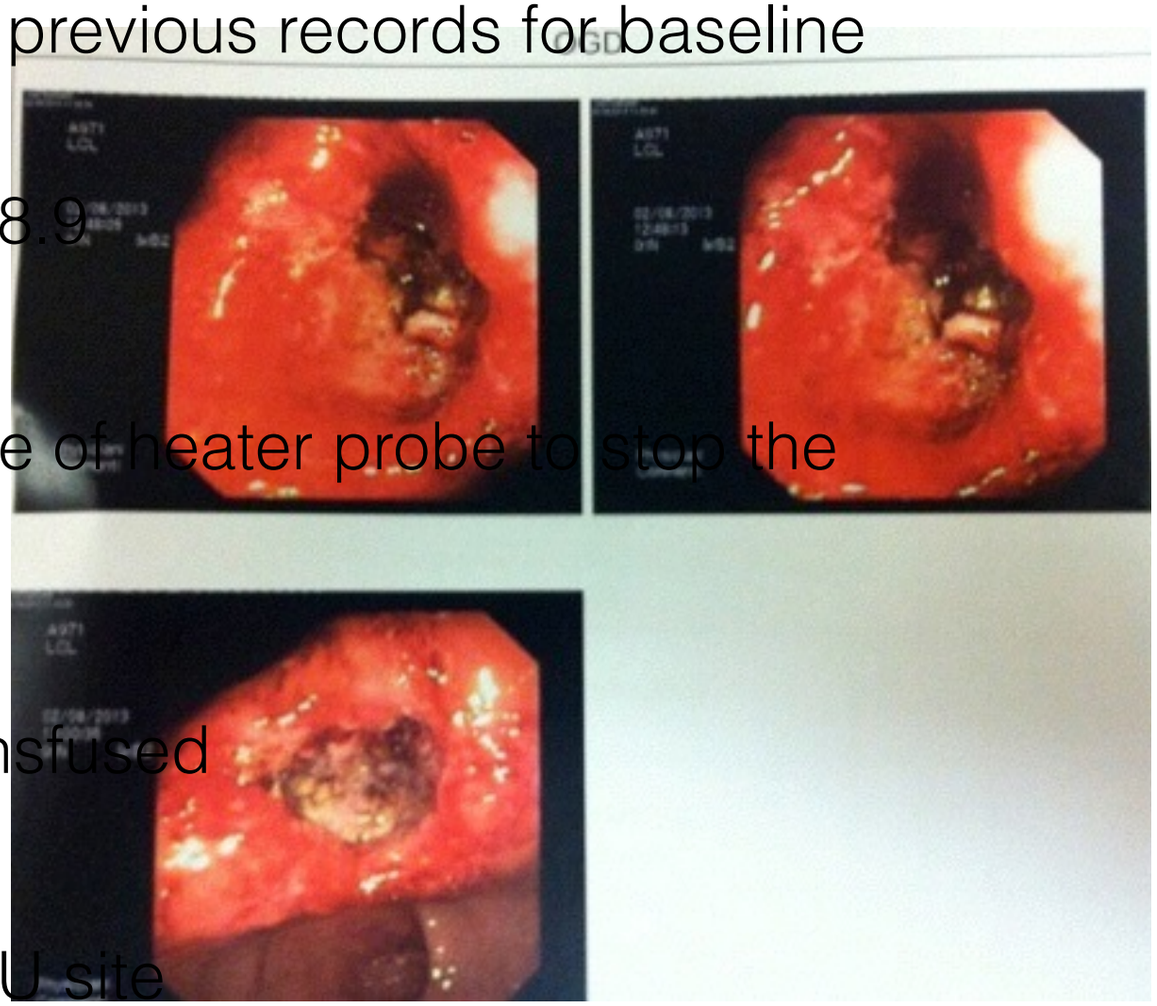
- BP: 99/62 P: 72
- Afebrile
- Witnessed vomiting of 100ml of coffee ground substances
- BP drop: 84/54 P: 91
- Given fluid challenge
- Urgently admitted to Surgical Ward for UGIB

# AT SUR WARD

- BP: 102/67 P: 69, afebrile, not required oxygen supplement
- Abdominal examination: soft abdomen, non-tender, no signs of peritonism
- Per-rectal examination: old malena, no hemorrhoid or rectal mass detected
- ECG: sinus rhythm, no ischaemic changes
- CXR: normal, no free gas under diaphragm
- Patient reported his use of indomethacin for joint pain
- SUR Dx: NSAID (indomethacin) induced UGIB
- Started IV Nexium

# OGD x 2

- 1st blood test: Hb: 11.8 g/dL (without previous records for baseline level), NcNc
- LRFT Amylase CK TropI normal, Ur: 18.9
- Urgent OGD (2/8/2013) morning:
  - Bleeding gastric ulcer, required use of heater probe to stop the bleeding;
  - RUT: negative
- Hb 11.8 -> 8.8 g/dL (3/8/2013) -> transfused
- Urgent re-scope OGD:
  - no evidence of re-bleeding from GU site
  - Biopsy results: no evidence of malignancy, moderately active chronic gastritis, Helicobacter negative; re-epitheliazied ULCER



# PROGRESS

- FEVER  (3/8/2013) with newly onset left knee swelling with pain
- Xray Left knee: no fracture seen, mild OA changes
- Treated as recurrent gouty attack with colchicine 0.5mg tds po and ICE therapy
- Persistent fever;  Serum CRP: 285
- Urgent consulted O&T 6/8/2013 for suspected septic arthritis
  - Lt knee tapping done: straw colour fluid, increased WCC, bacterial culture: negative,  AFB smear: negative, no malignant cells detected
  - Serum urate: 0.4
  - Patient reported another episode of Left knee gouty attack 1 week before this admission, self treated with indomethacin tablets
  - Imp: Recurrent gouty attack; not septic arthritis

# PROGRESS

- Fever down but persistent swelling and pain
- Consulted Rheumatology Team 2 days later (8/8/2013)
  - Asked laboratory to examine joint fluid by light microscopy:
    - Presence of urate crystals; absence of calcium pyrophosphate dihydrate (CPPD) crystal
    - Reviewed old Xray reports: soft tissue swellings and bone erosions affected bilateral 1st MTPJs, Rt big thumb MCPJ and Rt index finger PIPJ -> findings compatible with gout; no chondrocalcinosis
- Dx: recurrent gouty attack, aggravated by concurrent use of diuretics for treatment of hypertension; unlikely pseudogout
- Advised not to resume Apo-amilzide; added Zestril with Betaloc for BP control
- Suggested to start allopurinol 100mg daily 2 weeks after this attack subsided, with colchicine for prevention of acute attacks for 6 months, aim Urate <0.36

# PROGRESS

- Stopped colchicine 12/8/2013 (completed 8 days of treatment) due to diarrhoea
- Changed to 1 week course of low dose prednisolone but ineffective
- Mildly decreased in left ankle swelling, but persistant pain in his left knee and left ankle
  - severely affected his walking -> walk with frame with 2 maximal assistance (pre-morbid walk unaided)
- Failed wean off Foley 14/8/2013 (Foley inserted for monitoring I/O upon admission)
- Seen by URO 15/8/2013 -> treated as BPH with LUTS with Xatral XL
- Confirmed Fe deficiency anaemia, added Fortifer
- Plan colonoscopy later
- Consult GERI for rehabilitation 19/8/2013

# SHORT SUMMARY

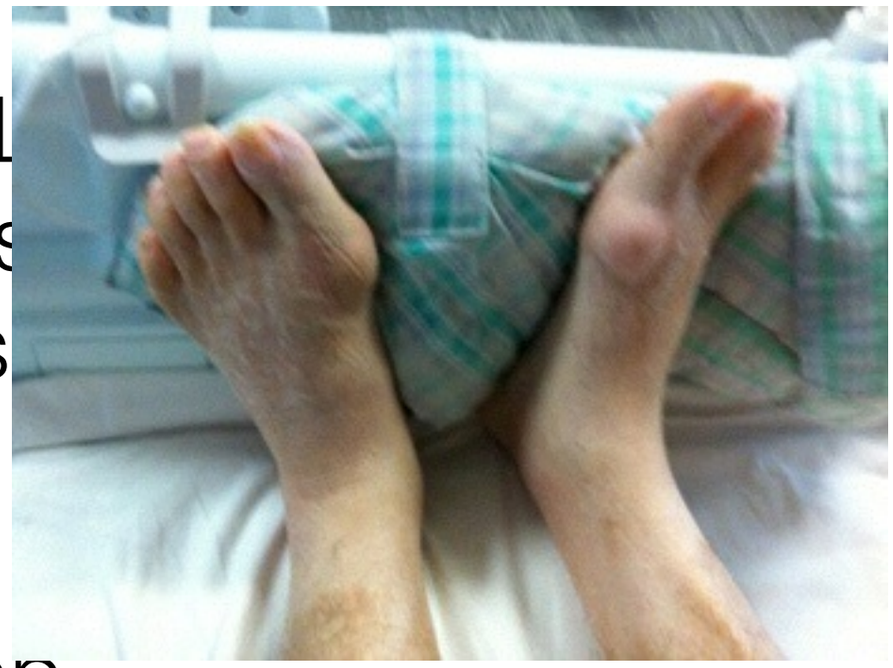
| | Before admission | Stay in SUR ward (20 days) |
|---|---|---|
| MEDICATION LIST | Apo-amilzide<br>Minax<br>Indomethacin<br>Panadol | + Nexium<br>+/- Colchicine<br>+/- Prednisolone<br>Betaloc<br>+ Zestril<br>Panadol<br>+ Xatral XL<br>+ Fortifer<br>- Apo-amilzide<br>- Indomethacin |
| Possible ADR or exacerbation of underlying disease | **Apo-amilzide + Minax: hypotension**<br>**Apo-amilzide: Gout**<br>**Indomethacin: Bleeding GU** | **Colchicine: Diarrhoea** |

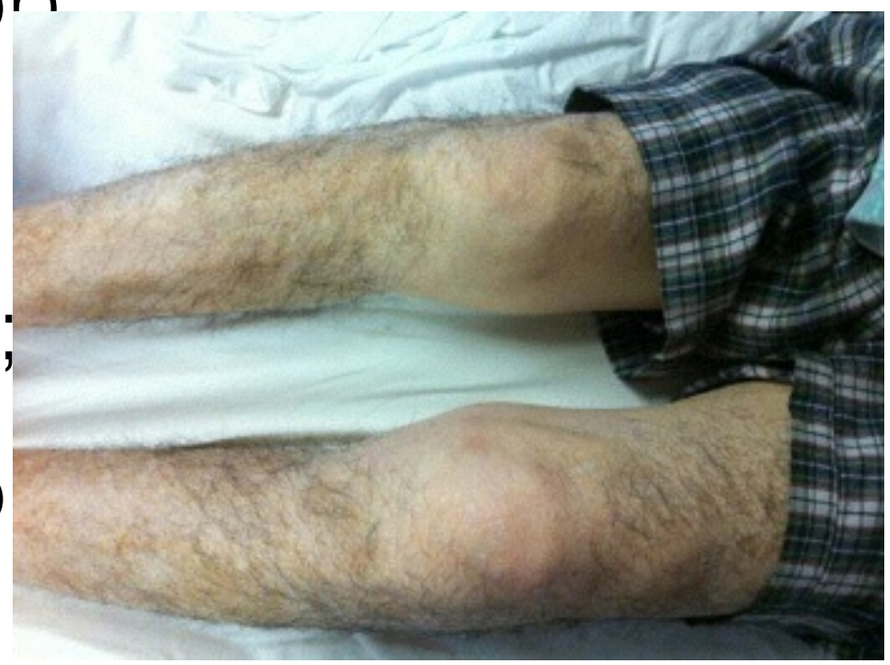
# 20/8/2013 D20

- Transferred to GERI bed
  - BP: 135/75, P: 100, T: 37.5 C
  - Power: Bilateral lower limbs MRC 4/5 -> limited by left knee pain and bilateral ankle pain
  - Could not flex his left knee due to swelling and pain
  - Bilateral lower limb non-pitting edema up to mid-shin
  - On Foley
  - Stage II Sacral bedsore
    - Patient reported restrained and lack of exercise at SUR ward, mainly bed-bound, not allowed to go to toilet, put him on napkin, felt de-conditioned and not confident to walk

# GERI

- Recurrence gouty attack over L
  ankle joints, bilateral 1st MTPJs
  hand 2nd MPJ soon after trans
- Blood tests:
  - Hb: 8.5 NcNc, no further drop
  - LFT:  ALP/ALT/Bil: normal
  - Alb: 23 (31 upon admission);
  - CSU C/ST (20/8/2013): E. co





# PROBLEM LIST

1. NSAID (indomethacin) induced bleeding gastric ulcer
2. Fe deficiency anaemia caused by chronic GI blood loss
3. Tophaceous gout with recurrent gouty attack, suspected precipitated and aggravated by use of diuretics for treatment of hypertension
4. Stage II bedsore caused by immobilization
5. Hypoalbuminaemia, could be related to poor appetite due to GI upset caused by NSAIDS
6. AROU, failed wean off Foley, caused by BPH, UTI, immobilization
7. Hypertension for titration of anti-hypertensives
8. De-conditioning require rehabilitation

# AT GERIATRIC WARD

- Left knee pain and swelling persisted while pain and swelling of other joints quickly subsided
- Affected walking training and ADL training
- Given another course of prednisolone → left knee pain and swelling subsided after 3 days of treatment
- Started allopurinol as planned at 100mg daily with colchicine cover
- Patient felt decreased in exercise tolerance in training, Hb was topped  up to 11g/dL by transfusion

# MULTIDISCIPLINARY TEAM

- Nurse: continued daily care and management of bedsore, Foley ->  bedsore healed before discharge and Foley weaned off
- PT: ICE therapy, continue walking exercise, started muscle strengthening exercise after gouty attack subsided -> able to walk unaided after 2 weeks of training
- OT: ADL training -> focused on hand function training after Lt hand gouty attack subsided -> ADLI
- Dietitian: patient dislike hospital food, decreased intake since admission, given advice on low purine diet for gout, increase calorie intake for hypoalbuminaemia, allowed non-hospital food to improve appetite
- MSW: explored background of patient, with assistance given, patient's wife was taken care by neighbors during patient's stay in hospital
- Bedsore sore team: advised on bedsore management
- SUR, O&T and Rheumatology Team: review

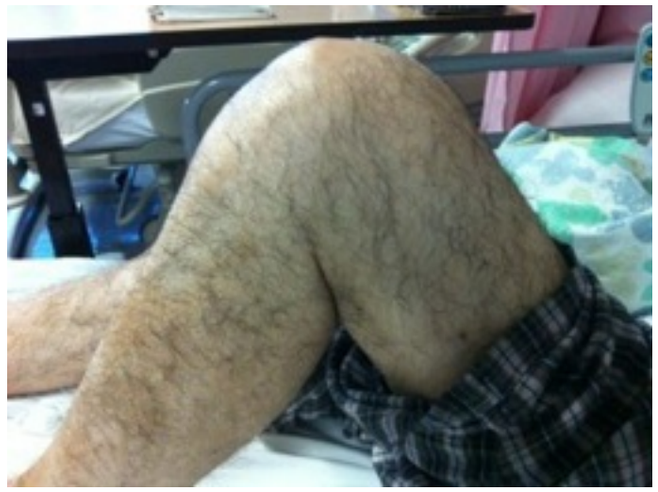
# HOW DID HE GET HIS NSAIDS?

- Discussed with patient about his source of NSAIDs:
  - 2 years ago for the first time, he tried to bring back the old packets of indomethacin, given by his private GP in previous consultations to a local pharmacy (without any documented dosages on those packets)
  - ‘I want this pain killer for my joint pain‘ - the pharmacist sold him the tablets without further questioning
  - He later learned the drug name indomethacin from the pharmacist, and now could remember the drug name and buy it from same pharmacy whenever out of stock at home
  - He doesn’t know about the correct dosage to treat his gouty attack
  - He doesn’t know about the possible side effects - he only wants to stop the pain and swelling immediately
  - Believing that is the prophylactic dosage, he has taken indomethacin at least one dose per week

# DISCHARGE

- Discharged on 16/9/2013 (admission duration: 5 weeks)
- GDH rehabilitation
- ICM for meal delivery service and home help
- FU GERI SOPD for titration of  anti-hypertensives and monitoring gout
- Educated him about proper use of medications for his gouty attack
    - Allopurinol with colchicine cover
    - + Panadol PRN if flare up of gouty attack
    - Low purine diet
    - Not to buy indomethacin again

  from pharmacy without doctor's advice



# CASE 2 MR CHAN

- M/85y
- NKDA, No known ADR
- Retired manual worker
- Premorbid: ADLI, walked unaided, out-going
- Lives with son, daytime alone
- Ex-heavy drinker, quitted 30 years
- PHx:
  - Hypertension with renal impairment, latest Cr: ~200, on Norvasc and Betaloc for BP control
  - Atrial fibrillation
  - Lacunar stroke 2009 with good neurological recovery, on warfarin

# HPI

- Admitted to PYNEH Acute MED bed (14/4/2013) for decreased GC for 1 week

- 1 month before, admitted EMW for suspected Rt jaw dental abscess, treated with I&D by OMS and an empirical course of augmentin, abscess resolved

- URTI 1 week before, treated by private GP with Dimefort (an anti-histamine), Panadol,  Vitamin B complex and an antibiotic

# P/E

- Hypothermia 33.8 C at AED; Hstix: 2.4
- BP 120/80 P: 80
- Confused, not cooperative for physical examination, limb movements observed
- PERL, no neck stiffness
- Respiratory: Chest: clear
- Cardiovascular: HS dual, no murmur, no signs of heart failure
- Abdomen: soft, non-tender

# INVESTIGATIONS

- Hb: 10.5 g/dL (baseline around 11g/dL)
- WCC: 9
- Cr: 212 -> 519, Na & K normal range
- INR: >8  (no past history of overdose)
- Bil: 28  ALT: 967 -> 1394 NH3: 117 (Normal LFT1 month ago)
- HbsAg: negative
- CXR: no consolidations, not congested
- ECG:  AF, no ischemic changes
- CT brain: mild cerebral atrophy, no new infarcts, no ICH

# PROGRESS

- Working Dx:
  - Acute on chronic renal failure
  - Acute liver failure with hepatic encephalopathy
  - Warfarin overdose due to warfarin effect + acute liver failure causing coagulopathy
- Started empirical augmentin to treat as sepsis (hypothermia and mildly elevated WCC)
- Vitamin K given for warfarin overdose
- Consulted GI Team:
  - Urgent USG abdomen: biliary trees not dilated, no liver lesions seen, multiple renal cysts, suspected polycystic kidney disease
  - Imp: acute liver failure suspected secondary to sepsis or transient ischaemia
- Urine C/ST: Enterococcus, sensitive to augmentin

# GERI

- Transferred to GERI bed on 24/4/2013 (Day 11 admission)
- Initial assessment:
  - BP/P stable, afebrile, no hypothermia; Hstix normal range; GCS 15/15, oriented to T/P/P
  - Chest examination/ cardiovascular examination: unremarkable
  - Abdomen: soft, non-tender; on Foley, urine clear in BSB
  - Bilateral knees with degenerative changes
  - Bilateral non-pitting ankle edema
  - No bedsores

- Blood tests:
  - Cr: 210 (back to baseline before admission)
  - CRP: 54
  - Bil: 64 -> 48 ALP: 217 -> 155  ALT: 100
  - INR: 3.5
  - Alb: 25

# GERI

- Stopped panadol in view of liver failure
- Stopped Norvasc and Betaloc in view of low BP
- Traced blood tests results of liver failure:
  - Anti-HAV/Anti-HEV/ Anti-HCV: all negative
  - Anti-HBs: 422
  - ANA/AMA/ASMA: all negative
- What caused liver failure???

# C/O

- Bilateral knee pain on walking Rt > Lt
- Analgesic balm and ICE therapy
- Serum urate: 0.57
- O&T: severe OA knees with gouty attack, suggested colchicine effective
- Increased knee pain with swelling over Rt knee, treated as gout empirically with short course of prednisolone, pain partially relieved only

# PROGRESS

- 1 week later, Hb drop 10.5 -> 8.1 g/dL
- Clinically no signs of GIB
- Started IV Pantoloc
- Urgent OGD next morning (3/5/2013):
  - Acute bleeding duodenal ulcer, RUT: negative,
  - Biopsy: Chronic gastritis, Helicobacter: negative
- 4 days later, Hb drop again to 6.5 g/dL; transfused
- Urgent re-scope OGD same day: bleeding DU required clipping of bleeding sites
- Stopped warfarin, family agreed to change to Plavix for secondary prevention of CVA with underlying AF

# DRUG HISTORY

- Son was very concern about the pain as patient keep complaining to him about the knee pain each visit
- He reported patient actually using an over-the-counter medication for his knee pain for many years
- He is worried of any side effects of those medications
- Son tried to trace the medication from home: many old packets labelled of Panadol, Mefenamic acid (only with name on drug bag, no dosage)
- Patient nearly taken them daily, self increased dosage if recurrence of pain within short time or pain not relieved
- Patient refill the medications by bringing the old drug bag to a local pharmacy near his home
- No antacid/H2 blockers/PPI cover
- No Hx of abdominal pain/GIB/OGD before this admission

# PROBLEM LIST

- Acute on chronic renal failure
- Acute liver failure with hepatic encephalopathy
- Warfarin overdose due to warfarin effect, acute liver failure causing coagulopathy + recent use of antibiotics causing drug-drug interactions with warfarin
- UTI, may contribute to renal failure
- RECURRENT GOUTY ATTACK
- OA KNEES
  - ??NSAID induced ARF/Acute liver failure/DU due to prolonged use and suspected overdose
  - ? Steroid from local pharmacy
- *Educated son and patient to stop using pain killers without medical advice.

# PROGRESS

- Fluid overload -> treated as CHF with Lasix
- Failed wean off Foley -> Recurrent UTI -> E. coli, treated with another course of Augmentin
- Fast AF during UTI, treated with Betaloc and amiodarone -> later switched to digoxin (clinically HF and AF)
- Deteriorated RFT, pre-renal pattern -> over-diuresis by maintainence low dose of Lasix -> to PRN Lasix
- ECHO: normal LV function, mod MR, AR, PR, mildly dilated LA
- ?? NSAIDs related fluid overload + effect of hypoalbuminaemia

# PROGRESS

- Difficulty in control of right knee pain and swelling
- Consulted Rheumatologist:
  - Knee tapping done: straw colored fluid, urate crystals seen from microscopy, raised WCC, polymorphs,  AFB smear:negative, bacterial C/ST: negative, no malignant cells
    - Suggested to use colchicine at lower dose (renal impairment)
- Swelling of Rt knee gradually subsided, but still with pain on walking
- Son and patient refused surgical treatment for symptomatic severe OA knee
- LFT normalized, resumed panadol for pain control

# DISCHARGE

- BI: 37 -> 76/100
- Walk with stick with minimal assistance; lying to sitting independent, dressing independent, bathing independent, sit to stand required supervision
- Son arranged OAH for patient because patient daytime alone, he worried of fall or other incidents during daytime without supervision
- GDH rehabilitation arranged
- Discharged to OAH 11/6/2013 ( ~ 2 months stay)

# FOLLOW-UP & READMISSION

- Well after discharge
- Started allopurinol at 100mg daily at post-d/c 1st FU
- Readmitted again for severe right knee/ankle/foot pain soon after FU
- Dx: Acute flare up of gout due to initiation of allopurinol
- Treated with colchicine
- Pain subsided
- d/c after 1 week stay
- Continues GDH rehabilitation

# DRUG AND ADR SUMMARY OF MR CHAN

| TIME | Before admission | Admission (2 months) | FU & readmission |
|---|---|---|---|
| MEDICATION LIST | Norvasc<br>Betaloc<br>Warfarin<br>Mefenamic acid<br>Dimefort<br>Vitamin B complex<br>Panadol<br>Antibiotic | - Warfarin, Norvasc, Betaloc, Mefenamic acid, Dimefort<br><br>+/- Vitamin K, Lasix, Amiodarone<br><br>+ Digoxin, colchicine, Plavix<br><br>= Panadol, Vitamin Bco | + allopurinol<br>+ colchicine |
| Possible ADR or exacerbation of underlying disease | **Antibiotic + Mefenamic acid: Warfarin overdose**<br>**Mefenamic acid: bleeding DU**<br>**Panadol + Mefenamic acid: liver failure** | **Norvasc, betaloc: hypotension**<br>**Mefenamic acid: fluid overload**<br>**Lasix: over-diuresis** | **Allopurinol: acute flare up of gout** |

# PART II: DISCUSSION

# 2 CASES

- Common scenario
- ‘Young’ elderly (67y) vs ‘old’ elderly (85 y)
- GOUT -> Used self bought NSAIDs from local pharmacy -> Peptic ulcers with GIB -> Prolonged stay with multiple co-morbidities

- IATROGENESIS:
  - SELF MEDICATIONS
  - Adverse drug reactions

# SELF MEDICATIONS

# HOW COMMON IS THE USE OF OTC MEDICATIONS in HK ?

- 90 out of the 567 (15.8%) who experienced symptoms undertook self-management strategies, which included over-the-counter western allopathic medications (n=54) (9.5%), or traditional Chinese remedies (n=14) or both (n=2), dietary modification (n=1) and rest (n=15).

[Leung et al (HKU) The ecology of health care in Hong Kong. Soc Sci MED 2005]

- In another local survey, 65% of the respondents used OTC medications [Lam CLK, Catarivas MG, Munro C, Lauder IJ: Self-medication among Hong Kong Chinese. Soc Sci Med 1994, 39(12):1641-7.]

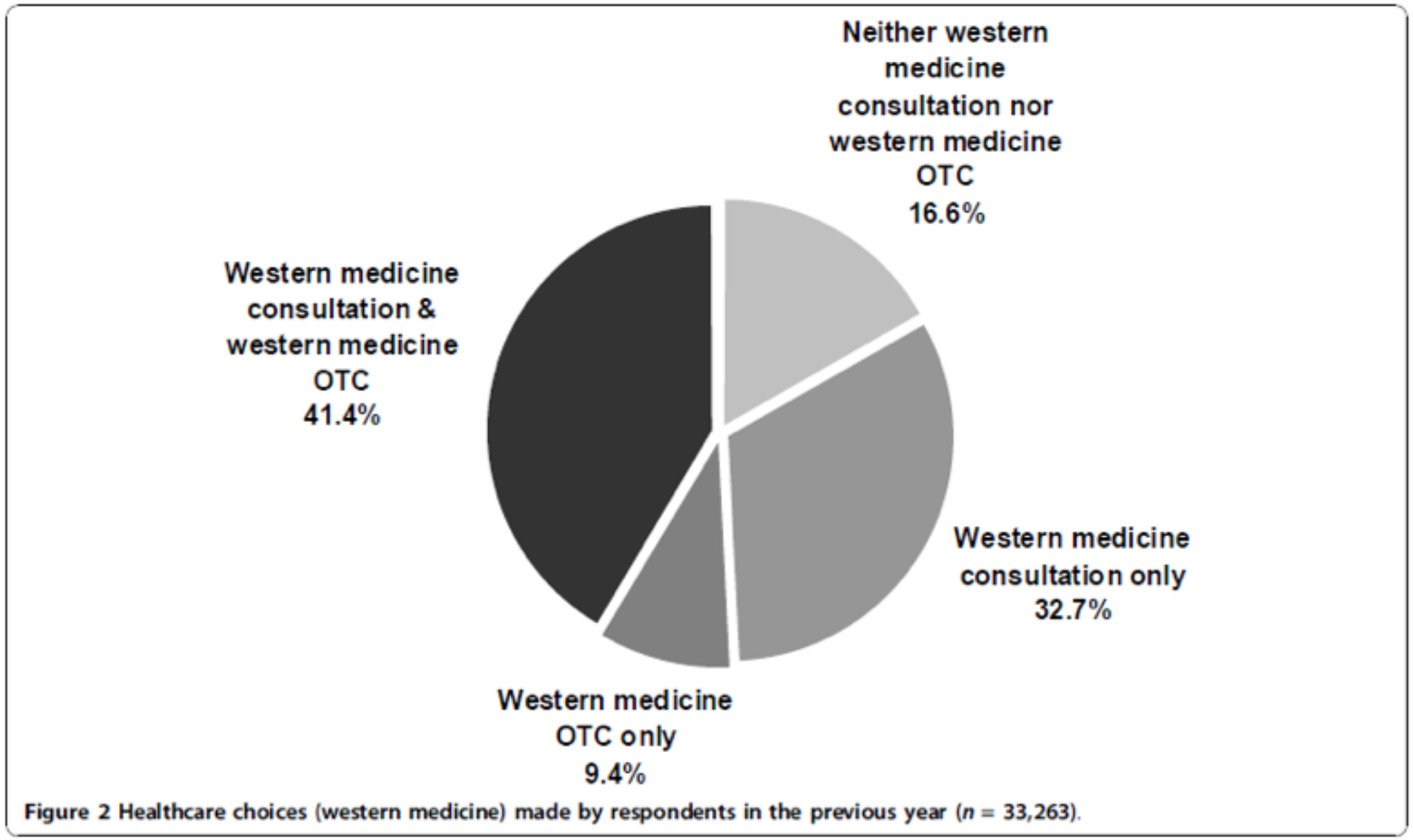



Figure 2 Healthcare choices (western medicine) made by respondents in the previous year ($n$ = 33,263).

Chung et al, Chinese Medicine

# PRESCRIBED MEDICINES VS OVER-THE-COUNTER MEDICINES

- Over-the-counter (OTC) medicines are drugs you can buy without a doctor's prescription

- In the above 2 cases, if by definition, mefanemic acid, indomethacin, Minax, Apo-amilzide are not OTC medications, should be refer to as self using prescription-only medications obtained inappropriately from pharmacy without a doctor's prescription and pharmacy's act may be illegal

# WHAT ARE THE REGULATIONS FOR MEDICATIONS IN HK?

- In Hong Kong the Department of Health (DH) is responsible for overseeing the safety, efficacy and quality of all medicines marketed in Hong Kong.
- In the United States, the Food and Drug Administration (FDA) decides whether a medicine is safe enough to sell over-the-counter

| | |
|---|---|
| Non-Chinese Medicine (including Western Medicines | Pharmacy and Poisons Ordinance (Cap. 138) |
| Chinese Medicine | Chinese Medicine Ordinance (Cap. 549) |

# Pharmacy and Poisons Ordinance (Cap. 138)

- According to the Pharmacy and Poisons Ordinance (Cap. 138), medicines to be applied on human or animal bodies for diagnosis, treatment, relief or prevention of diseases must be registered with the Pharmacy and Poisons Board (PBB) prior to their sale in the market.

http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/drug_regulatory_system.html

# Classification and Control of drugs in HK

- Category 1 [Prescription-only medicine]: Medicines in this category must be dispensed and sold *on doctor's prescription in *registered pharmacies under the direct *supervision of registered pharmacists.
  - Examples include antihypertensive medicines, oral antidiabetics, antibiotics and tranquillisers. Such "prescription medicines" are used to treat serious diseases. Incorrect dosage or improper use may bring about serious health damage.
- Category 2 [Pharmacy-only medicine]: Medicines in this category do not require doctor's prescription but have to be sold in registered pharmacies under the direction and *supervision of registered pharmacists. The method of use and dosage must be followed to avoid health risks.
- Category 1 and Category 2 medicines need to be labelled 'POISON' in their drug packages
- Category 3 [Over-the-counter medicine]: Medicines in this category can be sold in pharmacies or medicine stores without resident pharmacists and examples include drugs for common cold, antipyretics and painkillers. They are often used to treat or alleviate minor illnesses and their side effects are fewer.

# REGULATIONS TO RETAILERS OF MEDICINE

- Listed Seller of Poisons (LSP)
  LSPs, commonly known as “medicine companies”, are only allowed to sell the category 3 medicines.
- Authorized Seller of Poisons (ASP)
  ASPs, commonly known as “pharmacies” or “dispensaries”, are authorized to sell all 3 categories of medicines under specific conditions. They are distinguished from other unlicensed drug retailers or LSPs by displaying the “℞” logo. The name, the certificate of registration and working hours of the pharmacist must be displayed in a conspicuous location inside the ASP. The Ordinance requires that medicines in categories 1 and 2 must be sold under the supervision of registered pharmacists at the premises of ASP. Illegal sale of controlled medicine is an offence and subject to a maximum penalty of $100,000 fine and 2 years’ imprisonment.
- DH conducts, on average, two unannounced inspections against medicine retailers to ensure their compliance with legal requirements

## Search Drug Database

Detail Information

Last Updated: 11-Oct-2013

| | | |
|---|---|---|
| Product Name | : | APO-INDOMETHACIN CAP 25MG |
| Registration No. | : | HK- 41105 |
| Certificate Holder | : | HIND WING CO LTD |
| Certificate Holder Address | : | UNIT 3B 11/F BLK B SEAVIEW ESTATE,<br>2-8 WATSON RD,NORTH POINT,HK |
| Legal Classification | : | Part I, First & Third Schedule Poison |
| Sale Requirement* | : | Prescription only Medicine |
| Ingredients | : | INDOMETHACIN |
| Date of Registration | : | 03 Aug, 1996 |

*Notes:

-**Prescription Only Medicines** are medicines which must only be purchased with a prescription in a pharmacy.
-**Pharmacy Only Medicines** are medicines which can be purchased in a pharmacy in the presence and under the supervision of a registered pharmacist, but without the need of a prescription.
-**Over-the-Counter Medicines** are in general medicines classified as Part II poison and 'Not a Poison'. For medicines which are classified as 'Not a Poison', they can be freely purchased from a pharmacy (Authorized Seller of Poisons), a medicine store (Listed Seller of Poisons), or any other non-licensed premises; whereas for Part II Poisons, they can be purchased only from a pharmacy or a medicine store.

| | | |
|---|---|---|
| Product Name | : | MEFA TAB 250MG |
| Registration No. | : | HK- 01689 |
| Certificate Holder | : | JEAN-MARIE PHARMACAL CO LTD |
| Certificate Holder Address | : | 1/F GMP CENTRE 12 DAI FU ST,<br>TAI PO IND ESTATE,TAI PO,NT |
| Legal Classification | : | Part I, First & Third Schedule Poison |
| Sale Requirement* | : | Prescription only Medicine |
| Ingredients | : | MEFENAMIC ACID |
| Date of Registration | : | 24 Oct, 1978 |

| | | |
|---|---|---|
| Product Name | : | ACETAMINOPHEN CAP 500MG (JEAN-MARIE) |
| Registration No. | : | HK- 46309 |
| Certificate Holder | : | JEAN-MARIE PHARMACAL CO LTD |
| Certificate Holder Address | : | 1/F GMP CENTRE 12 DAI FU ST,<br>TAI PO IND ESTATE,TAI PO,NT |
| Legal Classification | : | Not A Poison |
| Sale Requirement* | : | Over The Counter Medicine |
| Ingredients | : | PARACETAMOL |
| Date of Registration | : | 31 May, 2000 |

| | | |
|---|---|---|
| Product Name | : | MINAX 50 TAB |
| Registration No. | : | HK- 36512 |
| Certificate Holder | : | LUEN CHEONG HONG LTD |
| Certificate Holder Address | : | 25/F 200 GLOUCESTER RD,<br>WAN CHAI,HK |
| Legal Classification | : | Part I, First & Third Schedule Poison |
| Sale Requirement* | : | Prescription only Medicine |
| Ingredients | : | METOPROLOL |
| Date of Registration | : | 26 Oct, 1992 |

| | | |
|---|---|---|
| Product Name | : | PIRITON TAB 4MG |
| Registration No. | : | HK- 44233 |
| Certificate Holder | : | GLAXOSMITHKLINE LIMITED |
| Certificate Holder Address | : | UNIT 2201 2214 AND 23/F TOWER 6,<br>THE GATEWAY HARBOUR CITY 9 CANTON RD,TSIM SHA TSUI,KLN |
| Legal Classification | : | Part II Poison |
| Sale Requirement* | : | Over The Counter Medicine |
| Ingredients | : | CHLORPHENIRAMINE |
| Date of Registration | : | 21 Jan, 1999 |

| | | |
|---|---|---|
| Product Name | : | APO-AMILZIDE TAB 50/5MG |
| Registration No. | : | HK- 42186 |
| Certificate Holder | : | HIND WING CO LTD |
| Certificate Holder Address | : | UNIT 3B 11/F BLK B SEAVIEW ESTATE,<br>2-8 WATSON RD,NORTH POINT,HK |
| Legal Classification | : | Part I, First & Third Schedule Poison |
| Sale Requirement* | : | Prescription only Medicine |
| Ingredients | : | HYDROCHLOROTHIAZIDE<br>AMILORIDE |
| Date of Registration | : | 24 Jun, 1997 |

**Adverse Drug Reaction**

| Drug | Adverse Drug Reaction | Additional Information | L |
|---|---|---|---|
| INDOMETHACIN | Gastric Ulcer; Gastrointestinal Hemorrhage | | Se |

**Alert**

| Details | Additional Information | Validity From | Val |
|---|---|---|---|

Print Preview

**Adverse Drug Reaction**

| Drug | Adverse Drug Reaction | Additional Information |
|---|---|---|
| MEFENAMIC ACID | Anemia; Drug-Induced Hepatitis; Gastrointestinal Hemorrhage; Nephrotoxicity; Peptic Ulcer; Renal Failure | |

**Alert**

| Details | Additional Information | Validity Fr |
|---|---|---|

# ADVERSE DRUG REACTIONS

- World Health Organization (WHO):
  - A ‘response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function’

# CLASSIFICATION OF ADR

- The traditional classification for ADRs comprises type A (augmented) reactions and type B (bizarre or idiosyncratic) reactions and generally encompasses most observed ADRs.

- Subsequently four further divisions were added to produce a six-category classification (A-F)

| Type of reaction | Mnemonic | Features | Examples | Management |
|---|---|---|---|---|
| **A: Dose-related** | Augmented | • Common<br>• Related to a pharmacological action of the drug<br>• Predictable<br>• Low mortality | • Toxic effects:<br>Digoxin toxicity; serotonin syndrome with SSRIs<br>• Side effects:<br>Anticholinergic effects of tricyclic antidepressants | • Reduce dose or withhold<br>• Consider effects of concomitant therapy |
| **B: Non-dose-related** | Bizarre | • Uncommon<br>• Not related to a pharmacological action of the drug<br>• Unpredictable<br>• High mortality | • Immunological reactions:<br>Penicillin hypersensitivity<br>• Idiosyncratic reactions:<br>Acute porphyria<br>Malignant hyperthermia<br>Pseudoallergy (eg, ampicillin rash) | • Withhold and avoid in future |
| **C: Dose-related and time-related** | Chronic | • Uncommon<br>• Related to the cumulative dose | • Hypothalamic-pituitary-adrenal axis suppression by corticosteroids | • Reduce dose or withhold; withdrawal may have to be prolonged |
| **D: Time-related** | Delayed | • Uncommon<br>• Usually dose-related<br>• Occurs or becomes apparent some time after the use of the drug | • Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol)<br>• Carcinogenesis<br>• Tardive dyskinesia | • Often intractable |
| **E: Withdrawal** | End of use | • Uncommon<br>• Occurs soon after withdrawal of the drug | • Opiate withdrawal syndrome<br>• Myocardial ischaemia (β-blocker withdrawal) | • Reintroduce and withdraw slowly |
| **F: Unexpected failure of therapy** | Failure | • Common<br>• Dose-related<br>• Often caused by drug interactions | • Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers | • Increase dosage<br>• Consider effects of concomitant therapy |

Edwards et al Lance

## Immune-mediated hypersensitivity reactions

| | | | |
|---|---|---|---|
| I | Anaphylactic | Anaphylaxis, angioedema, atopy | IgE |
| II | Cytotoxic | Goodpasture's syndrome, transfusion reaction | IgG, IgM |
| III | Immune complex | SLE, rheumatoid arthritis | IgG, IgM |
| IV | Delayed | Contact dermatitis, tuberculin test | T-cells |

Ig, immunoglobulin; SLE, systemic lupus erythematosus.

[Aronson and Ferner]

# HOW COMMON IS ADR?

- 6.5% of all hospital admissions in UK due to ADR [Pirmohamed el al BMJ 2004]
- 5 to 10% of medical in-patients suffered from ADR [Ferner and Butt et al]
- In HK, a study of PWH in 1990 [Chan et al, Drug Safety 1992]
  - 74 of 1700  admissions (4.4%) were attributed to ADRs.
  - The most frequent ADRs
    - Hypoglycaemia (43%): cause: hypoglycaemia agents (sulphonyureas, insulins)
    - Gastrointestinal haemorrhage (29.7%), cause: NSAIDs
  - Both old age and impaired renal function were important risk factors for ADRs.

# WARD SURVEY OF ADR
# July 2013 PYNEH MALE GERIATRIC BED ADMISSIONS

| | | | |
|---|---|---|---|
| Total number of cases | 50 | | |
| No of patients suffered from ADR in current admission | 24 (48%) | 1 ADR | 20 |
| | | 2 ADRs | 3 |
| | | 3 ADRs | 1 |
| Hx of ADR (from CMS alert and old ePR notes) | 21 (42 %) | | |
| Polypharmacy (Use >=5 medications) | 23 (46%) | | |

# ADR

| | |
|---|---|
| Warfarin | Overdose, interaction with antibiotics |
| Alpha-blockers: Minipress, Hytrin, Cardura XL | Postural hypotension/ dizziness |
| ACEI: Lisinopril | Intractable cough |
| Beta-blocker: Betaloc | Sinus bradycardia |
| Calcium channel blocker: Adalat Retard | Peripheral edema |
| Natrilix | Hypokalaemia, hyponatraemia |
| Moduretic | Hypokalaemia |
| Aldactone | Renal failure |
| Aldomet | Drowsiness, severe hypotension |
| Dexopte Maxitol eyedrops | Blurred vision |

| | |
|---|---|
| NSAIDs: Voltaren, indomethacin | Proctitis, gastric ulcer, renal failure |
| Insulin: Mixtard 30 HM, Protaphane HM | Severe hypoglycaemia |
| Lorazepam, Diazepam | Decreased GC, drowsiness |
| Imovane | Prolonged decreased GC |
| Quetiapine | Dizziness |
| Elantan | Postural dizziness |
| Oxybutinin | Sinus bradycardia |
| Digoxin | Overdose with severe bradycardia |
| Aspirin | Gastric ulcer |
| Colchicine | Diarrhoea |
| Tramadol | Dizziness, diarrhoea |

# DRUGS CAUSING ADR

- The most common drug classes associated with ADRs
  - cardiovascular drugs
  - diuretics
  - anticoagulants
  - non-steroidal anti-inflammatory drugs
  - antibiotics
  - hypoglycemics

Gurwitz et al JAMA 2003
Hol CM el al Ann

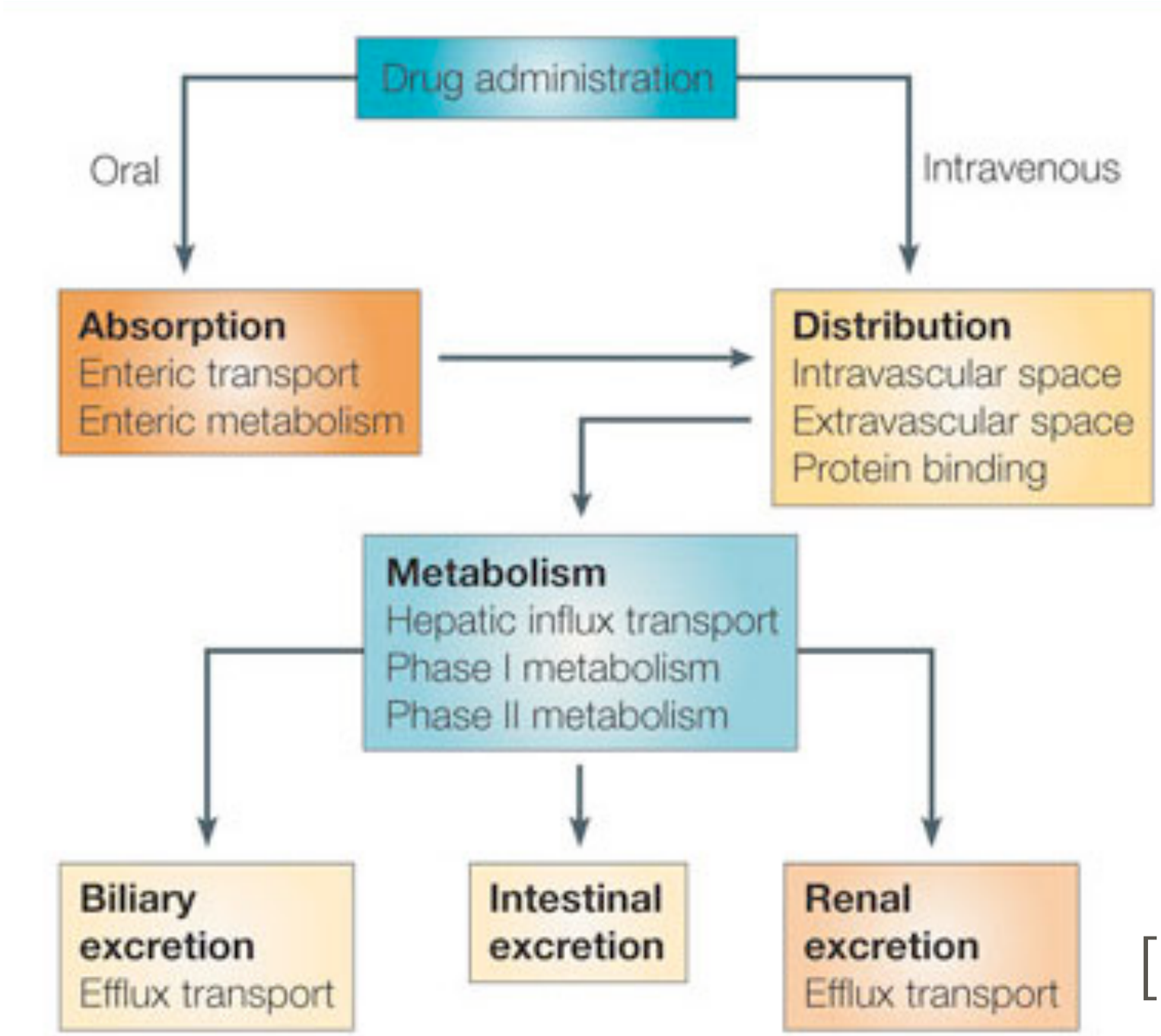
# CAUSES OF ADR IN ELDERLY

- Polypharmacy
- Inadequate clinical assessment and inaccurate clinical diagnosis
- Excessive prescribing
- Inappropriate prescribing
- Multiple prescriptions
- Lack of supervision and review
- Non-compliance
- Altered pharmacokinetics and pharmacodynamics
- Drug-drug and drug-disease interactions

HKGS curriculum Ch.

# WHY DO GERIATRIC PATIENTS SUFFER MORE ADRS?

# PHARMACOKINETICS




[Medscape]

# AGE RELATED PHYSIOLOGICAL CHANGES AFFECTING PHARMACOKINETICS

| PHARMACOLOGICAL PARAMETER | ALTERED PHYSIOLOGICAL FUNCTIONS IN ELDERLY | EFFECT ON PHARMACOKINETICS |
|---|---|---|
| ABSORPTION | ↑ Gastric pH<br>↓ Splanchnic blood flow<br>↓ Gut motility | Decreased absorptions of medications |
| DISTRIBUTION | ↓ Total body water<br>↓ Lean body mass<br>↑ Fat<br>↓ Serum albumin | ↑ Relative dose per body weight<br>Water soluble: ↓ Vd, ↑ blood level e.g. digoxin<br>Fat soluble: ↑ Vd, ↑ half life e.g. diazepam<br>Protein binding drugs: ↑ free fraction of drugs e.g warfarin, lasix |

# PROPERTIES OF MEDICATION AND EFFECT OF AGING

| Drug | Effect of Age |
|---|---|
| Hydrophilic | Volume of distribution decreases |
| Ethanol | Plasma concentration increases |
| Cimetidine | Half-life decreases |
| Digoxin | |
| Levodopa | |
| Morphine | |
| Propicillin | |
| Lipophilic | Volume of distribution increases |
| Thiopental | Plasma concentration decreases |
| Amitriptyline | Half-life increases |
| Diazepam | |
| Clomethiazole | |
| Tolbutamide | |

# AGE RELATED PHYSIOLOGICAL CHANGES AFFECTING PHARMACOKINETICS (2)

| PHARMACOLOGICAL PARAMETER | ALTERED PHYSIOLOGICAL FUNCTIONS IN ELDERLY | EFFECT ON PHARMACOKINETICS |
|---|---|---|
| LIVER: METABOLISM & EXCRETION | ↓ Liver blood flow<br>↓Enzyme activity<br>↓Enzyme inducibility<br>↓ Liver mass | ↑First pass availability of some drugs<br>↓Hepatic clearance |
| KIDNEY: EXCRETION | ↓ Renal blood flow<br>↓ GFR<br>↓Tubular secretion | ↓ Renal excretion of drugs and their metabolites<br>↑ Half life of water soluble drugs |

# AGE RELATED PHYSIOLOGICAL CHANGES AFFECTING PHARMACODYNAMICS

| PHARMACOLOGICAL PARAMETER | ALTERED PHYSIOLOGICAL FUNCTIONS IN ELDERLY | EFFECT |
|---|---|---|
| TISSUE SENSITIVITY | Changes in :<br>receptor number<br>receptor affinity<br>second-messenger function<br>cellular response<br>nuclear response | a) ↑ sensitivity of drugs:<br>required lower dose to exert effect/higher chance to get adverse effect at standard dose<br><br>b) ↓ sensitivity of drugs:<br>required relatively higher dose |

# UNDERESTIMATION OF ADR

- The detection of ADRs relies heavily on spontaneous reporting, stimulated post-marketing surveillance, and case-control studies.
- There is under-reporting of drug reactions in the community and in the hospital setting in HK [Chan, Thomas YK et al, Pharmacoepidemiology & Drug Safety 1994]
- The drug reaction may not be recognized by the patient.
- The drug reaction may not be recognized by the doctor.
- If recognized by the patient, the doctor may not report it to the company manufacturing the drug.
- When the report is received by the drug monitor in the pharmaceutical company, the report may not contain enough detailed information to assess the relationship between drug intake and side effect.

# Elderly knowledge of NSAIDs ADR

- [Use of NSAIDs for osteoarthritis amongst older-aged primary care patients: engagement with information and perceptions of risk Tamara et al Age and Aging 2011]
- A semi-structured interviews were conducted with 15 patients who were recruited from four general practices located in Sydney, Australia. Patients were aged at least 65 years and were currently taking, or in the past 2 years had taken an NSAIDs for osteoarthritis.
- Patients demonstrated three key ‘modes of disengagement’ from medication-specific risk information, each of which could also be a mode of modulating a sense of danger and each of which would demand a unique clinical response. These were:

  (A)‘transference of responsibility’—transferring the responsibility to their GP,

  (B)‘general versus specific risk’—considering the risk of taking medicine in general as opposed to the specific risk of taking an NSAID

  - ‘personal immunity’— some patients with a long history of NSAID use without apparent toxicity believed they were, therefore, not at risk of future adverse effects, while a few patients believed they were immune to adverse effects of drugs in general.

# PATIENT'S KNOWLEDGE ON ADR

- Communications about the risks of adverse drug reactions (ADRs) can be compromised by time constraints during consultations, and patient inhibitions, preventing them from asking questions about the potential harms from prescribed medicines
- Prescribers may focus more on the benefits of the medication, rather than potential harms
- An analysis of 462 transcripts of doctor– patient interactions found adverse outcomes were among the least discussed issues in these consultations, with only 8.2% discussing possible ADRs, 2% discussing the risk of occurrence, and 2.3% discussing precautions to avoid the ADR. [Richard et al Patient Educ Couns 2006]
- It was also found that in doctor consultations, the limitations of medicines were discussed less often than their effectiveness, with strategies for coping with potential ADRs discussed in only 10.3% of cases. [Feng et al.Health Commun 2011]

# Dx of ADR

- Any patient is taking medicines, the differential diagnosis of any symptoms or complaints should include the possibility of an adverse drug reaction.
- Taking the DRUG HISTORY is very important.
  - First is to find out whether a patient is taking a medicinal product, including: *over-the-counter formulations; products that may not be thought of as medicines (such as herbal or traditional remedies, *recreational drugs, or drugs of abuse); and *long-term treatments that the **patient may forget (such as oral contraceptives).
  - Second is to find out whether the effect could be due to a medicine.
  - Third is to distinguish which medicine is causative for ADR if patient is taking multiple medications
  - Fourth is to take into account of drug-drug interactions, drug-disease interactions

# ADRs OF MR CHAN AND MR LUK

| *AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults* | | |
|---|---|---|
| **Drugs and Categories of Drugs** | **Why these drugs may be inappropriate for older adults** | **Recommendations** |
| Non–COX-selective Non-Steroidal Anti-inflammatory Drugs (NSAIDs), oral<br>• Aspirin at doses higher than 325 milligrams per day<br>• Diclofenac<br>• Diflunisal<br>• Etodolac<br>• Fenoprofen<br>• Ibuprofen<br>• Ketoprofen<br>• Meclofenamate<br>• Mefenamic acid ★<br>• Meloxicam<br>• Nabumetone<br>• Naproxen<br>• Oxaprozin<br>• Piroxicam<br>• Sulindac<br>• Tolmetin | These medications increase the chance of stomach and intestinal bleeding in adults 75 or older, and adults 65 and older taking certain other medications (like prednisone warfarin, and clopidogrel) and medicines to prevent stroke.<br><br>Taking a powerful stomach medication like a proton-pump inhibitor (omeprazole) or misoprostol at the same time as these drugs lowers—but doesn't eliminate—these risks. | Do not use these medications regularly unless there are no other effective alternatives and they are prescribed along with a proton-pump inhibitor or misoprostol. |
| Indomethacin ★<br>Ketorolac | These drugs are NSAIDs that are even more likely to increase the chance of stomach and intestinal bleeding and ulcers or to cause other harmful effects. | Avoid |

# Guidelines for Prevention of NSAID-Related Ulcer Complications

Frank L. Lanza, MD, FACG[1,2], Francis K.L. Chan, MD, FRCP, FACG[3], Eamonn M.M. Quigley, MD, FACG[4] and the Practice Parameters Committee of the American College of Gastroenterology

*Am J Gastroenterol* 2009; 104:728–738; doi:10.1038/ajg.2009.

**Table 1. Patients at increased risk for NSAID GI toxicity**

| |
|---|
| *High risk* |
| 1. History of a previously complicated ulcer, especially recent |
| 2. Multiple (>2) risk factors |
| *Moderate risk (1–2 risk factors)* |
| 1. Age >65 years |
| 2. High dose NSAID therapy |
| 3. A previous history of uncomplicated ulcer |
| 4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants |
| *Low risk* |
| 1. No risk factors |
| *H. pylori* is an independent and additive risk factor and needs to be addressed separately (see text and recommendations). |

# Guidelines for Prevention of NSAID-Related Ulcer Complications

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**Table 2. Summary of recommendations for prevention of NSAID-related ulcer complications**

| | Gastrointestinal risk[a] | | |
|---|---|---|---|
| | Low | Moderate | High |
| Low CV risk | NSAID alone (the least ulcerogenic NSAID at the lowest effective dose) | NSAID+PPI/misoprostol | Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol |
| High CV risk[b] (low-dose aspirin required) | Naproxen + PPI/misoprostol | Naproxen + PPI/misoprostol | Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy |

[a]Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants). [b]High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H. pylori*, and if the infection is present, eradication therapy should be given.

*Naproxen may have some cardio-protective properties

# Risk of serious NSAID-related gastrointestinal events during long-term exposure: a systematic review

**Objective:** Exposure to non-steroidal anti-inflammatory drugs (NSAIDs) is associated with increased risk of serious gastrointestinal (GI) events compared with non-exposure. We investigated whether that risk is sustained over time.

**Data sources:** Cochrane Controlled Trials Register (to 2002); MEDLINE, EMBASE, Derwent Drug File and Current Contents (1999–2002); manual searching of reviews (1999–2002).

**Study selection:** From 479 search results reviewed and 221 articles retrieved, seven studies of patients exposed to prescription non-selective NSAIDs for more than 6 months and reporting time-dependent serious GI event rates were selected for quantitative data synthesis. These were stratified into two groups by study design.

**Data extraction:** Incidence of GI events and number of patients at specific time points were extracted.

**Data synthesis:** Meta-regression analyses were performed. Change in risk was evaluated by testing whether the slope of the regression line declined over time. Four randomised controlled trials (RCTs) provided evaluable data from five NSAID arms (aspirin, naproxen, two ibuprofen arms, and diclofenac). When the RCT data were combined, a small significant decline in annualised risk was seen: –0.005% (95% CI, –0.008% to –0.001%) per month. Sensitivity analyses were conducted because there was disparity within the RCT data. The pooled estimate from three cohort studies showed no significant decline in annualised risk over periods up to 2 years: –0.003% (95% CI, –0.008% to 0.003%) per month.

**Conclusions:** Small decreases in risk over time were observed; these were of negligible clinical importance. For patients who need long-term (> 6 months) treatment, precautionary measures should be considered to reduce the net probability of serious GI events over the anticipated treatment duration. The effect of intermittent versus regular daily therapy on long-term risk needs further investigation.

MJA 2006; 185: 501–506

# Mefenamic Acid and Renal failure

- Mefenamic acid can produce a rather distinct type of renal injury characterised by interstitial nephritis and rapid reversibility on withdrawal of the drug.

- Renal impairment may develop (a) after a few days of treatment, or (b) after many months of treatment in conventional doses.

- [Woods et al, BMJ 1985]

# Mefenamic Acid and Renal Failure

[BMJ 1985 Poulton et al ]

## Non-oliguric renal failure during treatment with mefenamic acid in elderly patients

An 83 year old woman living in a social services home was admitted with a two week history of immobility and diarrhoea. Before this episode she could take short walks indoors with a walking frame. Her mobility was impaired because of a previous mild hemiparesis and widespread osteoarthrosis. Drug treatment was with mefenamic acid 500 mg three times a day, Navidrex-K (cyclopenthiazide 250 μg and potassium chloride 600 mg) two tablets daily, prochlorperazine 5 mg three times a day, and quinine sulphate 300 mg at night. She was treated with oral rehydration, withdrawal of her mefenamic acid and Navidrex-K, and gradual remobilisation. Her biochemical profile reverted to normal after one week (table).

*Change in biochemical profile after withdrawal of mefenamic acid*

| | Urea (mmol/l) | Creatinine (μmol/l) | Bicarbonate (total) (mmol/l) |
|---|---|---|---|
| Premorbid | 8·31 | 107 | 29 |
| Morbid | 34·3 | 253 | 15·3 |
| After withdrawal of drugs | 4·8 | 91 | 26·2 |

*Conversion: SI to traditional units*—Bicarbonate: 1 mmol/l = 1 mEq/l. Creatinine: 1 μmol/l≈0·0113 mg/100 ml. Urea: 1 mmol/l≈6 mg/100 ml.

# NSAIDs and Hepatotoxicity

- Drug insertions of any NSAIDs included the following statement:

Hepatic Effects

  - Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs
  - These laboratory abnormalities may (a) progress, (b) remain unchanged, or (c) transient with continuing therapy.
  - Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

# HK CASE REPORT

## A Case of Stevens-Johnson Syndrome, Cholestatic Hepatitis and Haemolytic Anaemia Associated with Use of Mefenamic Acid

*Juliana C.N. Chan, Fernand M. Lai* and *Julian A.J.H. Critchley*
Departments of Clinical Pharmacology and Anatomical and Cellular Pathology, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong

***Summary*** A woman with a history of drug allergy, renal impairment and carcinoma of the breast with pulmonary micrometastases developed haemolytic anaemia and Stevens-Johnson syndrome following the use of mefenamic acid, paracetamol (acetaminophen) and furosemide (frusemide). In addition there was severe cholestatic hepatitis in the absence of clinical evidence of sepsis, biliary obstruction or recurrent metastases. The rash resolved on steroid therapy but the patient eventually died from both renal and liver failure. Acute tubular necrosis with a background of chronic tubulointerstitial nephritis was also found at autopsy. Although in the presence of multiple drug therapy the causative agent cannot be identified with absolute certainty, the association of these severe idiosyncratic hepatic and dermatological reactions with haemolytic anaemia strongly suggests mefenamic acid as the most likely culprit.

Mr Chan: mefenamic acid and panadol

# WARFARIN ADR

- Risk for hemorrhage associated with anticoagulant therapy also increases in elderly
- Polypharmacy and drug-drug interactions often are responsible for upsetting the delicate balance between anticoagulation and hemorrhage.
- Warfarin is extensively metabolized by the cytochrome P450 enzymes 2C9, 2C19, 1A2, and 3A4
- Drugs that inhibit these enzymes can increase the INR, and potentially increase the risk for bleeding, whereas drugs that induce these enzymes may decrease the INR and consequently decrease the effectiveness of warfarin

# WARFARIN AND NSAIDs

- Compared with non-users of either drug, the relative risk of hemorrhagic peptic ulcer disease among current users of both anticoagulants and NSAIDs was 12.7 (95% confidence interval, 6.3 to 25.7)

- Patients taking non-steroidal anti-inflammatory drugs while on oral anticoagulation therapy are at a higher risk for gastrointestinal bleeding, particularly those patients over the age of 65

[Shorr et al. Arch Intern Med 199

# TREATMENT OF GOUT

Drugs Aging. 2011 Aug 1;28(8):591-603. doi: 10.2165/11592750-000000000-00000.

# GOUT T ELDERLY

**The challenges of gout management in the elderly.**

Stamp LK, Jordan S.

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- Gout management in elderly is frequently complicated
  - co-morbid conditions
    - medications prescribed for other conditions.
- Renal impairment is of particular concern in the elderly and may preclude the use of NSAIDs and colchicine.
- The IL-1 inhibitors are rapidly effective but data in the elderly are limited.

# GOUT TREATMENT OVERVIEW

- Acute:
  - NSAIDs
  - Corticosteroids
  - Colchicine
  - Anti- IL-1 therapy

- Chronic treatment:
  - Allopurinol
  - Probenicid
  - Febuxostat
  - Pegloticase

# Chronic treatment

Aim:

(1)Prevent recurrent attacks by using uric acid lowering therapy and thereby alleviate complications of chronic gouty arthritis

(2)‘Treat to target’ to prevent MSU crystal saturation and dissolve crystals already deposited in joints and soft tissue by reducing serum urate effectively (BSR <0.3 mmol/l; EULAR <0.36mmol/l)

(3)Assess and modify contributing risk factors [e.g. hypertension, diabetes mellitus, hyperlipidaemia, heart failure, obesity, osteoarthritis, drugs (diuretics and ciclosporin)]

(4)Provide long-term follow-up and monitoring of gout including serum urate (sUA)

# NON-PHARMACOLOGICAL TREATMENT

- Low purine diet
- Weight loss
- Regular exercise
- Avoid dehydration

# IF RENAL IMPAIRMENT

- Like MR CHAN's condition
- Treatment option:
  - Oral glucocorticoids: prednisolone
  - Allopurinol, lower dose for renal impairment with colchicine as acute attack prophylasis at start of treatment
    - Aware of idiosyncratic reactions, SJS which is more common in Asians (HLA 5801)
- Feboxustat: although no dose reduction required for renal impairment, still need to be careful if CrCl <= 30ml/minute
  - C/I: Theophylline
- Consider to change to Losartan if patient require use of ACEI/ARB treatment for urate lower effect

# JOINT PAIN

- DDX:
  - OA
  - GOUT
  - PSEUDOGOUT
  - RA

# OUR ROLE

- ☑ Always do a comprehensive review of medications of patient at in-patient and out-patient settings
- ☑ Aware of any self medications including non-prescription medications, OTC medications, Chinese medicine or other health care products
- ☑ Aware of ADRs and try to identify them
- ☑ Aware of drug-drug interactions, drug-disease interactions
- ☑ Stop inappropriate medications
- ☑ Try to avoid polypharmacy
- ☑ Try to decrease use of medications which has increase chance of ADR in elderly
- ☑ Try to simplify the drug regime to improve drug compliance
- ☑ Communicate with patients and their carers, if in doubt, interview them again to get more information
- ☑ Educate patient, carers
- ☑ Document ADR properly in ePR to alert other doctors and health care providers about the ADRs of patient
- ☑ Report ADR to Drug Office of DH

# SUMMARY

- Two elderly patients with gout, suffered from severe joint pain, tried to use medications for pain control by themselves in-appropriately, pain not controlled but suffered from drug adverse side effects, suffered from multiple co-morbidities and needed a prolonged stay for treatment and rehabilitation

- Aware of the problem of self medications

- Aware of Adverse drug reactions

- Difficulty of Gout treatment in elderly

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29.The challenges of gout management in elderly; Stamp and Jordon et al Drugs Aging 2011

30.Gout  Tuhina Neogi, M.D., Ph.D. NEJM 2011

31. Gout Pascal Richette, Thomas Bardin Lancet 2010

32. Washington Manual Geriatric Subspecialty Consult 2003

33. Essentials of Clinical Geriatrics 6th edition

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# BACKUP SLIDES

Panel 1: **Some adverse drug reaction terms and their definitions**

**"Unexpected adverse reaction"**

- An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug

**"Serious adverse effect"**

- Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening

- Cancers and congenital anomalies or birth defects should be regarded as serious

- Medical events that would be regarded as serious if they had not responded to acute treatment should also be considered serious

- The term "severe" is often used to describe the intensity (severity) of a medical event, as in the grading "mild", "moderate", and "severe"; thus a severe skin reaction need not be serious

**"Adverse event/adverse experience"**

- Any untoward occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relation to the treatment

**"Signal"**

- Reported information on a possible causal relation between an adverse event and a drug, the relation being previously unknown or incompletely documented

- Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information

[Edwards and Aronson 2000 Lancet]

Panel 2: **Causality assessment of suspected adverse drug reactions**

**Certain**

- A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals
- The response to withdrawal of the drug (dechallenge) should be clinically plausible
- The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary

**Probable/likely**

- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge)
- Rechallenge information is not required to fulfil this definition

**Possible**

- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals
- Information on drug withdrawal may be lacking or unclear

**Unlikely**

- A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations

**Conditional/unclassified**

- A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are being examined

**Unassessable/unclassifiable**

- A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified

[Edwards and Aronson 2000 Lancet]

## Pharmacokinetic changes in the elderly

| Process | Effect on Drug Disposition |
|---|---|
| Absorption | • Possibly reduced intestinal absorption of agents requiring active transport<br>• Reduced first-pass metabolism<br>  ○ Increased absorption of some high-clearance drugs<br>  ○ Decreased absorption of drugs from prodrugs |
| Distribution | • Altered free fraction of some drugs<br>  ○ Increased free fraction of albumin-bound drugs<br>  ★ Decreased free fraction of $\alpha$ 1-glycoprotein-bound drugs<br>• Altered volume of distribution<br>  ○ Increased half-life for lipophilic drugs<br>★ Increased permeability of blood-brain barrier |
| Metabolism | • Delayed metabolism of high clearance drugs |
| Excretion | • Increased half-life for water-soluble drugs |

Leah et al Clin Geriatr Med 28 (2012) 273–286

## DoTS (dosed relatedness, time course and susceptibility) classification of adverse drug reactions[3]

| Classification | Sub-classification | Explanation/further classification |
|---|---|---|
| Dose | Toxic | Reactions occurring at supra-therapeutic doses |
| | Collateral | Reactions occurring at standard doses |
| | Hyper-susceptibility | Reactions at sub-therapeutic doses in susceptible individuals |
| Time course | Time-independent | Occur at any time during therapy |
| | Time-dependent | Occur due to *rapid* administration |
| | | Occur after the *first dose* of a medication, but not always after subsequent doses |
| | | *Early reactions* that resolve (usually due to tolerance) |
| | | *Intermediate reactions* that occur after some time, usually non-allergic hypersensitivity reactions |
| | | *Late reactions* incidence increases with longer duration of drug administration, or withdrawal reactions |
| | | *Delayed reactions* occur much later after administration, even after cessation of the drug (e.g. carcinogenesis) |
| Susceptibility | Genetic | Factors associated with risk of a reaction to a particular drug. May be single or multiple factors. |
| | Age | |
| | Gender | |
| | Physiological variation | |
| | Exogenous factors | |
| | Diseases | |

[Aronson and Ferner e
al 2003
Scott and Thompson e

# Examples of DoTS

- Dose-relatedness
  - toxic effects: nephrotoxicity with high doses of aminoglycosides;
  - collateral effects: Clostridium difficile infection with broad-spectrum antibiotics;
  - hypersusceptibility reactions: anaphylactoid reactions to iodinated contrast media and acetylcysteine.
- Time-course
  - time-dependent:  ‘red man syndrome’, due to rapid administration of vancomycin, or
  - time-independent: drug-drug interactions.
- Rare ADRs due to genetic variation: e,g: drug-induced haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

# AGS BEERS CRITERIA 2012

- The research panel reviewed more  than 2,000 high-quality research studies about medications prescribed for older adults.
- Based on the review of this research, the experts identified: 34 medications and types of medications that are “potentially inappropriate” for older people.
- Suggested to healthcare providers to consider avoiding drugs on this list when prescribing for adults 65 or older.  These medications pose a higher risk of side effects,  may not work as well in an older person, and may be replaced with safer or more effective medications or non-drug remedies.
- •Medications used for 14 common health problems that are potentially inappropriate for older adults. Older adults often have other diseases or disorders in addition to these 14 health problems that the medications may make worse.
- 14 types of drugs that are potentially inappropriate and should be used only with caution in older adults. Drugs on this list may cause medication-related problems and may not be completely effective.
- http://www.americangeriatrics.org/files/documents/beers/BeersCriteriaPublicTranslation.pdf

[British Society for Rheumatology 2007]

## GOUT: MANAGEMENT PATHWAY

**Exclude septic arthritis** & suppress pain and inflammation

← Treat as soon as possible

**NSAID** (including coxibs) ± PPI
or
**Colchicine**
or
**Corticosteroid** (i.a., oral, i.m., i.v.)

→ ***Review at 4–6 weeks***

Assess lifestyle factors, blood pressure
& perform serum urate, renal function
& glucose in all patients

**Further attacks** (or risk factors +++)
Treat acute attack, when resolved add

**Allopurinol*** + prophylactic cover with low dose NSAID ± PPI or colchicine
*(Risk of precipitating acute attacks for approx 12 months)*

*Titrate allopurinol dose dependent on SUA, may require doses up to 900 mg/day

**DO NOT STOP ALLOPURINOL DURING ACUTE ATTACKS**

**Resolution**

→ ***All patients***

- Optimize weight
- Increase exercise
- Modify diet
- Reduce alcohol intake
- Maintain fluid intake
- Treat underlying cardiovascular risk factors

(target serum urate <0.3 mmol/L)

**Continuing acute attacks**

Treat acute attack and when resolved go to

**No renal impairment**
Change to
Sulphinpyrazone
*or*
Benzbromarone
*or*
Probenecid

Consider combination therapy

**Renal impairment**
Change to
Benzbromarone

Consider combination therapy
with low dose allopurinol

# URATE LOWERING THERAPY (ULT)

A. Uricostatic agents that decrease serum urate production

B. Uricosuric agents that increase renal excretion of serum urate

C. Uricolytic agents that metabolize seurm urate

# EULAR 2006

- Recommended drugs for acute attacks were oral non-steroidal anti-inflammatory drugs (NSAIDs), oral colchicine (ES = 0.87 (95% confidence interval, 0.25 to 1.50)), or joint aspiration and injection of corticosteroid.
- Urate lowering therapy (ULT) is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout. Allopurinol was confirmed as effective long term ULT (ES = 1.39 (0.78 to 2.01)). If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, allopurinol desensitisation, or a uricosuric.
- When gout is associated with the use of diuretics, the diuretic should be stopped if possible.
- For prophylaxis against acute attacks, either colchicine 0.5–1 mg daily or an NSAID (with gastroprotection if indicated) are recommended.

# GOUT TREATMENT IN ELDERLY

- ULT aiming for a serum urate <0.36 mmol/L, or lower in severe tophaceous gout, is critical for the long-term management of gout.
- Urate lowering can be achieved by inhibiting the production of uric acid through xanthine oxidase inhibition (allopurinol, febuxostat), increasing uric acid excretion via the kidneys (uricosuric agents: probenecid, benzbromarone) or dissolving uric acid to the more water soluble allantoin (recombinant uricases: pegloticase, rasburicase).
- Allopurinol is the most commonly used ULT, but there is no consensus on dosing in renal impairment.
- Febuxostat is effective at lowering serum urate, but there are limited data in the elderly and patients with renal impairment.
- Probenecid is ineffective in patients with renal impairment (creatinine clearance <60 mL/min)
- Benzbromarone has concerns about its hepatotoxicity, withdrawal from use due to hepatotoxicity
- The recombinant uricases has limited data for their use in the elderly.
- They may precipitate a severe flare of gout and this will require treatment in its own right.

# NEJM 2011

**Table 1. Pharmacologic Management Options for Acute Gout Attacks.**

| Drug | Examples of Regimens from Randomized Clinical Trials | Alternative Regimens for Complete Attack Resolution* | Precautions |
|---|---|---|---|
| Nonsteroidal antiinflammatory drug† | | | Avoid in patients with renal or hepatic insufficiency, bleeding disorder, congestive heart failure, or allergy; associated with an increased risk of adverse thrombotic and gastrointestinal events; may be administered with a proton-pump inhibitor in patients at risk for gastrointestinal events. |
| Naproxen | 500 mg orally twice daily for 5 days | 375–500 mg orally twice daily for 3 days, then 250–375 mg orally twice daily for 4–7 days or until attack resolves | |
| Indomethacin | 50 mg orally three times daily for 2 days, then 25 mg orally three times daily for 3 days | 50 mg orally three times daily for 3 days, then 25 mg orally three times daily for 4–7 days or until attack resolves | |
| Colchicine | 1.2 mg orally at first sign of gout flare, followed by 0.6 mg orally 1 hr later | Consider additional acute gout regimen to continue managing attack 12–24 hr after colchicine regimen (e.g., 0.6 mg of colchicine twice daily, a nonsteroidal antiinflammatory drug regimen, or an oral glucocorticoid regimen until attack resolves) | Avoid (or use lower dose) in older adults and those with renal insufficiency, hepatic dysfunction, or known gastrointestinal symptoms; adjust dose (and avoid in patients with renal or hepatic impairment) if used in conjunction with P-glycoprotein or CYP3A4 inhibitors (e.g., cyclosporine, clarithromycin, certain antiretroviral agents, certain antifungal agents, certain calcium-channel blockers, and grapefruit juice); avoid for gout-flare therapy in patients with renal or hepatic impairment who are already receiving colchicine prophylaxis; monitor for gastrointestinal symptoms, myotoxicity, and blood dyscrasias (details are available at www.fda.gov). |
| Oral glucocorticoids (prednisone or prednisolone)‡ | Prednisolone, 30–35 mg daily for 5 days | Prednisone, 30–60 mg daily for 2 days (depending on severity of attack), then reduce by 5–10 mg every 2 days (depending on starting dose) in 10-day taper | Use caution in patients with hyperglycemia or congestive heart failure; may be used in patients with moderate-to-severe renal impairment. |

# NEJM 2011

**Table 2. Pharmacologic Options for Hyperuricemia Therapy in Gout.***

| Drug | Example of Regimen | Considerations or Precautions |
|---|---|---|
| **Urate-lowering therapy** | | Aim to maintain serum urate levels below 6 mg per deciliter, which requires regular monitoring and may require dose adjustments. Accompany the initiation of therapy with flare prophylaxis. |
| Xanthine oxidase inhibitor | | Use in patients with urate overproduction or underexcretion. Avoid use (or monitor closely) in patients receiving azathioprine or 6-mercaptopurine because these drugs are metabolized by xanthine oxidase. |
| Allopurinol | Starting dose: 50–100 mg orally daily; increase dose every 2–4 wk to achieve serum urate target, with dose based on creatinine clearance; average daily dose, 300 mg, although many patients require higher doses | Use with caution in patients with renal insufficiency (based on creatinine clearance). The maximal dose may be as high as 800 mg daily, but there are limited data for doses above 300 mg daily. A mild rash occurs in approximately 2% of patients, and the risk is potentially increased by coadministration of ampicillin, amoxicillin, thiazide diuretics, or ACE inhibitors. Allopurinol hypersensitivity is rare, occurring in approximately 0.1% of patients, but can be fatal (rate of death, 20%). If the target serum urate level is not achieved, consider dose escalation beyond the level suggested by guidelines in patients with renal impairment (with close monitoring) or consider the use of an alternative therapy (e.g., febuxostat). Allopurinol can increase the anticoagulant effect of warfarin. |
| Febuxostat | Starting dose: 40 mg orally daily; increase to 80 mg orally daily after 2–4 wk to achieve serum urate target, if necessary† | Use as a second-line agent for patients who have contraindications or an inadequate response to allopurinol or uricosuric therapy. Although no dose adjustment is required for patients with mild-to-moderate renal or hepatic insufficiency, there are insufficient data for use in patients with a creatinine clearance of <30 ml per minute or severe hepatic impairment. Currently contraindicated for use with theophylline. Febuxostat has a higher cost than allopurinol. |
| Uricosuric agent (probenecid)‡ | Starting dose: 250 mg orally daily; increase by 500 mg per mo to a maximal dose of 2–3 g per day (2 divided doses) in patients with normal renal function to achieve serum urate target | Avoid in patients with a history of nephrolithiasis and a creatinine clearance of <30 ml per minute. Adequate hydration is required to reduce risk of nephrolithiasis. The use of this drug can increase serum penicillin levels. Evaluate for renal uric acid excretion in patients with a family history of early onset of gout, onset of gout at <25 yr, or a history of nephrolithiasis, since this may identify patients with an overproduction of urate in whom uricosuric therapy should be avoided because of the risk of nephrolithiasis. |

# NEJM 2011

| | | |
|---|---|---|
| Uricase (pegloticase) | Intravenous infusion of 8 mg every 2 wk; requires premedication with antihistamines and glucocorticoids; start gout-flare prophylaxis ≥7 days before initiating treatment | Use for chronic gout in adults whose disease is refractory to conventional therapy (e.g., lack of normalization of serum urate, inadequate control of signs and symptoms with the use of a xanthine oxidase inhibitor at maximum medically appropriate dose, or other contraindication). There is a risk of infusion reactions (26%, vs. 5% in placebo group) even with premedication, particularly in patients without a therapeutic response (in whom serum urate levels increase to above 6 mg per deciliter, particularly on two consecutive occasions) or with antibodies against pegloticase. Anaphylaxis occurs in 5% of patients (vs. 0% in placebo group). No data are available regarding retreatment after stopping treatment for longer than 4 weeks. Do not use in patients with G6PD deficiency, and use caution in patients with congestive heart failure (insufficient safety data; some exacerbations in clinical trials). Cost is higher than for other therapies. |

# PATTERN OF USE OF MEDICATIONS IN US

- In a telephone survey, among 2590 participants aged at least 18 years, 81% used at least 1 medication in the preceding week; 50% took at least 1 prescription drug; and 7% took 5 or more.
- The highest overall prevalence of medication use was among women aged at least 65 years, of whom 12% took at least 10 medications and 23% took at least 5 prescription drugs.
- Herbals/supplements were taken by 14% of the population. Among prescription drug users, 16% also took an herbal/supplement
- Reasons for drug use varied widely, with hypertension and headache mentioned most often (9% for each). Vitamins/minerals were frequently used for nonspecific reasons such as "health" (35%); herbals/supplements were also most commonly used for "health" (16%).)

Kauffman et al JAMA 2

Stoehr J Am Geri Soc

# PATTERN OF USE OF MEDICATIONS IN US

- The most common non-prescription medications consumed by older adults were
  - analgesics (aspirin, acetaminophen, and ibuprofen),
  - cough and cold medications (diphenhydramine and pseudoephedrine),
  - antacids,
  - laxatives,
  - vitamins and minerals (multivitamins,  Vitamins E and C, calcium), and
  - herbal products (ginseng, Ginkgo biloba)

Kauffman et al JAMA 20
Stoehr J Am Geri Soc
1997

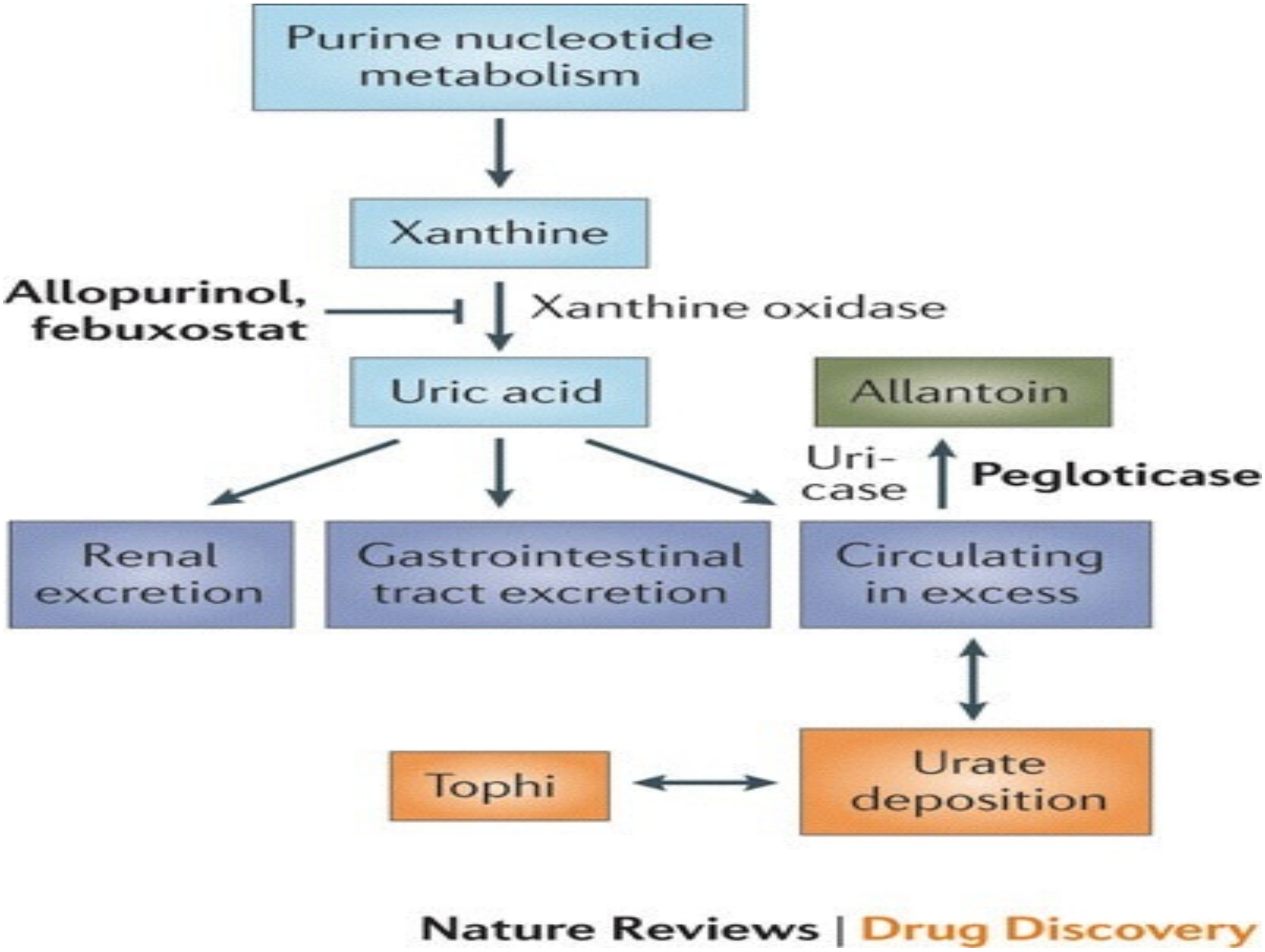
**Drugs that raise serum urate concentrations**

- ★ Diuretics
- Tacrolimus
- Ciclosporin
- Ethambutol
- Pyrazinamide
- Cytotoxic chemotherapy
- ★ Ethanol
- ★ Salicylates (low dose)
- Levodopa
- Ribavirin and interferon
- Teriparatide

[Lancet 2010 GOUT Richard and Bardin]

**Drugs that lower serum urate concentrations**

- ★ Ascorbic acid
- Benzbromarone
- Calcitonin
- Citrate
- Oestrogens
- ★ Fenofibrate
- ★ Losartan
- Probenecid
- Salicylates (high dose)
- Sulfinpyrazone

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## Interference Colors in Gout and Pseudo-Gout Crystals

Monosodium Urate (Gout) Crystals

Pseudo-Gout Pyrophosphate Crystals

Figure 6