Predicting and Preventing Adverse Drug Reactions and Interactions

Malcolm Tingle

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"Those who don't know history are destined to repeat it"

Edmund Burke (1729-1797)

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Definitions

1. Adverse Event (or Adverse Experience)

   Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment

2. Adverse Drug Reaction (ADR)

   In the *pre-approval clinical experience* with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: *all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions*

- Unexpected Adverse Drug Reaction

  An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

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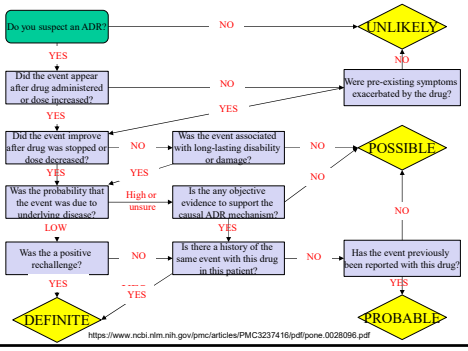
Liverpool Causality Tool for ADR



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3237416/pdf/pone.0028096.pdf

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Severe vs. Serious

- The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).
- This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

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Serious ADR

- *A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:*
  - results in death
  - is life-threatening
  - requires inpatient hospitalisation or results in prolongation of existing hospitalisation
  - * results in persistent or significant disability/incapacity
  - is a congenital anomaly/birth defect
  - * is a medically important event or reaction.

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Common Terminology Criteria for Adverse Events: Severity Grades

1. Mild: symptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2. Moderate: minimal, local or non-invasive intervention indicated;
   - limiting age-dependent daily living such as preparing meals, shopping, telephone, managing money
3. Severe or medically-significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation; disabling
   -limiting bathing, (un)dressing, use of toilet, taking medications
4. Life-threatening consequences: urgent intervention indicated
5. Death

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

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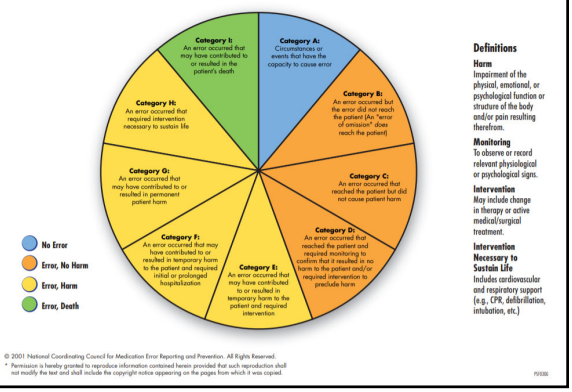
NCC MERP Index for Categorizing Medication Errors



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Reported ADR Frequency

Term	Frequency	
Very common	≥ 1/10	(≥10%)
Common (frequent)	≥ 1/100 ≤ 1/10	
Uncommon (infrequent)	≥ 1/1000 ≤ 1/100	
Rare	≥ 1/10000 ≤ 1/1000	
Very rare	≤ 1/10000	(≤ 0.01%)

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ADR –Dependent Hospital Admissions in the UK

- **Design** Prospective observational study.
- **Setting** Two large general hospitals in Merseyside, England.
- **Participants** 18 820 patients aged > 16 years admitted over six months and assessed for cause of admission.
- **Main outcome measures** Prevalence of admissions due to an ADR, length of stay, avoidability and outcome.

Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004;329:15-9

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ADR –Dependent Hospital Admissions in the UK

- **Results** There were 1225 admissions related to an ADR, giving a prevalence of 6.5%,
  - ADR directly leading to the admission in 80% of cases.
  - The median bed stay was eight days, accounting for 4% of the hospital bed capacity
  - The projected annual cost of such admissions to the NHS is £466m (€706m, $847m).
- The overall fatality was 0.15%.
- Most reactions were either definitely or possibly avoidable.
- Drugs most commonly implicated in causing these admissions included low dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs other than aspirin, the most common reaction being gastrointestinal bleeding.

Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004;329:15-9

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Drug-Related Deaths in Europe

- A systematic review of drug-related deaths in patients requiring hospitalisation or whilst hospitalised suggest an overall rate of 7.3%
- During hospitalisation, acquired DRD represented 2.7% of deaths and occurred in 0.05% of hospitalised patients.
  - Doesn't sound much but = 1 in 2000

Montané, E, Castells, X. Epidemiology of drug-related deaths in European hospitals: A systematic review and meta-analysis of observational studies. *Brit Jnl Clinical Pharma*. 2021; 1– 13. https://doi.org/10.1111/bcp.14799

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EXECUTIVE SUMMARY

MEDICATION-RELATED HOSPITAL ADMISSIONS

EXTENT OF PROBLEM

- 250,000 hospital admissions annually are a result of medication-related problems
- Annual cost $1.4 billion
- 400,000 additional presentations to emergency departments are likely to be due to medication-related problems
- 50% of this harm is preventable

AFTER HOSPITAL DISCHARGE

- 3 in 5 hospital discharge summaries where pharmacists are not involved in their preparation have at least one medication error
- For 1 in 5 people at high risk of readmission, timely provision of the discharge summary did not occur
- Only 1 in 5 changes made to the medication regimen during hospital admission were explained in the discharge summary
- Over 90% of patients have at least one medication-related problem post-discharge from hospital

RESIDENTIAL AGED CARE

- 98% of residents have at least one medication-related problem
- Over half are exposed to at least one potentially inappropriate medicine

COMMUNITY

- 1 in 5 people are suffering an adverse medication reaction at the time they receive a Home Medicines Review
- 1.2 million Australians have experienced an adverse medication event in the last 6 months
- Almost 1 in 4 older people prescribed medicines cleared by the kidneys are prescribed an excessive dose

Pharmaceutical Society of Australia 2019. Medicine Safety: Take Care. Canberra: PSA

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Medication-related patient harm in NZ hospitals: 2013-2015

Table 1: ADE triggers.

ADE triggers (n=5 DHBs)		GTT medication module triggers (n=1 DHB)
1	Vitamin K use	Vitamin K use
2	Antihistamine use	Antihistamine use
3	Flumazenil use	Flumazenil use
4	Naloxone use	Naloxone use
5	Anti-emetic use	Anti-emetic use
6	Over-sedation/hypotension	Over-sedation/hypotension
7	Abrupt medication stop	Abrupt medication stop
8	Raised urea/creatinine (>2 x baseline)	Raised urea/creatinine (>2 x baseline)
9	International normalised ratio (INR) >4	INR >4
10	Activated partial thromboplastin time (APTT) >100 seconds	APTT >100 seconds
11	*C. difficile* positive	*C. difficile* positive
12	Hypoglycaemia: serum glucose <3.0mmol/L	Hypoglycaemia: serum glucose <3.0mmol/L
13	Laxatives	
14	Anti-diarrhoeal	
15	Resonium/calcium/sodium polystyrene sulfonate	
16	White blood count <3 x 10^9/L	
17	Platelet count <50 x 10^9/L	
18	Digoxin level >2nmol/L	
19	Rash	
20	Transferred to a higher level of care/rapid response team/arrest	Code/arrest/rapid response; transfer to higher level of care (cares module GTT)
21	Other	Other

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Medication-related patient harm in NZ hospitals: 2013-2015

Table 2: Harm severity categories.

Category	Description
Categories A-D	No harm
Category E	Temporary harm to the patient and required intervention
Category F	Temporary harm to the patient and required initial or prolonged hospitalisation
Category G	Permanent patient harm
Category H	Intervention required to sustain life
Category I	Patient death

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Medication-related patient harm in NZ hospitals: 2013-2015

Table 4: Where harm occurred.

Code	Definition	Example
Inpatient	Medication-related ADE occurred during this hospital admission.	Patient had anaphylactic reaction to chlorhexidine.
Re-admission	Medication-related ADE present on admission, related to a prior discharge, within 30 days of the index admission.	Patient admitted with constipation after being discharged on morphine.
Non-inpatient	Medication-related ADE that occurred in the community and precipitated an admission.	Patient on metoprolol admitted with a fracture due to a fall resulting from a hypotensive episode.

Table 6: ADEs by harm severity and status.

Harm type	Inpatient	Non-inpatient	Readmission	All
E	484	72	4	560 (61%)
F	98	185	42	325 (35%)
G	6	7	0	13 (1.4%)
H	15	5	2	22 (2.4%)
I	1	0	1	2 (0.2%)
Total	604 (65.5%)	269 (29%)	49 (5.5%)	922

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Medication-related patient harm in NZ hospitals: 2013-2015

Table 8: Medication implicated in patient harm by harm severity.

Medicine classes	E	F	G	H	I	Total	%
Opioids (includes tramadol)	250	33		9		292	31.64%
Anticoagulants/antiplatelet agents	25	52		6	1	84	9.10%
Antibiotics	40	30		1		71	7.69%
Beta-blockers, nitrates, calcium channel blockers and other antianginal agents	33	27		1		61	6.61%
Diuretics	14	23				37	4.01%
Other cardiovascular medicines (ACE inhibitors, ARBs, centrally acting agents, lipid lowering agents	18	15	1	2		36	3.9%
Not recorded/name queried	70	56	4		1	131	14.19%
Other (groups of medicines with less than 30 harms recorded)	112	88	8	3		211	22.9%
Total	562	324	13	22	2	923	100.00%

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What is being reported?

In 2019, the Centre for Adverse Reactions Monitoring (CARM) received a total of 4,247 reports of suspected adverse reactions. These included 2,688 reports associated with medicines, 1,531 reports associated with vaccines and 28 reports associated with complementary or alternative medicines (CAMs). The reporting pattern is similar to previous years (Figure 1).

Figure 1: Adverse reactions to medicines, vaccines and CAMs, reported to the Centre for Adverse Reactions Monitoring, 2015–2019

Of all reports received in 2019, 18.7 percent were considered serious. Serious reports accounted for 27.7 percent of medicine reports, 2.8 percent of vaccine reports and 28.6 percent of CAM reports. A serious adverse reaction is defined as any reaction that results in death or is life-threatening, causes or prolongs hospitalisation, results in persistent or significant disability/incapacity, is a congenital abnormality or is a medically important event.

https://www.medsafe.govt.nz/profs/PUArticles/March2020/Adverse-reaction-reporting-2019.html

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ADR Mechanisms

The mechanisms involved may vary widely, but involves:

- interaction with receptor or enzymes (pharmacological?)
  - **Type I or A:** Predictable, dose-dependent based on the known pharmacology of the drug

LAWSUIT

- alteration of structural proteins, DNA or Lipids (chemical)
  - **Type II or B:** Not predictable, no clear dose-dependency and not due to the known pharmacology of the drug

PUBLICATION

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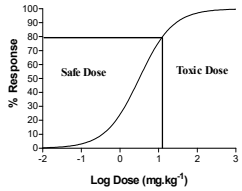
Safe *versus* Toxic Dose

- Reactions are due to the known pharmacology of the drug and are therefore dose-dependent and predictable



- Take too much drug (wrong dose/frequency/duration)
- Take 2 or more drugs with overlapping pharmacology
- Take 2 drugs or more that have metabolic interaction

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nzherald.co.nz

Drug death: Nurse stood down

By Amelia Wade
5:30 AM Friday May 13, 2011

A North Shore Hospital nurse with an "unblemished record" has been stood down after a 60-year-old grandmother died when she was given 10 times too much heart medication.

North Shore Hospital. Photo / Paul Estcourt

Shirley Curtis, who had earlier had a triple bypass operation, was admitted to North Shore Hospital with breathing problems and swollen feet just before Easter.

She was treated for five days and was due to be discharged.

But she received 10 times the prescribed dose of metaprolol, a beta blocker which slows the heart.

"Things were going off and red lights were flashing and they said they can't get a pulse and I just burst into tears," niece Donna Stanton told One News.

"We were told that the doctor had prescribed 12.5ml and the nurse had given her 125ml, which caused severe heart failure and then multiple organ failure."

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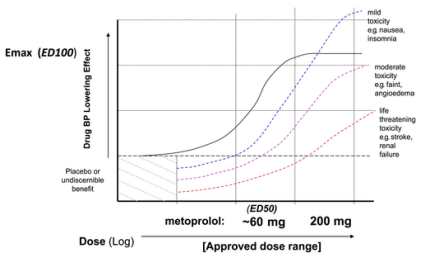
Efficacy and toxicity of antihypertensive pharmacotherapy relative to effective dose 50



British Journal of Clinical Pharmacology, First published: 20 June 2019, DOI: (10.1111/bcp.14033)

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Preventability of Adverse Drug Reactions: Schumock & Thornton

- Was the drug involved in the ADR *not* considered appropriate for the patient's clinical condition?
- Was the dose, route, and frequency of administration *not* appropriate for the patient's age, weight and disease state?
- Was the require therapeutic drug monitoring or other laboratory test *not* performed?
- Was there a history of allergy or previous reactions to the drug?
- Was a drug interaction involved in the reaction?
- Was a toxic serum drug level documented?
- Was poor compliance involved in the reaction?

Schumock, G.T. & Thornton, J.P. Focusing on the Preventability of Adverse Drug Reactions July 1992 Hospital pharmacy 27(6):538

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Preventing ADR

'Safety Pharmacology'

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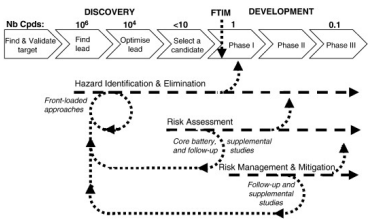

Fig. 1 Objectives of safety pharmacology studies and their alignment to the drug discovery and development process. Abbreviation: Nb cpds, approximate number of compounds evaluated for each discovery/development phase; FTIM, First Time In Man.

Jean-Pierre Valentin , Russell Bialecki , Lorna Ewart , Tim Hammond , Derek Leishmann , Silvana Lindgren , Vicente...

A framework to assess the translation of safety pharmacology data to humans

Journal of Pharmacological and Toxicological Methods, Volume 60, Issue 2, 2009, 152 - 158

http://dx.doi.org/10.1016/j.vascn.2009.05.011

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Limitations of Animal Testing

- There are many limitations to evaluation of drug toxicity in animals including;
  - Limited choice of species for various tests
  - Species switching between tests
  - Interspecies variability in metabolism
  - Interspecies variability in response
  - Lack of subjective ADR
  - Lack of suitable models for many human ADRs (e.g. hypersensitivity reactions)

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The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Efficacy Guidelines

- CLINICAL SAFETY
  - E1 The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions
  - E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
  - E2B(R2) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
  - E2C(R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
  - E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting
  - E2E Pharmacovigilance Planning
  - E2F Development Safety Update Report
- CLINICAL STUDY REPORTS
  - E3 Structure and Content of Clinical Study Reports
- DOSE-RESPONSE STUDIES
  - E4 Dose-Response Information to Support Drug Registration
- ETHNIC FACTORS
  - E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data
- GOOD CLINICAL PRACTICE
  - E6(R1) Good Clinical Practice: Consolidated Guideline

http://www.ich.org

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The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Efficacy Guidelines

- CLINICAL TRIALS
  - E7 Studies in Support of Special Populations: Geriatrics
  - E8 General Considerations for Clinical Trials
  - E9 Statistical Principles for Clinical Trials
  - E10 Choice of Control Group and Related Issues in Clinical Trials
  - E11 Clinical Investigation of Medicinal Products in the Pediatric Population
- PRINCIPLES FOR CLINICAL EVALUATION BY THERAPEUTIC CATEGORY
  - E12 Principles for Clinical Evaluation of New Antihypertensive Drugs
- CLINICAL EVALUATION
  - E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
- PHARMACOGENOMICS
  - E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics,
  - Genomic Data and Sample Coding Categories
  - E16 Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions

http://www.ich.org

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ACS AUCKLAND CLINICAL STUDIES

REGISTER INTEREST

Name	Eligibility
Spartan study	Healthy males and females of non child bearing potential Aged 25-55 years; BMI 18-30kg/m^2; Non-smoker No medications
Oracle study	ASIAN males (specifically Chinese, Japanese, Korean, Vietnamese or Taiwanese) Aged 18 – 55 years; BMI 18 to 30kg/m^2; Non-smoker; No medications
Neon MAD study	Healthy males and females Aged 18-55years; BMI 19-35kg/m^2; Non-smoker; No medications.
Zephyr study	Healthy males and females Aged 18-60 years; BMI 18-32kg/m^2; Non-smoker; No medications; No history of asthma (including childhood asthma)
Popeye study	Healthy males and females of non child bearing potential Aged 18-55 years; BMI 18-30kg/m^2; Non-smoker; No medications

https://www.clinicalstudies.co.nz/participant-info/current-clinical-trials/ Accessed 22 June 2018a

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Clinical Volunteers and TGN 1412 March 13 2006.

- 8 Men took part in a phase I trial for a monoclonal antibody TGN1412
  - immunomodulatory humanized agonistic anti-CD28 monoclonal antibody
  - developed for the treatment of immunological diseases, e.g. multiple sclerosis, rheumatoid arthritis and certain cancers

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Doses Administered and times

All subjects were dosed between 8-9 AM on the 13th Mar 2006 at ~10minute intervals. Six received active agent and two received placebo.

	Subjects ⇒	1	2	3	4	5	6
Body weight (Kg)		84.3	68.9	88.5	82.4	72.1	81.8
Dosing							
TGN1412		8.4 mg	6.8 mg	8.8 mg	8.24 mg	7.2 mg	8.2mg
Dosing time		08:00	08:20	08:30	08:40	08:50	09:00

Symptoms and timing

A number of symptoms were reported by the subjects fairly soon after administration of the investigational agent (drug/ placebo).

- In 5 of 6 subjects, headache was reported between 50-90 minutes.
- All reported lumbar myalgia.
- Rigors were reported between 58-120minutes in 4 subjects.
- Elevated temperatures >38°C were noted between 2.5 to 6.5 hrs

- Hypotension was noted between 3.5 to 4.6 hrs after administration
- Tachycardia noted at 2.5 to 4.6 hrs

http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf

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Transfer to Critical care

All 6 symptomatic subjects were transferred to the Critical Care Unit at Northwick Park hospital between 12 and 16 hours after dosing in view of the continued deterioration in clinical status.
On transfer to critical care unit, the following were the predominant and common features; dyspnoea and tachypnoea in 5 of the 6, respiratory fatigue in 4 of the 6, bilateral radiological pulmonary infiltrates in all, increased blood urea, significant base deficit, and features consistent with disseminated intravascular coagulation [elevated fibrin degradation products (FDP), low fibrinogen and altered prothrombin time]. There was general lymphopenia (values ranging between 0.04 to 0.07 x10^9/L in the ITU) compared to pre-dose (baseline 1.47 to 2.59 x 10^9/L) and this persisted for several days.

Treatment in Critical care

- Ventilation:

All subjects (patients) needed assisted ventilation: 4 of the 6 non-intubated patients received continuous positive pressure ventilation (CPAP) for durations of 4 -82 hours. Intermittent positive pressure ventilation (IPPV) was utilised in two subjects (12 -18 hours post dose). These two subjects needed IPPV.

http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf

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Cytokine table

	PREDOSE	1 HOUR	4 HOURS	DAY 2	DAY 3 00:10	DAY 3 11:50	DAY 4	DAY 5	DAY 6 am
Mean TNFalpha;	<2.8	1943	> 5000	836	107	136	<2.8	<2.8	3.00
Mean IFN g	<7.1	99	> 5000	4730	1366	270	89	43	27
MeanIL-10	<2.8	76	2158	1771	272	69	19	10	8
Mean-IL-6	< 3.0	29	1330	1204	96	475	466	95	43
Mean-IL4	<2.6	9	1205	13	24	3	3	3	3
Mean-IL2	4.70	57	3317	137	14.	9	4	3.	4

The table only shows mean values rounded to the closest Integer. This is only to provide a schematic representation of changes in Cytokine values. The symbols (<) and (>) indicates values below and above the assay limits and hence are not exact values.

All cytokines increased significantly on days 1 and 2. Very large increases (>500-1000 fold) were seen in TNF and Interferon gamma and especially at 4 hours and day 2. Interestingly, TNF rose sharply in all subjects within 1 hour of TGN 1412 administration. A downward trend was seen in all cytokines by day 3 after administration.

Conclusions

The investigation indicated that the adverse incident did not involve errors in the manufacture of TGN1412 or in its formulation, dilution or administration to trial participants. It was therefore concluded that an unpredicted biological action of the drug in humans was the most likely cause of the adverse reactions in the trial participants.

http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf

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The report made 22 recommendations

- "Special consideration should be given to new agents for which the primary pharmacological action, for the proposed therapeutic effect, cannot be demonstrated in an animal model"
- "When it is likely that pre-clinical information, for any reason, may be a poor guide to human responses *in vivo*, the starting doses in first-in-man trials should be calculated to err on the side of caution"
- "New agents in first-in-man trials should be administered sequentially to subjects with an appropriate period of observation between dosing of individual subjects"

http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf

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Why Humans?

- TGN 1412 interacts with 15 amino acids on the receptor
- Differences of up to 4% (9 of 220 amino acids) between rhesus and human CD28 have been found
  - Two variable positions in the rhesus CD28 sequence — amino acid 65 (glutamic acid or glycine) and 104 (asparagine or tyrosine) — are located on the edge of the contact region between human CD28 and TGN1412.
  - they are likely to substantially affect the strength of antibody–antigen interaction
  - Monkeys only had swollen lymph nodes

Villinger F, Bostik P, Mayne A, King CL, Genain CP, Weiss WR, et al. Cloning, sequencing, and homology analysis of nonhuman primate Fas/Fas-ligand and co-stimulatory molecules. Immunogenetics 2001;53:315-28

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Or…

- Mast cells also have CD28
- Activation of mast cells causes release of histamine and 5-HT
  - Mediators in anaphylaxis causing rapid increased vascular permeability, bronchoconstriction and nausea
- Also get release of TNFα and cytokines (e.g. IL-2, IL-4)
  - Responsible for "late-phase" reactions including vascular permeability and leukocyte infiltration
- There are species- inter-individual- and tissue-differences in responsiveness of mast cells that limit extrapolation of animal & in vitro data to the clinic

Tashiro M, Kawakami Y, Abe R, Han W, Hata D, Sugie K, et al. Increased secretion of TNF-alpha by costimulation of mast cells via CD28 and Fc epsilon RI. J Immunol 1997;158:2382-9
Forsythe P, Ennis M. Clinical consequences of mast cell heterogeneity. Inflammation Research 2000;49:147-54

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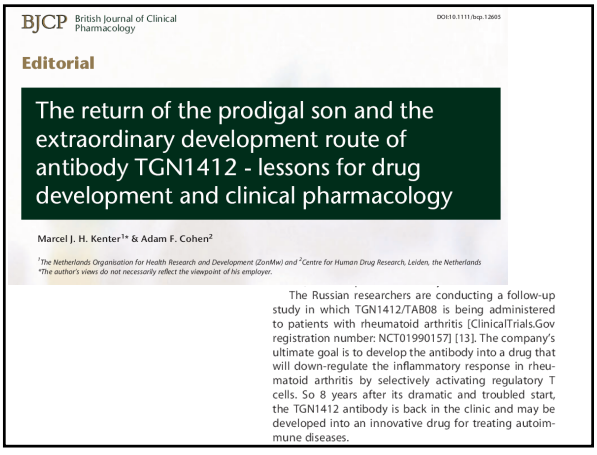

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Systemic release of IL-10, but not pro-inflammatory cytokines, by TAB08 in healthy volunteers

In the ill-fated FIH trial of TGN1412 in 2006, healthy volunteers (HVs) received a bolus injection of 100 μg/kg body weight, which led to a systemic release of pro-inflammatory cytokines, most notably TNF, IFN-γ, and IL-2, but also of IL-10, suggesting that both $CD4^+$EM and Treg cells had been activated [19]. In a new study, much lower doses of TAB08 were therefore applied under close clinical surveillance, starting with 0.1 μg/kg (1000-fold less than applied in the London trial), followed by several intermediate doses and a maximal dose of 7 μg/kg. The

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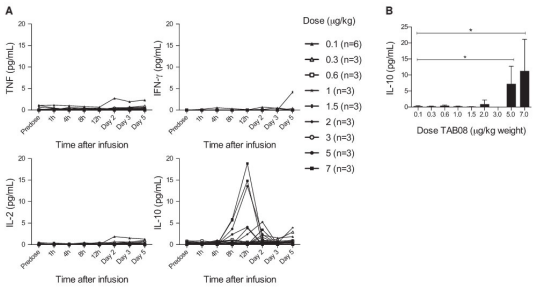

Figure 7. Cytokine response of healthy volunteers to TAB08 infusion. Samples of peripheral blood were taken from healthy volunteers before and at various time points after infusion with TAB08 at the doses indicated (infusion with 0.1 μg/kg: $n = 6$, infusion with 0.3, 0.6, 1, 1.5, 2, 3, 5, and 7 μg/kg: $n = 3$). Infusions were performed over 4, 8, or 12 h as detailed in Materials and methods. Plasma was isolated via centrifugation and kept at −80°C until analysis. (A) Serum levels of TNF, IFN-γ, IL-2, and IL-10 of all participants. Cytokines were measured by Enhanced Sensitivity CBA. (B) Dose-dependent release of IL-10 at 12 h after TAB08 infusion. Data are shown as mean ± SD of the IL-10 serum levels of the participants in each cohort. *$p \leq 0.03$ (unpaired t-test).

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Probability of Detecting an Adverse Event during Clinical Trials

Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

	Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
Very Rare	0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
	0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
	0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
	0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
	0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
Rare	0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
	0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
	0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
	0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
	0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
	0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
	0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
Uncommon	1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
	2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
	3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
	5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
	7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
Common	10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

42

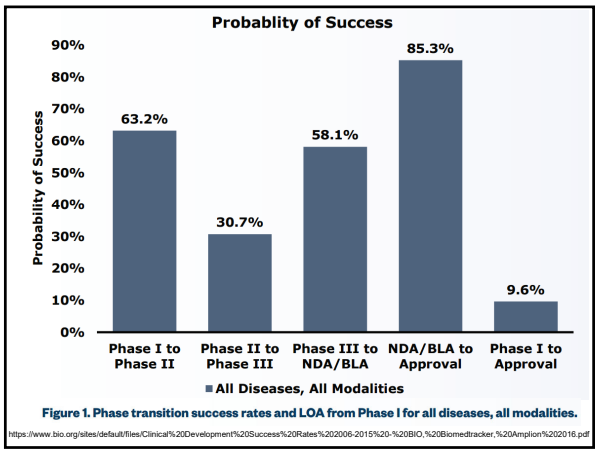

Figure 1. Phase transition success rates and LOA from Phase I for all diseases, all modalities.

https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

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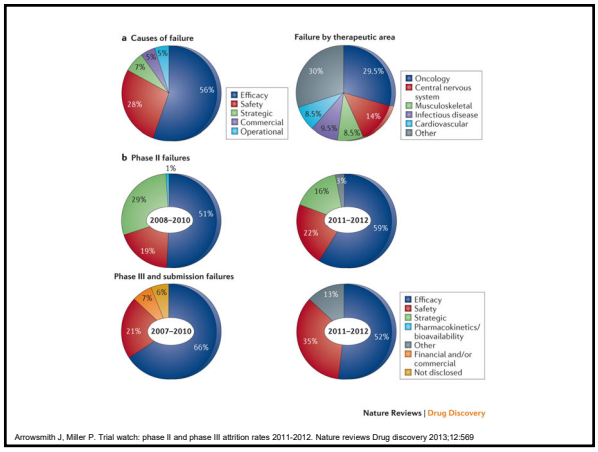

Arrowsmith J, Miller P. Trial watch: phase II and phase III attrition rates 2011-2012. Nature reviews Drug discovery 2013;12:569

44

The need for Pharmacovigilance

- Clinical trials may fail to identify rare adverse reactions
  - Many ADR mimic spontaneously occurring medical conditions, so incidence is not 0 in the control population
  - A low incidence may occur in the clinical trials due to patient selection criteria or duration of trials
- ADR do not occur in the context of the trials
  - Dosage may be increased post-marketing to “increase effectiveness”
  - May be used for long-term indications
  - Interactions may occur with new drugs not previously screened
  - Used for new indications

Amery WK. Why there is a need for pharmacovigilance. Pharmacoepidemiology and Drug Safety 1999;8:61-4

45

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2013
EMA/458028/2013

European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole

Benefit of oral ketoconazole does not outweigh risk of liver injury in fungal infections

The European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) has recommended that the marketing authorisations of oral ketoconazole-containing medicines should be suspended throughout the European Union (EU). The CHMP concluded that the risk of liver injury is greater than the benefits in treating fungal infections.

More about the medicine

Ketoconazole is an antifungal medicine used to treat infections caused by dermatophytes and yeasts. Ketoconazole taken orally (by mouth) has been authorised in the EU since 1980, and later topical (on the skin) formulations, such as creams, ointments and shampoos, have become available.

Oral formulations of ketoconazole have been authorised in the EU via national procedures, and are currently available in several EU Member States under various trade names, including Nizoral and Fungoral.

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/07/WC500146613.pdf

46

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2011.04138.x

Unexpected frequent hepatotoxicity of a prescription drug, flupirtine, marketed for about 30 years

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Keywords
flupirtine, hepatotoxicity, overactive bladder syndrome

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Accepted Article Published Online
2 October 2011

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Flupirtine has been on the market for about 30 years in several European countries as an analgesic. This use has not resulted in regulatory action concerning hepatotoxicity.

WHAT THIS STUDY ADDS

- When used in a novel indication, hepatotoxicity was frequent with flupirtine, questioning the general assumption that the safety profile in one indication can be extrapolated to other indications.

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Inter-individual Variability & 'Type II' ADR

Can We Predict the 'Unpredictable' and Prevent ADR?

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Inter-individual Variability in Drug Metabolism

- Lack of metabolism: enhanced plasma concentrations and exaggerated pharmacological responses.
- Lack of a metabolic pathway in certain individuals: compound is bioactivated by a different enzyme.
- Enhanced toxicity due the lack of a detoxification pathway.
- Lack of a bioactivation pathway: poor metabolisers at less risk
- Increased protein expression or catalytic activity, with subsequent increase in the formation of toxic metabolites.

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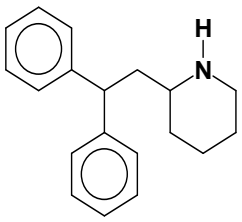
Lack of detoxication resulting in secondary effects: Perhexiline

- Perhexiline is an anti-angina drug that has cationic, amphiphilic properties.
- If it is not metabolised (by CYP2D6), perhexiline accumulates in lysosomes resulting in hepatotoxicity and neuropathy



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Perhexiline

- In UK, a total of 543 reports of ADR, with 20 fatal
- Withdrawn from most of the world but….
- In NZ:

Monitoring of Plasma Levels

Plasma perhexiline concentrations should be maintained between 0.15 and 0.60mcg/ml. Because of perhexiline's slow and variable clearance, the marked inter-subject variability in metabolism of the medicine and the potential for serious toxicity, regular monitoring of plasma levels of perhexiline is essential commencing at the end of the first week of use. Dosage should not be increased unless the plasma concentrations are sub-therapeutic and at least two to four weeks have elapsed since commencement, or last increase in dose, of perhexiline. **If facilities for determining plasma levels are not available, PEXSIG should not be prescribed**.

http://www.medsafe.govt.nz/profs/datasheet/p/pexsigtab.pdf

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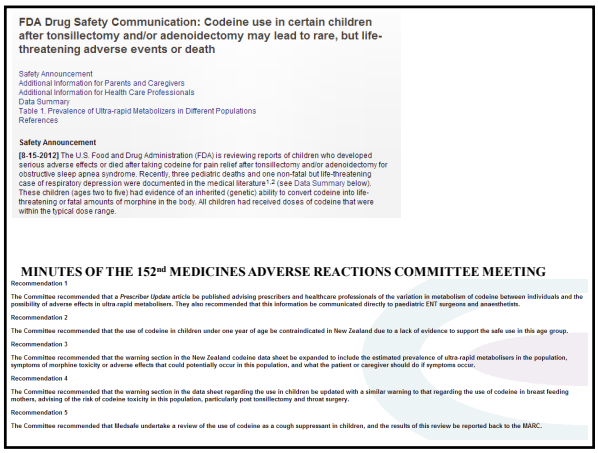

FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death

Safety Announcement
Additional Information for Parents and Caregivers
Additional Information for Health Care Professionals
Data Summary
Table 1. Prevalence of Ultra-rapid Metabolizers in Different Populations
References

Safety Announcement

[8-15-2012] The U.S. Food and Drug Administration (FDA) is reviewing reports of children who developed serious adverse effects or died after taking codeine for pain relief after tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome. Recently, three pediatric deaths and one non-fatal but life-threatening case of respiratory depression were documented in the medical literature[1,2] (see Data Summary below). These children (ages two to five) had evidence of an inherited (genetic) ability to convert codeine into life-threatening or fatal amounts of morphine in the body. All children had received doses of codeine that were within the typical dose range.

MINUTES OF THE 152nd MEDICINES ADVERSE REACTIONS COMMITTEE MEETING

Recommendation 1

The Committee recommended that a *Prescriber Update* article be published advising prescribers and healthcare professionals of the variation in metabolism of codeine between individuals and the possibility of adverse effects in ultra-rapid metabolisers. They also recommended that this information be communicated directly to paediatric ENT surgeons and anaesthetists.

Recommendation 2

The Committee recommended that the use of codeine in children under one year of age be contraindicated in New Zealand due to a lack of evidence to support the safe use in this age group.

Recommendation 3

The Committee recommended that the warning section in the New Zealand codeine data sheet be expanded to include the estimated prevalence of ultra-rapid metabolisers in the population, symptoms of morphine toxicity or adverse effects that could potentially occur in this population, and what the patient or caregiver should do if symptoms occur.

Recommendation 4

The Committee recommended that the warning section in the data sheet regarding the use in children be updated with a similar warning to that regarding the use of codeine in breast feeding mothers, advising of the risk of codeine toxicity in this population, particularly post tonsillectomy and throat surgery.

Recommendation 5

The Committee recommended that Medsafe undertake a review of the use of codeine as a cough suppressant in children, and the results of this review be reported back to the MARC.

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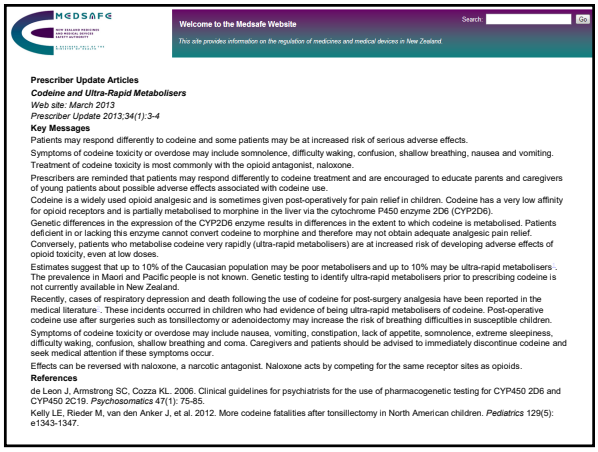

MEDSAFE

Welcome to the Medsafe Website

Search: GO

This site provides information on the regulation of medicines and medical devices in New Zealand.

Prescriber Update Articles

Codeine and Ultra-Rapid Metabolisers

Web site: March 2013

Prescriber Update 2013;34(1):3-4

Key Messages

Patients may respond differently to codeine and some patients may be at increased risk of serious adverse effects.

Symptoms of codeine toxicity or overdose may include somnolence, difficulty waking, confusion, shallow breathing, nausea and vomiting.

Treatment of codeine toxicity is most commonly with the opioid antagonist, naloxone.

Prescribers are reminded that patients may respond differently to codeine treatment and are encouraged to educate parents and caregivers of young patients about possible adverse effects associated with codeine use.

Codeine is a widely used opioid analgesic and is sometimes given post-operatively for pain relief in children. Codeine has a very low affinity for opioid receptors and is partially metabolised to morphine in the liver via the cytochrome P450 enzyme 2D6 (CYP2D6).

Genetic differences in the expression of the CYP2D6 enzyme results in differences in the extent to which codeine is metabolised. Patients deficient in or lacking this enzyme cannot convert codeine to morphine and therefore may not obtain adequate analgesic pain relief. Conversely, patients who metabolise codeine very rapidly (ultra-rapid metabolisers) are at increased risk of developing adverse effects of opioid toxicity, even at low doses.

Estimates suggest that up to 10% of the Caucasian population may be poor metabolisers and up to 10% may be ultra-rapid metabolisers . The prevalence in Maori and Pacific people is not known. Genetic testing to identify ultra-rapid metabolisers prior to prescribing codeine is not currently available in New Zealand.

Recently, cases of respiratory depression and death following the use of codeine for post-surgery analgesia have been reported in the medical literature . These incidents occurred in children who had evidence of being ultra-rapid metabolisers of codeine. Post-operative codeine use after surgeries such as tonsillectomy or adenoidectomy may increase the risk of breathing difficulties in susceptible children.

Symptoms of codeine toxicity or overdose may include nausea, vomiting, constipation, lack of appetite, somnolence, extreme sleepiness, difficulty waking, confusion, shallow breathing and coma. Caregivers and patients should be advised to immediately discontinue codeine and seek medical attention if these symptoms occur.

Effects can be reversed with naloxone, a narcotic antagonist. Naloxone acts by competing for the same receptor sites as opioids.

References

de Leon J, Armstrong SC, Cozza KL. 2006. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics* 47(1): 75-85.

Kelly LE, Rieder M, van den Anker J, et al. 2012. More codeine fatalities after tonsillectomy in North American children. *Pediatrics* 129(5): e1343-1347.

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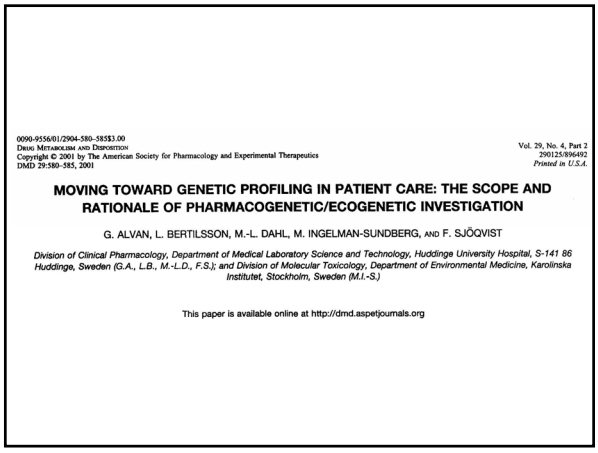

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DRUG METABOLISM AND DISPOSITION
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DMD 29:580–585, 2001

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290125/896492
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MOVING TOWARD GENETIC PROFILING IN PATIENT CARE: THE SCOPE AND RATIONALE OF PHARMACOGENETIC/ECOGENETIC INVESTIGATION

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HLA-B*5701 genotype in DILI due to flucloxacillin

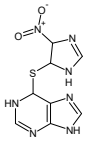
- ~1 in 500 - 1,000 individuals with this genotype will develop DILI when treated with flucloxacillin.
  - No use as a 'predictor'
  - Clinically, HLA-B*5701 genotyping of suspected cases of flucloxacillin DILI may prove to be a useful diagnostic test
  - If a prompt test is available, substituting flucloxacillin with alternative anti-staphylococcal agents such as cloxacillin and dicloxacillin in these suspected cases should be feasible

Daly AK, Donaldson PT, Bhatnagar P, Shen Y, Pe'er I, Floratos A, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nature Genetics 2009;41:816-9

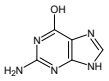
55

Azathioprine & 6-Mercaptopurine

- Azathioprine is used as an immunosuppressant in Crohn's disease and organ transplantation
- Its metabolite, 6-MP, is used for acute lymphoblastic leukaemia & acute myelogenous leukaemia
- 6-MP works by
  - blockade of protein -SH groups by alkylation.
  - inhibition of nucleic acid biosynthesis, hence proliferation and immune responses
  - Direct damage to DNA by incorporation of purine thio analogues


Azathioprine


Adenine


Guanine


6-Mercaptopurine


Hypoxanthine

56

Azathioprine & 6-Mercaptopurine

- Treatment with 6-MP may cause bone marrow suppression, leading to leucopenia, thrombocytopenia and, less frequently, anaemia
  - Pharmacokinetic interaction with xanthine oxidase inhibitors (e.g. allopurinol)
  - Patients deficient in Thiopurine Methyl Transferase (TPMT)

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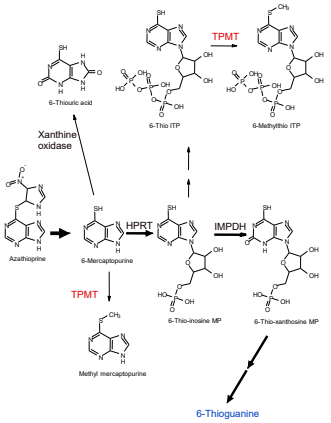

Aberra FN, Lichtenstein GR. Monitoring of immunomodulators in inflammatory bowel disease. Alimentary Pharmacology and Therapeutics 2005;21:307-19

58

TPMT

- **89%** of individuals have high **TPMT** activity, **11%** have intermediate activity and **~1 in 300** patients are at high risk of potentially fatal **haematopoietic toxicity**
  - **TPMT** activity exhibits autosomal co-dominant genetic polymorphism: there are 2 main mutant alleles in humans, **TPMT*2** and **TPMT*3A** (**~75%** of mutations)
  - The mechanism(s) for loss of activity have not been fully elucidated, although the mutant proteins have a shorter $t_{½}$ than the wild type (**TPMT*1**)
- Toxicity is due to accumulation of thioguanine nucleotides in haematopoietic tissues
  - Dose reduction in patients is necessary

McLeod HL, Lin JS, Scott EP, Pui CH, Evans WE. Thiopurine methyltransferase activity in American white subjects and black subjects. Clinical Pharmacology and Therapeutics 1994;55:15-20.
Tai HL, Krynetski EY, Schuetz EG, Yanishevski Y, Evans WE. Enhanced proteolysis of thiopurine S-methyltransferase (TPMT) encoded by mutant alleles in humans (TPMT*3A, TPMT*2): mechanisms for the genetic polymorphism of TPMT activity. Proc Natl Acad Sci 1997;94:6444-9

59

More then TPMT….

- TPMT genotype does not predict adverse drug reactions to thiopurine drugs in patients with inflammatory bowel disease
  - Mutations in *IMPDH1* & *GMPS* appear exclusively in patients with severe thiopurine resistance
  - Leads to less of the active metabolite (6TGN) and more of 6MMP which may be hepatotoxic

Gearry RB, Barclay ML, Burt MJ, Collett JA, Chapman BA, Roberts RL, et al. Thiopurine S-methyltransferase (TPMT) genotype does not predict adverse drug reactions to thiopurine drugs in patients with inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 2003;18:395-400

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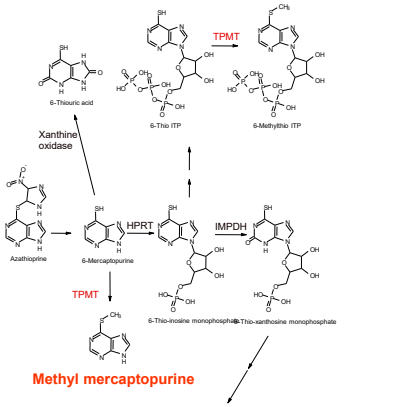

Aberra FN, Lichtenstein GR. Monitoring of immunomodulators in inflammatory bowel disease. Alimentary Pharmacology and Therapeutics 2005;21:307-19

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PHENOTYPE *versus* GENOTYPE

- Possible to determine TPMT enzyme activity
  - now routine in New Zealand: used to predict severe leucopenia in 1:200 cases of deficiency
- 6-TGN & 6-MMP determination in RBC
  - becoming routine in New Zealand
  - 6-TGN range 235 – 450 pmol/8x10^8 RBC
  - 6-MMP <5700 pmol/8x10^8 RBC
- Very poor correlation between AZA dose and 6-TGN concentration (r^2 = 0.002):
  - Need to monitor 6-TGN concentrations instead of relying on dose per kg body weight to individualize therapy.

Gearry RB, Barclay ML, Roberts RL, Harraway J, Zhang M, Pike LS, et al. Thiopurine methyltransferase and 6-thioguanine nucleotide measurement: early experience of use in clinical practice. Internal Medicine Journal 2005;35:580-5

62

Warfarin

- Warfarin is used in the prophylaxis and treatment of venous thrombosis & pulmonary embolism
  - it inhibits the synthesis of vitamin K dependent coagulation factors
  - This results in a sequential depression of Factors II, VII, IX and X activities
- In overdose or poisoning:
  - Appearance of blood in stools or urine, haematuria, excessive menstrual bleeding, excessive bruising or persistent oozing from superficial injuries (early signs)
  - Necrosis and/or gangrene of skin and other tissues, which may require amputation
  - Death: It is also used as a rodenticide!

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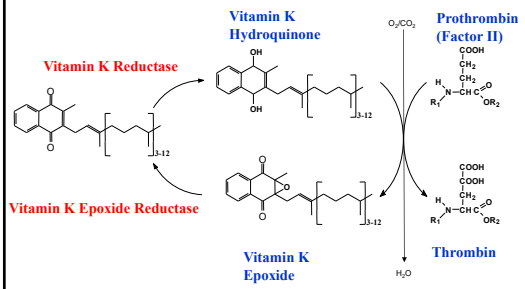
Warfarin Mode of Action

- Warfarin inhibits the vitamin K epoxide reductase multi-protein complex (VKOR)
- The Vitamin K Epoxide Reductase Complex, Subunit 1gene (*VKORC1*) encodes a small transmembrane protein of the endoplasmic reticulum
  - Missense mutations of *VKORC1* lead to warfarin resistance
  - Patients with the mutation require a higher dose

Rost S, Fregin A, Ivaskevicius V, Conzelmann E, Hortnagel K, Pelz H-J, et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature 2004;427:537-41

64

Vitamin K Cycle



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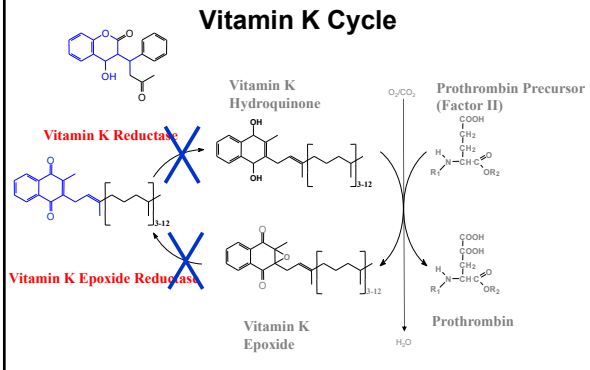
Vitamin K Cycle



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Warfarin Metabolism

- Warfarin is racemic:
  - the *S*-isomer is 3-5 times more potent than the *R*-isomer.
- *S* –Warfarin is metabolised by CYP2C9 to the 7-hydroxy metabolite
  - *R*-warfarin inhibits this metabolic clearance
- Allelic variants CYP2C9*2 and CYP2C9*3 differ from CYP2C9*1 by single amino acid substitutions
  - The allelic variants are associated with impaired hydroxylation of *S*-warfarin
  - There is a strong association between CYP2C9 variant alleles and low warfarin dose requirement.
  - "CYP2C9 genotyping may identify a subgroup of patients who have difficulty at induction of warfarin therapy and are potentially at a higher risk of bleeding complications"

Aithal GP, Day CP, Kesteven PJL, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. The Lancet **1999**; 353: 717-9

67

Warfarin Pharmacogenomics

- In a study, combining the *CYP2C9*2*, *CYP2C9*3*, and *VKORC1* 1173C>T genotype results, as much as **56%** of the inter-individual variability of the warfarin pharmacodynamic response
- Large inter-ethnic variability in allele frequencies

Ethnic Group	*CYP2C9*2*	*CYP2C9*3*	*VKORC1 1173C>T*
Caucasian	0.9 -20%	0- 14.5%	37%
African	0.8-7%	0.4-3%	14%
Asian	0%	0-8.2%	89%

Wadelius M et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics Journal 2005; 5: 262-70

68

On September 17th 2007, the FDA cleared for marketing a genetic test manufactured by Nanosphere Inc.

"The Nanosphere test is not designed to be a stand-alone tool to determine optimum drug dosing, but should be used along with clinical evaluation and other tools, including INR [*International Normalized Ratio*] to determine the best treatment for patients"

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GWAS and genetic determinants of warfarin dose

- GWAS has confirmed role for *CYP2C9* & *VKORC1* but also revealed that *CYP4F2* also helps to predict dose variance
- CYP4F2 is a vitamin K oxidase
  - Mutation in *CYP4F2*
  - => ↓ oxidation of vitamin K1
  - => ↑ hepatic levels of vitamin K1
  - => ↑ warfarin dose to achieve anticoagulation

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"Large clinical trials have been unable to demonstrate any real advantage of using genotype data for predicting doses and achieving target concentrations so I usually try to downplay the genotype side of warfarin clinical pharmacology."

Genotype does not completely predict phenotype

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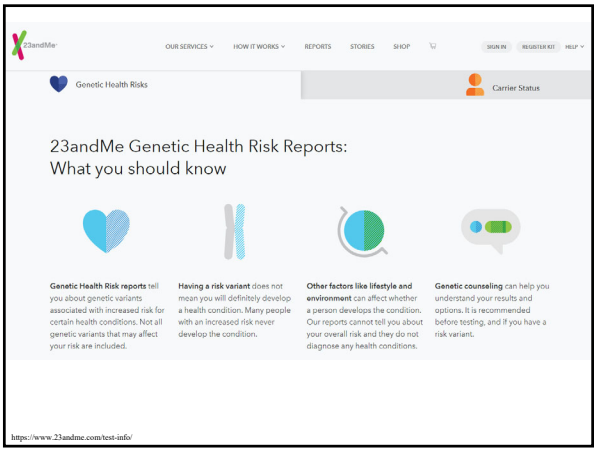

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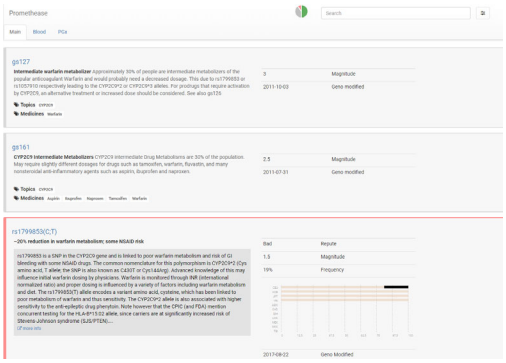

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Table 1 Pharmacokinetics of vitamin K_1 and vitamin K_1 2, 3-epoxide in healthy volunteers at steady state warfarin (1 mg or 0.2 mg daily), after a single dose of vitamin K_1 (10 mg i.v.)

Volunteer		*Vitamin K_1* $t_{\frac{1}{2}\beta}$ *(h)*	*Vitamin K_1 2, 3-epoxide* $C_p max$ *(ng ml^{-1})*	*AUC (ng ml^{-1} h)*	*Plasma warfarin (ng ml^{-1})*
IC	1 mg	2.01	212	1367	269
	0.2 mg	1.37	205	1149	99
PW	1 mg	1.33	207	1215	180
	0.2 mg	1.06	68	277	ND
BH	1 mg	3.14	248	1537	157
	0.2 mg	1.49	70	329	72
MT	1 mg	3.46	176	1050	242
	0.2 mg	1.61	49	153	92
GP	1 mg	1.66	342	1958	215
	0.2 mg	2.32	110	537	70
JB	1 mg	2.23	302	1596	260
	0.2 mg	1.78	31	113	41
JF	1 mg	2.21	409	2221	292
	0.2 mg	2.07	126	534	47
Mean	1 mg	2.29	271	1563	231
	0.2 mg	1.67	94	442	60

Choonara *et al* (1988). "The relationship between inhibition of vitamin K1 2,3-epoxide reductase and reduction of clotting factor activity with warfarin." British Journal of Clinical Pharmacology **25**(1): 1-7.

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Clin Pharmacokinet (2013) 52:59–68
DOI 10.1007/s40262-012-0017-6

ORIGINAL RESEARCH ARTICLE

A Bayesian Dose-Individualization Method for Warfarin

Daniel F. B. Wright · Stephen B. Duffull

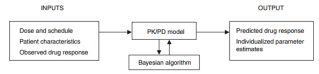

Fig. 1 The components of the TCTWorks Bayesian dose-individualization method. *PK/PD* pharmacokinetic/pharmacodynamic

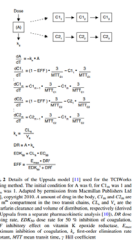

Fig. 2 Details of the Uppsala model [11] used for the TCTWorks dosing method. The initial condition for A was 0, for CL_w was 1 and CL_m was 1. Adapted by permission from Macmillan Publishers Ltd [11], copyright 2010. A amount of drug in the body, CL_w and CL_m are the warfarin and metabolite clearance, V_w and V_m are the warfarin clearance and volume of distribution, respectively (derived by Uppsala from a separate pharmacokinetic analysis [10]). *DR* dose driving rate, EDR_{50} dose rate for 50 % inhibition of coagulation, *EFF* inhibitory effect on vitamin K epoxide reductase, E_{max} maximum inhibition of coagulation, k_e first-order elimination rate constant, *MTT* mean transit time, γ Hill coefficient

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"Guangda Ma and I have reported that NextDose with its theory based model performs better than TCIworks with its empirical model using the same evaluation data set used by the Otago group https://www.page-meeting.org/default.asp?abstract=8562.
Guangda did this work as part of his Masters Dissertation last year.
Guangda's PhD proposal is to undertake a clinical trial with NextDose to see if it can be shown to improve outcome compared to standard of care."

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Warfarin and NextDose

- Theory-based modelling of pharmacokinetics and pharmacodynamics of *S*- and *R*-warfarin on INR included *CYP2C9*, *VKORC1* and *CYP4F2* as well as age, sex body mass and height
  - Fat-free mass was the best predictor of body size influencing CL and V
  - Nick Holford has incorporated this into NextDose (https://www.nextdose.org/), a Bayesian dose forecaster

Xue L, Holford N, Ding X-l, Shen Z-y, Huang C-r, Zhang H, et al. Theory-based pharmacokinetics and pharmacodynamics of S- and R-warfarin and effects on international normalized ratio: influence of body size, composition and genotype in cardiac surgery patients. Br J Clin Pharmacol. 2017;83(4):823-35

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"Anybody beginning a course of warfarin medicine is advised to keep the vitamin K content of their diet constant. If the warfarin dose is established with a constant level of vitamin K intake the INR will not be affected. Problems may arise when vitamin K intakes are varied. If a patient suddenly lowers their vitamin K intake, the INR will increase, and if a patient increases their vitamin K intake the INR will decrease."

http://www.nzfsa.govt.nz/consumers/food-safety-topics/chemicals-in-food/vitamin-k/index.htm

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Warfarin Activity and Diet

- Food sources of vitamin K include:
  - green and/or leafy vegetables, e.g. broccoli, spinach, Brussels sprouts, cabbage & lettuce
  - soybean and canola oil, spirulina, green tea, wheatgerm, alfalfa
  - Beef liver
- Dietary supplements may also contain vitamin K
  - E.g. multivitamins and bone health supplements
  - some milk and health drinks fortified with vitamin K

http://www.nzfsa.govt.nz/consumers/food-safety-topics/chemicals-in-food/vitamin-k/index.htm

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Penicillins

- The most common reactions to oral penicillin are nausea, vomiting, epigastric distress, diarrhoea, and black, hairy tongue.
- Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy, and nephropathy are infrequent reactions and are usually associated with high doses of parenteral penicillin.
- Hypersensitivity reactions include:
  - skin eruptions (ranging from maculopapular to exfoliative dermatitis);
  - urticaria;
  - reactions resembling serum sickness, including chills, fever, edema, arthralgia, and prostration;
  - laryngeal edema
  - anaphylaxis.

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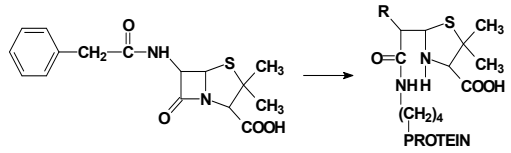

We understand the chemistry, but not inter-individual susceptibility!

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(Hyper)Polypharmacy

- Polypharmacy coined as a term to refer to taking several medicines at the same time
  - Generally refers to 4 or 5+ medicines per day
  - Associated with increased risks of adverse drug reactions, adverse drug events, inappropriate prescribing, inappropriate drug use, falls, hospitalization, institutionalization, mortality, and other important negative outcomes in studies of older adults
- Hyperpolypharmacy coined more recently refers to 10 or more medicines
- Has given rise to the concept of deprescribing
  - Rational withdrawal of medications may be the appropriate clinical decision and may result in significant clinical and functional benefits

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Polypharmacy

Table 1

Percentage of patients on different numbers of regular medications

Percentage of patients on different numbers of regular medications	0	1–3	4–6	7–9	≥10
All patients	53.3	25.2	11.0	5.9	4.6
Gender					
Female	46.6	29.5	12.1	6.6	5.2
Male	60.3	20.8	9.8	5.2	3.9
Age (years)					
20–39	77.1	19.7	2.3	0.6	0.3
40–59	60.0	27.2	7.5	3.1	2.1
60–79	24.9	30.2	22.2	12.7	10.1
≥80	8.4	21.2	29.9	22.0	18.6
Scottish Index of Multiple Deprivation quintile					
1, least deprived	59.1	25.0	9.3	4.0	2.5
2	55.0	25.6	10.5	5.1	3.8
3	51.8	26.2	11.2	6.1	4.7
4	51.0	24.8	11.8	6.9	5.5
5, most deprived	50.5	24.1	11.9	7.3	6.2
Number of clinical conditions					
None	88.8	10.7	0.4	0.05	0.02
1	54.5	37.2	6.8	1.2	0.3
2	30.8	43.1	18.5	5.8	1.9
3	16.5	36.8	27.6	13.4	5.7
4 or 5	6.1	23.1	31.1	22.9	16.8
≥6	1.3	7.7	19.0	27.5	44.5

Payne et al. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol 2014;77:1073-82

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Polypharmacy and hospitalization BJCP

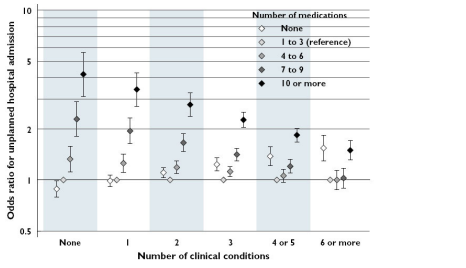

Figure 1

Adjusted odds ratios showing the association between admission and number of regular medications (relative to 1–3 regular medications), for different degrees of multimorbidity. For each number of clinical conditions, the clusters represent different numbers of medications, from none (white), through one to three, four to six, seven to nine, and 10 or more medications (black). Error bars are 95% confidence intervals. The point estimates shown in the figure can be calculated from the adjusted odds ratios reported in Appendix 2

Payne et al. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol 2014;77:1073-82

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Pharmacokinetic Interactions

- Inhibition
  - results in higher than expected plasma concentrations so pharmacology is exaggerated
  - Inhibition of one pathway results in a greater clearance through the bioactivation pathway
  - Inhibition of detoxification pathways or repair mechanisms
- Induction
  - Enhanced bioactivation may increase incidence of ADR
  - Enhanced metabolic clearance: decreased clinical effectiveness

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Pharmacodynamic Interactions

- Adverse drug reactions may be due to a pharmacodynamic interaction between 2 or more drugs, so that the pharmacological effect is too great
- **Ethanol** has many pharmacological effects, including acting act **$GABA_A$** receptors
- Drinking **alcohol** with sedatives, **hypnotics** and some **antihistamines** can result in additive or synergistic effects
- Outcome is too much sedation or **coma** and **death**

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Anna Nicole Smith: A Pharmacology Basket Case

- Chloral hydrate
  - Hypnotic used for short–term treatment of insomnia or sedative before minor surgery
  - Has activity at $GABA_A$
- Diphenylhydramine
  - 1st Generation antihistamine with sedative & anti-tussive effects
  - Central H_1 effects causes drowsiness but also antagonist at muscarinic receptors and it is a serotonin reuptake inhibitor
- Clonazepam/diazepam/nordiazepam/temazepam/oxazepam/ lorazepam
  - Anxiolytics/hypnotics working through $GABA_A$
- Topiramate
  - Anticonvulsant but also has some $GABA_A$ activity

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