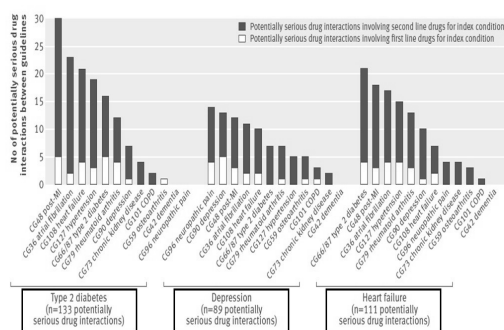


## 진료현장에서 알아야 할 약물부작용과 대처

조 비 룡

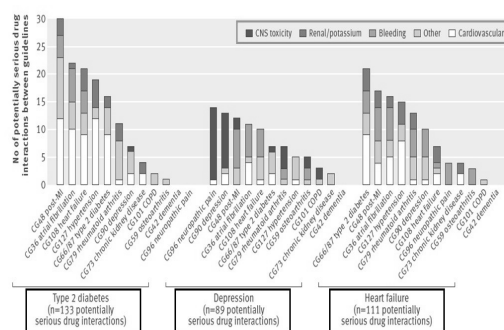
서울의대, 서울대학교병원 가정의학과/건강증진센터

### 주요가이드라인 Drug-Drug Interactions



Dumbreck S, et al. BMJ 2015

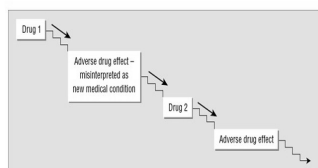
### 주요가이드라인 Drug-Drug Interactions



Dumbreck S, et al. BMJ 2015

### Prescribing cascades

- The "prescribing cascade" begins when an adverse drug reaction is misinterpreted as a new medical condition.
- Another drug is then prescribed, and the patient is placed at risk of developing additional adverse effects relating to this potentially unnecessary treatment.

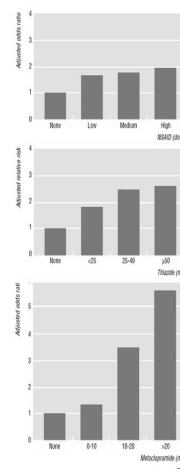


Rochon RA, et al. BMJ 1997

### Prescribing cascades

Examples of prescribing cascade

Initial treatment	Adverse effect	Subsequent treatment
Non-steroidal anti-inflammatory drugs <sup>8</sup>	Rise in blood pressure	Antihypertensive treatment
Thiazide diuretics <sup>9</sup>	Hyperuricaemia	Treatment for gout
Metoclopramide treatment <sup>10</sup>	Parkinsonian symptoms	Treatment with levodopa



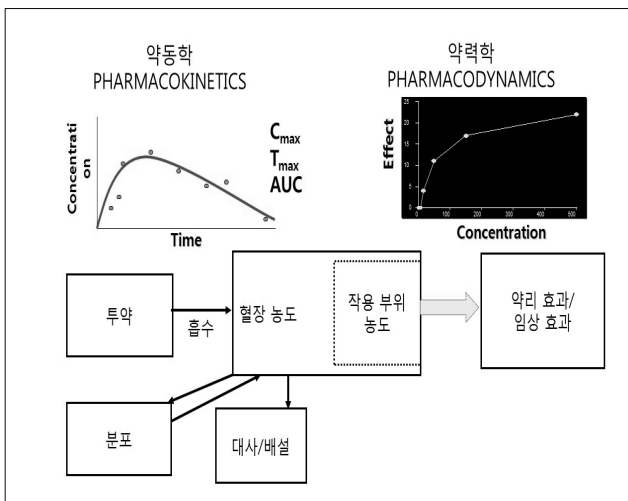
Rochon RA, et al. BMJ 1997

Table 1. Percentage of patients receiving high risk prescription

Prescribing safety indicator	No of patients receiving high risk prescription No of patients particularly vulnerable to ADE	% (95% CI)	Reliability for practice with median denominator size*	% of practices with reliability >0.7	% of practices with reliability >0.8
NSAID prescribed in patient with peptic ulcer disease without gastroprotection	4371/49 574	8.8 (8.6 to 9.1)	0.84	77.5	59.7
NSAID prescribed in patients 75 and over without gastroprotection	4464/6840	50.5 (49.5 to 51.5)	0.64	31.7	7.6
NSAID prescribed in patients aged 65 and over prescribed angiotensin converting enzyme inhibitor or angiotensin receptor blocker and diuretic	3908/44 492	8.8 (8.5 to 9.0)	0.88	90.5	79.4
NSAID prescribed in patients aged 65 and over with estimated glomerular filtration rate <60	2272/27 668	8.2 (7.1 to 9.3)	0.76	61.6	40.3
NSAID prescribed to current warfarin user	550/16 182	3.4 (3.1 to 3.7)	0.86	86.0	72.7
Antiplatelet prescribed to current warfarin user	1554/16 182	9.6 (9.2 to 10.1)	0.76	66.7	36.8
High risk antibiotic prescribed to current warfarin user	1271/16 182	7.9 (6.4 to 9.3)	0.67	42.2	13.3
Oral azole antifungal prescribed to current warfarin user	116/16 182	0.7 (0.6 to 0.8)	0.74	60.3	29.2
NSAID prescribed to patient with heart failure	2181/19 052	11.4 (11.0 to 11.9)	0.73	59.4	33.6
Tricyclic prescribed to patient with heart failure	1246/19 052	6.5 (6.2 to 6.9)	0.74	60.3	35.9
Thiazolidinedione prescribed to patient with heart failure	278/19 052	1.5 (1.3 to 1.6)	0.80	71.1	47.3

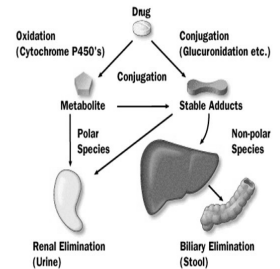
## 강의 내용

- 약물 동태와 유해반응
- 약물 유해반응의 기전과 분류
- 흔한 약물부작용과 대처
  - NSAID, 항생제
  - 고혈압, 당뇨, 고지혈증 약제
  - 기타



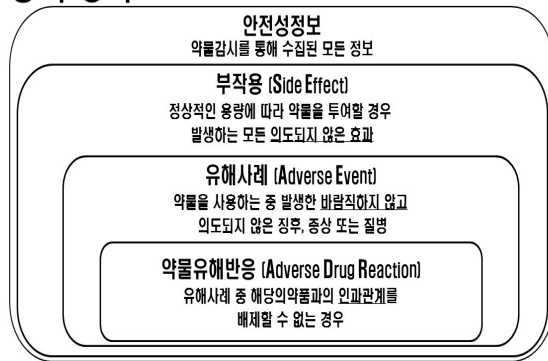
## Drug Metabolism: Goal

- Detoxify
- More water soluble (for excretion in urine) *or*
- More fat soluble (for excretion in the bile, and then into the feces)



Patrick D. Drug Metabolism, University of Texas Pharm 143M Class Notes, Fall 2008

## 용어 정리



## 강의 내용

- 약물 동태와 유해반응
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  - 기타

## 약물유해반응의 분류

Type A (예측가능)	Type B (예측 불가능)
<ul style="list-style-type: none"> <li>70~80%</li> <li>고유약리작용과 관련</li> <li>용량에 비례</li> <li>모든 사람에서 가능</li> </ul>	<ul style="list-style-type: none"> <li>20~30%</li> <li>고유약리작용과 무관</li> <li>용량에 비례하지 않음</li> <li>일부 취약인에서 발생</li> </ul>
<ul style="list-style-type: none"> <li>Overdose: toxicity</li> <li>Side effects</li> <li>Secondary or indirect effects</li> <li>Drug-drug interaction</li> </ul>	<ul style="list-style-type: none"> <li>Intolerance</li> <li>Idiosyncratic reactions</li> <li>Pseudoallergic reactions</li> <li>Allergic (hypersensitivity) reactions</li> </ul>

## 약물유해반응의 인과관계 평가

1. **Timing** of the event, relative to the drug exposure
2. Presence or absence of **other factors** which might also cause the event
3. Result of **withdrawing** the drug (de-challenge)
4. Result of **reintroduction** the drug (re-challenge)
5. **Other data** supporting an association, e.g. previous cases.

Nelson Irey (1976), Karch and Lasagna (1977)

## UMC causality categories

Causality term	Assessment criteria
Certain	<ul style="list-style-type: none"> <li>Event or laboratory test abnormality, with plausible time relationship to drug intake</li> <li>Cannot be explained by <u>disease or other drugs</u></li> <li>Response to withdrawal plausible (pharmacologically, pathologically)</li> <li>Event definitive pharmacologically or phenomenologically</li> <li>Rechallenge satisfactory, if necessary</li> </ul>
Probable/likely	<ul style="list-style-type: none"> <li>Event or laboratory test abnormality, with reasonable time relationship to drug intake</li> <li>Unlikely to be attributed to <u>disease or other drugs</u></li> <li>Response to withdrawal clinically reasonable</li> <li>Rechallenge not required</li> </ul>
Possible	<ul style="list-style-type: none"> <li>Event or laboratory test abnormality, with reasonable time relationship to drug intake</li> <li>Could also be explained by <u>disease or other drugs</u></li> <li>Information on drug withdrawal may be lacking or unclear</li> </ul>
Unlikely	<ul style="list-style-type: none"> <li>Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)</li> <li>Disease or other drugs provide plausible explanations</li> </ul>

## 강의 내용

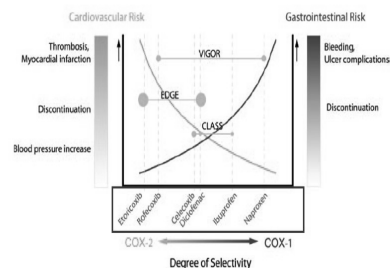
- 약물 동태와 유해반응
- 약물 유해반응의 기전과 분류
- 흔한 약물부작용과 대처
  - NSAID, 항생제
  - 고혈압, 당뇨, 고지혈증 약제
  - 기타

## 1) NSAIDs 라벨의 경고 문구 강화 내용

- The risk of heart attack or stroke can occur **as early as the first weeks**
- The risk appears **greater at higher doses**
- Information is not sufficient to determine that the risk of **any particular NSAID** is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients **with or without heart disease or risk factors** for heart disease.
- In general, **patients with heart disease or risk factors** for it have a greater likelihood of heart attack or stroke following NSAID use.
- Patients **treated with NSAIDs following a first heart attack** were more likely to die after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased **risk of heart failure** with NSAID use

2015 FDA Safety Announcement

## Selectivity에 따른 심혈관계/위장관계 부작용



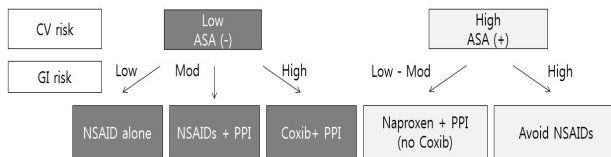
- Selectivity for COX-2 : 심혈관계 위험 증가
- Selectivity for COX-1 : 위장관계 위험 증가

2007 AHA Scientific Statement

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

	Gastrointestinal risk <sup>a</sup>		
	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 <sup>b</sup> (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

<sup>a</sup>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). <sup>b</sup>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.

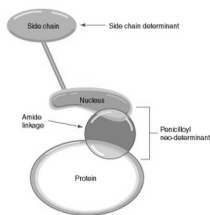


## NSAIDs 부작용 - 기타

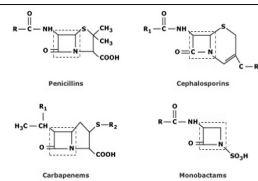
- Hepatotoxicity
- Anaphylaxis
- Pulmonary – AERD, Bronchospasm
- Hematologic – anemia, neutropenia
- CNS – psychosis, aseptic meningitis, tinnitus
- Skin reaction – TEN, SJS
- Non union – bone, tendon

## 2) $\beta$ lactam Allergy

- $\beta$ -lactam antibiotics
  - $\beta$ -lactam nucleus act as hapten
  - 26% of fatal drug induced anaphylaxis
  - 11% of all fatal anaphylaxis



1. Penicilloyl Neodeterminant
  - Strongly Cross-reactive
  - penicillin 계열
2. Side-Chain Determinant
  - Specific to each drug
  - cephalosporin 계열



## 3) 고혈압 약제의 대표적 부작용

약물	부작용
티아지드계 이뇨제	통풍, 고요산혈증, 저칼륨혈증, 저나트륨혈증, 고칼슘혈증, 이상지질혈증, 내당능장애, 발기장애
베타 차단제	천식, 방실차단, 서맥, 이상지질혈증, 내당능장애, 발기장애
칼슘 통로 차단제	말초부종, 두통, 안면홍조, 잇몸비대
안지오텐신환효소억제제	고칼륨혈증, 양측 신동맥 협착증에서 투약 시 급성 신부전증, 이상미각, 백혈구 감소증, 혈관부종, 발진
안지오텐신수용체차단제	고칼륨혈증, 양측 신동맥 협착증에서 투약 시 급성 신부전증, 이상미각, 백혈구 감소증, 혈관부종, 발진
알도스테론 차단제	급성 신부전증, 고칼륨혈증, 여성형 유방(남성의 경우)

## 4) HMG-CoA inhibitors (Statins)

### Elevation of liver transaminases (AST, ALT)

- 상승 폭 : **up to three times normal**  
( underlying liver disease가 있거나 alcoholism이면 더 상승할 수 있다.)
- 모니터링:  
약물 투여 전, 2-3개월 후, 이후 매년 AST/ALT 측정
- 대처
  - 무증상 & 정상인 3배 이내로 상승 → 유지해도 된다.
  - 무증상이더라도 정상인 3배 이상의 상승이 지속되면 → 중단

## 5) Clinically Significant Drug Interactions

### Warfarin + Antibiotics

Inhibition of the hepatic metabolism of warfarin

Drugs that inhibit warfarin's metabolism include **ciprofloxacin, clarithromycin, erythromycin, metronidazole and trimethoprim-sulfamethoxazole**.

Unless the prothrombin INR can be monitored every other day, **ciprofloxacin, macrolide antibiotics, metronidazole and trimethoprim-sulfamethoxazole** generally should not be prescribed to patients who are taking warfarin.

Alternative antimicrobial therapy is recommended for these patients.

## Clinically Significant Drug Interactions

### Tamoxifen + SSRI

Concomitant use with select SSRIs may result in **decreased tamoxifen efficacy**.

Strong CYP2D6 inhibitors(eg, **fluoxetine, paroxetine**) and moderate CYP2D6 inhibitors(eg, **sertraline**) are reported to interfere with transformation to the active metabolite endoxifen.

When possible, select alternative medications with minimal or no impact on endoxifen levels. Weak CYP2D6 inhibitors(eg, **venlafaxine, citalopram**) have minimal effect on the conversion to endoxifen. **Escitalopram** is also a weak CYP2D6 inhibitor.

In a retrospective analysis of breast cancer patients taking tamoxifen and SSRIs, concomitant use of **paroxetine and tamoxifen** was associated with an **increased risk of death due to breast cancer**.

NCCN Breast Cancer Risk Reduction Guidelines v.1.2013 Kelly CM, Juurlink DN, Gomes T, et al. BMJ 2010

## Clinically Significant Drug Interactions

### Oral contraceptives + Antibiotics

**Rifampin** can increase the activity of hepatic enzymes involved in the metabolism of exogenous estrogens. Concomitant use of rifampin and oral contraceptive pills can lead to breakthrough bleeding and an **increased risk of pregnancy**.

The interaction between oral contraceptives and other antibiotics is controversial.

Although insufficient evidence is available to make a firm conclusion, it appears possible that oral contraception may fail while patients are taking an antibiotic. Thus, patients should be encouraged to consider using an alternative method of contraception for the duration of the cycle.

Ament PW, et al. Am Fam Physician 2000

## 6) T cell 매개 피부 증상 (Drug eruption)

### 발진, 發疹 (Exanthem)

- 가장 흔함 ~80%
- 대개 약물 투여 1주일 이내
- measles-like (morbilliform) or erythematous maculopapules
- 체간이나 압력, 손상 받은 부위에서 시작하여 전신에 발생
- 대칭적, 여러 개가 합쳐질 수 있다.
- 가렵다.
- 대부분 기전을 모름
- Mononucleosis, **allopurinol** 복용 중인 사람에서 **ampicillin** 투여시 50-80%, HIV 감염에서 bacrim 사용시

## 7) 요오드화 조영제에 의한 즉시형 과민반응

- 비반세포에서 염증물질 유리

### 임상양상

- 경증 피부반응 ~ 아나필락시스
- 투여 후 5-15분 경에 발생하여, 30-60분 경 소실
- 비 IgE 매개반응: 첫번째 노출에도 발생
- IgE 매개반응: 조영제 간 교차반응 낮음 (조영제 선택이 중요)

### 빈도

	가려움증, 두드러기	아나필락시스
이온성	6%	0.071%
비이온성	0.9%	0.035%

### 위험인자

- 조영제 과민 병력, 천식, 아토피 소인
- β-차단제나 ACE 억제제 사용, 심혈관계 질환

## 8) Potentially Inappropriate Medication Use in Older Adults

American Geriatrics Society 2015 Updated **Beers Criteria** for Potentially Inappropriate Medication Use in Older Adults

By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel

## 약물 상호반응 및 부작용 검색

### 심사평가원 DUR

- <https://www.hira.or.kr/rg/dur/form.do?pgmid=HIRAA030033000000>

### 약품정보검색

- Kims online
- Drug Info

### FDA

### Pubmed

### Medscape

- Drug interaction checker