FARMAKOGENETIKK

- legemidler og etniske (geografiske) variasjoner

[Forelesning 16.11.2018]

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Diakonhjemmet

Somaliere kan trenge firedoblet dose av antipsykotika

Én av tre somaliere trenger minst dobbel dose av de fleste typer antipsykotika for å oppnå virkning. Genetiske forskjeller betyr mye for hvor store doser antipsykotika og antidepressiva pasienter trenger.

Publisert: 2006-12-07 00:00 Skrevet av: Redaktionen

Tailored treatment
Individualized therapy
Personalized medicine

For Immediate Release

January 30, 2015

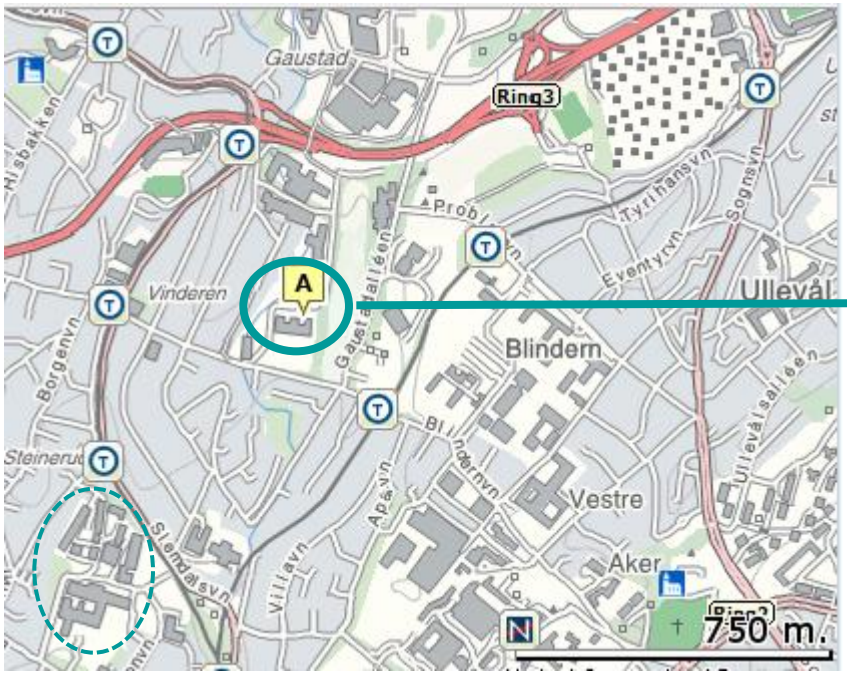
FACT SHEET: President Obama's Precision Medicine Initiative

'…Most medical treatments have been designed for the "average patient." As a result of this "one-size-fits-all-approach", treatments can be very successful for some patients but not for others. This is changing with the emergence of precision medicine, an innovative approach to disease prevention and treatment that takes into account individual differences in *people's genes*, environments, and lifestyles. Precision medicine gives clinicians tools to better understand the complex mechanisms underlying a patient's health, disease, or condition, and to better *predict which treatments will be most effective*.

better understand the complex mechanisms underlying a patient's health, disease, or condition, and to better predict which treatments will be most effective.

Riktig diagnose ↔ *Riktig legemiddelbehandling* ↔ *Riktig dosering*

Senter for Psykofarmakologi, Diakonhjemmet



[Anno 1926]

[Anno 2012]

- ***Lab** (serumkons./genetikk)*
  - **~50 000 pasientprøver/år**
- ***FoU***
- ***Poliklinikk***
- ***Undervisning***
- ***Rådgivning/tolkning***

www.psykofarmakologi.no

Senter for Psykofarmakologi

Legemidler og farmakogenetikk

Rekvirent	Pasient
ID:	Fødselsnr. (11 siffer): ☐ Kvinne ☐ Mann
Rekvirent navn:	
Postadr.:	
Postnr./-sted:	
Ekstra svarbrev ønskes sendt til:	

Kliniske opplysninger. Spesifiser

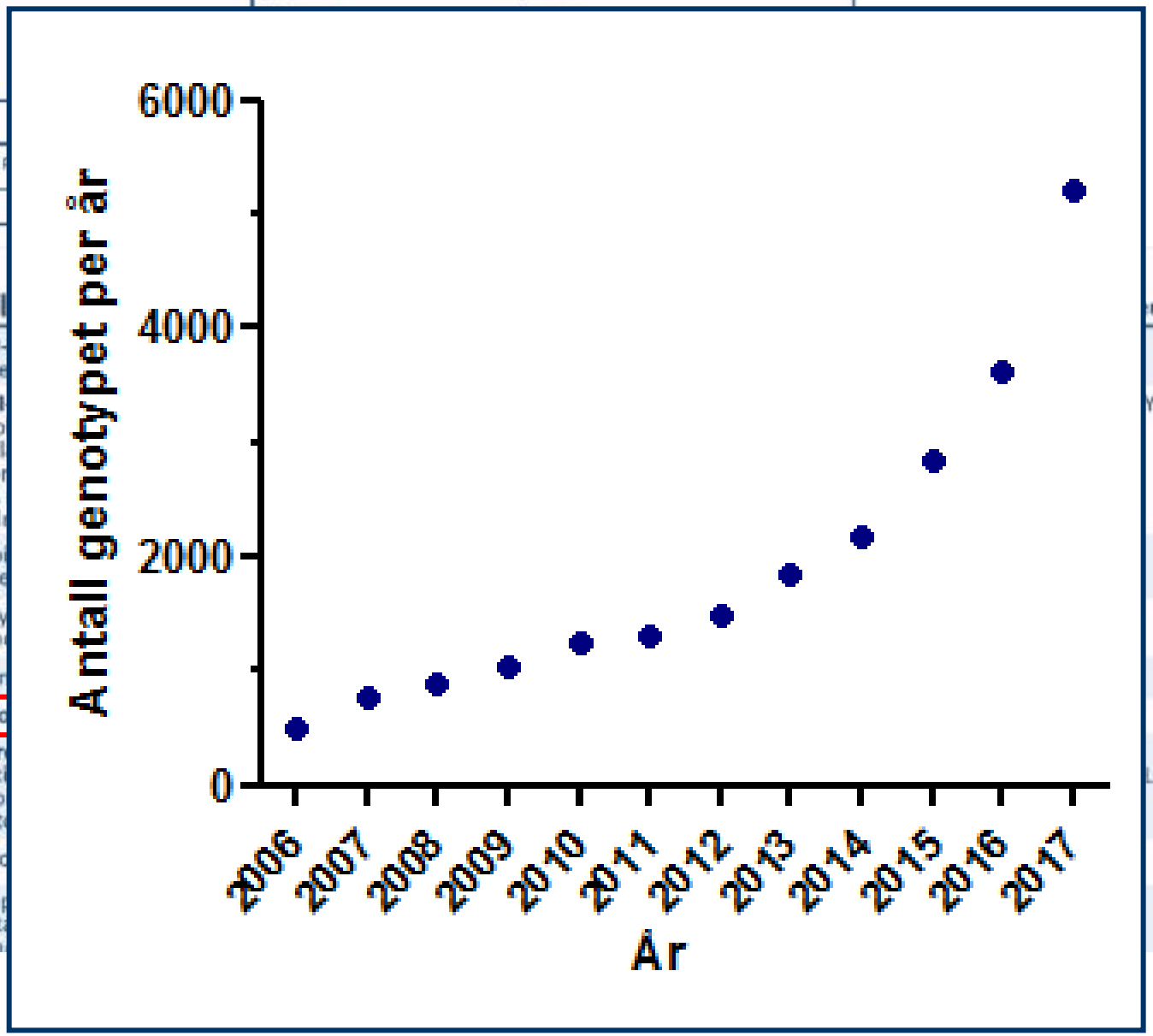
FARMAKOGENETI

CYP-analyse	☐ CYP- ☐ Enk
Depresjon	☐ SSRI- paro ☐ Venl ☐ Bupr ☐ TCA ☐ And
Psykose	☐ Arip risp
Epilepsi	☐ Feny ☐ Lam
ADHD	☐ Ator
Smerte	☐ Opio
Hjerte/kar	☐ Mar ☐ Stati ☐ Klop ☐ Met
Diabetes	☐ Sulfo
Andre	☐ Allop ☐ Met ☐ Tam

res

YP2C19

LCO1B1



Årsaker til farmakologisk variasjon

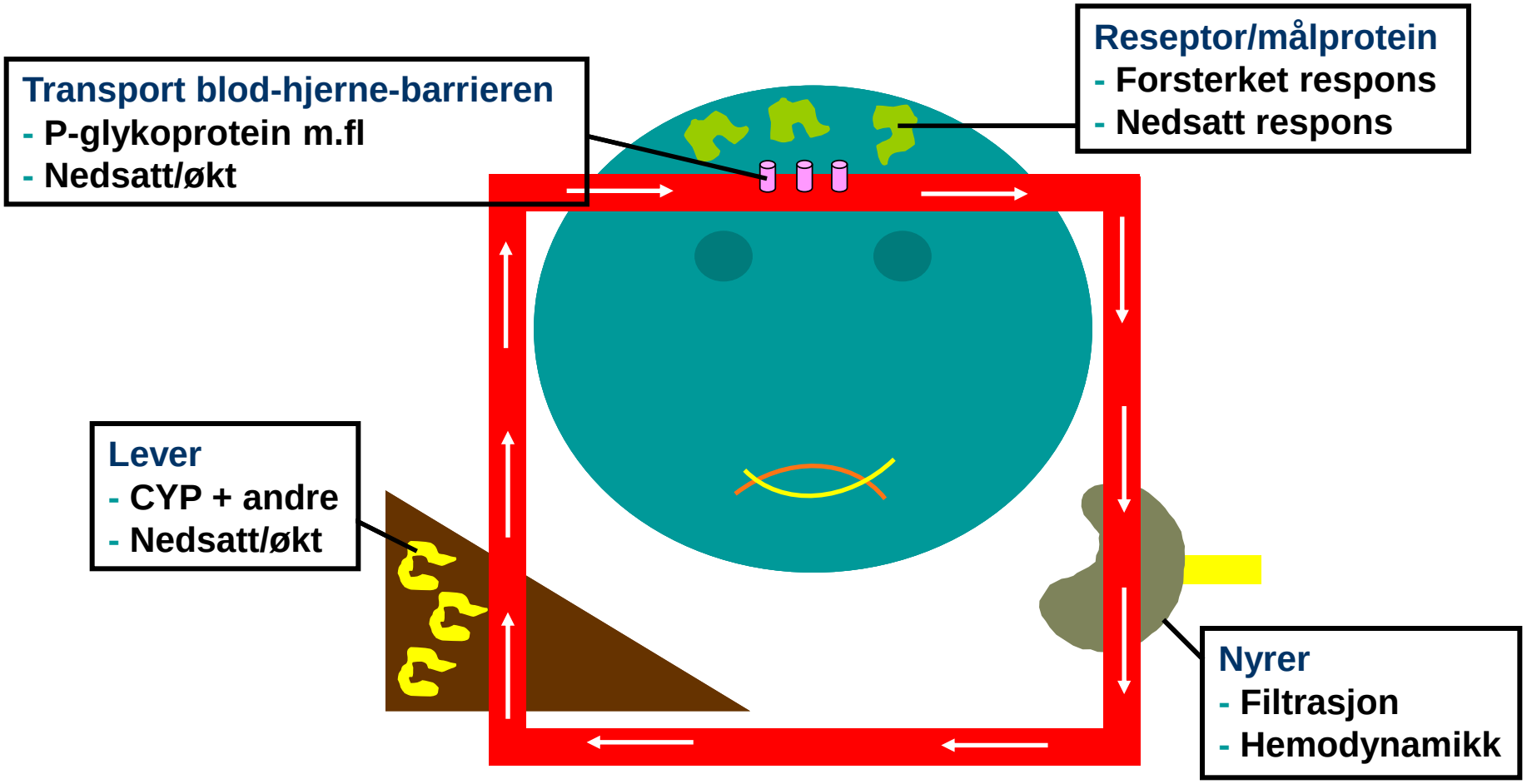
- **Kostholds(u)vaner, livsstil (røyking m.m.)**
- **Alder, kjønn**
- **Organfunksjon (nyrefunksjon/GFR m.m.)**
- **Inflammasjon, akutt sykdom**
- **Interaksjoner *(legemidler/naturmidler – 'drug/drug interactions')***
- **Farmakogenetikk/arv *(medfødt variasjon – 'gene/drug interactions')***

etnisitet

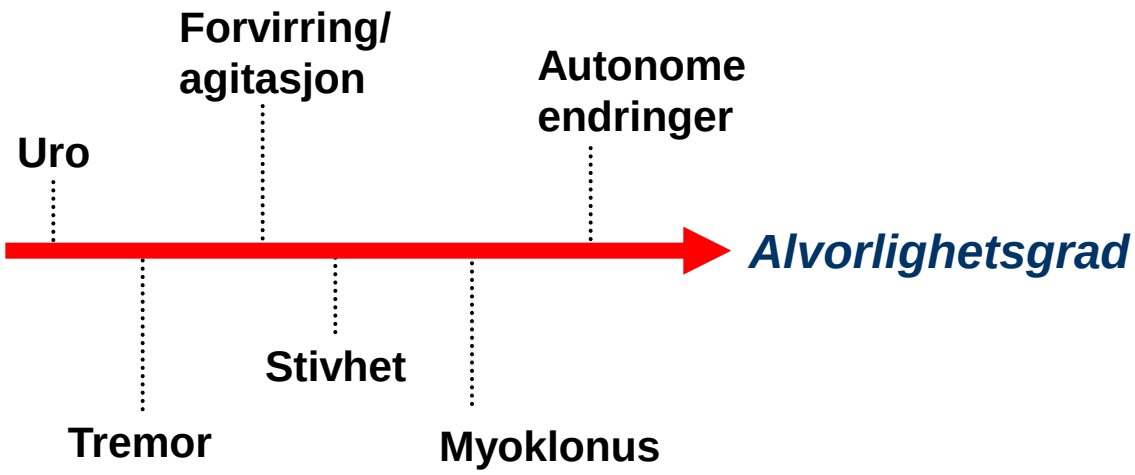
'Blitt sånn, eller født sånn' – *summen avgjør*

Farmakologiske interaksjoner – *ulike mekanismer/typer*

- Legemiddel/legemiddel-interaksjoner
- Gen/legemiddel-interaksjoner



Symptomer serotonerg overstimulering i CNS



Ikke-antidepressiva med serotonerge egenskaper
Buprenorfin (Temgesic)
Fentanyl (Durogesic)
Metoklopramid (Afipran)
Moklobemid (Aurorix)
Oksykodon (OxyContin)
Ondansetron (Zofran)
Triptaner
Tramadol (Nobligan)
Valproat (Orfiril)

- **Serotonergt syndrom sjelden i SRI monoterapi, nesten alltid ved kombinasjonsbehandling**
- **NB! Spesielt oppmerksom SRI + tramadol**

Deaths involving serotonergic drugs

J.L. Pilgrim, D. Gerostamoulos, Olaf H. Drummer *

Victorian Institute of Forensic Medicine, Department of Forensic Medicine, Monash University, 57-83 Kavanagh Street, Southbank 3006, Victoria, Australia

ARTICLE INFO

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Keywords:
Fatalities
Tramadol
Venlafaxine
SSRI
MDMA
Serotonin toxicity

ABSTRACT

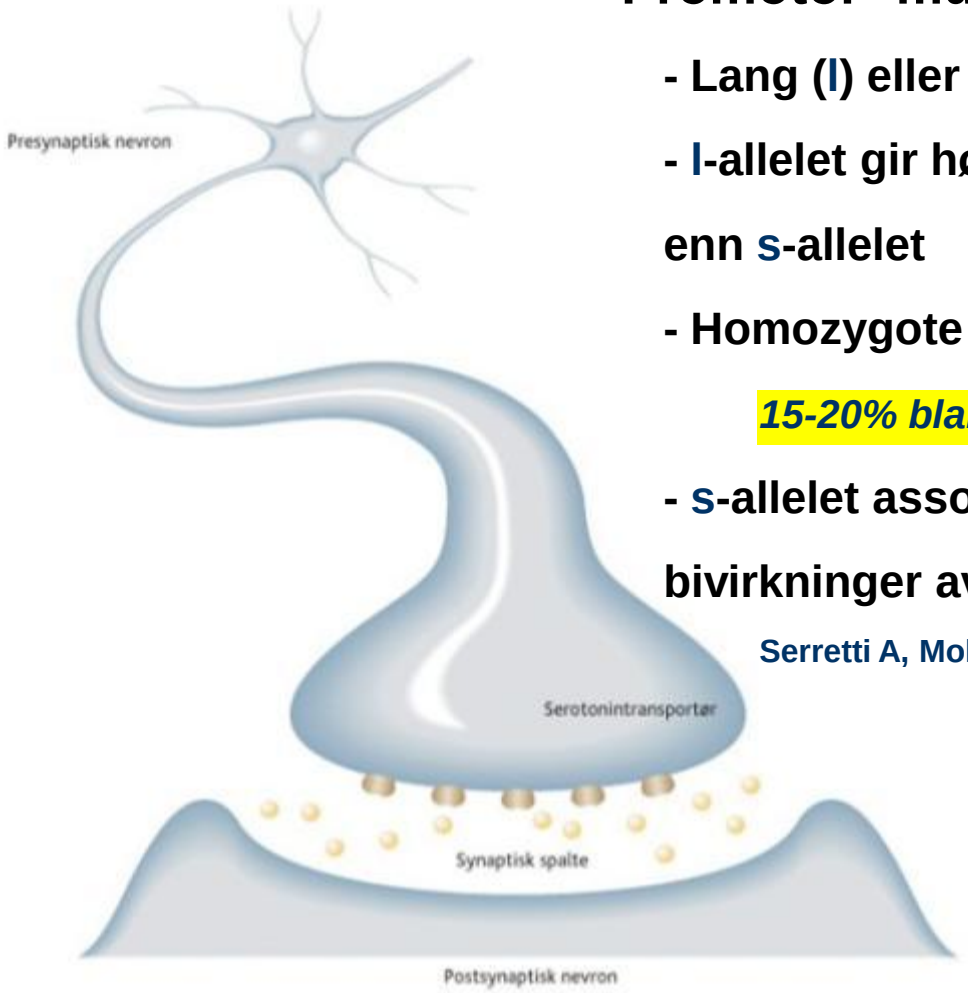
Serotonin-active drugs are detected relatively frequently in Victorian deaths. During 2002–2008, there were 1123 fatalities where one or more of the serotonin-active drugs tramadol, venlafaxine, fluoxetine, sertraline, citalopram, paroxetine and MDMA, were detected. These deaths were reviewed using pathology, toxicology and police reports, to determine the contribution of these drugs to the cause of death, particularly if serotonin toxicity was the mechanism of death. There were 28 cases of most interest to this research because of the presence of the target drugs and the circumstances suggesting the likelihood of serotonin toxicity involvement in death. There were 5 cases of reported serotonin toxicity and 23 other deaths suspected to have involved this form of toxicity. Tramadol featured most commonly out of the seven target drugs and was frequently detected in combination with serotonergic antidepressants. MDMA was also detected relatively commonly and was associated with moclobemide in 4 cases of confirmed serotonin toxicity. There were an additional 1095 cases where natural disease, external injury or the misuse of other drugs caused death, of which 2 reported the incidental contribution of serotonin toxicity.

...Tramadol featured most commonly out of the seven target drugs and was frequently detected in combination with serotonergic antidepressants...

Tramadol kombinert serotonin-reopptakshemmer og opioid

Solhaug V, Molden E. Scand J Pain. 2017 Oct 17;17:193-200.

Genetisk variasjon serotonin-reopptaktransportør (SLC6A4)



- **'Promotor'-mutasjon i serotonintransportørgenet**
  - **Lang (l) eller kort (s) promotorvariant**
  - **l-allelet gir høyere uttrykk/aktivitet av transportør enn s-allelet**
  - **Homozygote bærere av s-allelet:**

    15-20% blant kaukasere, 40-50% blant øst-asiatere

  - **s-allelet assosiert med nedsatt effekt og mer bivirkninger av SSRI**

Serretti A, Mol Psychi 2007;12:247-57; Kato M, Mol Psychi 2008:1-28

Ann Pharmacother. 2012 Dec;46(12):1712-6. doi: 10.1345/aph.1Q748. Epub 2012 Dec 4.

Avoiding serotonin syndrome: the nature of the interaction between tramadol and selective serotonin reuptake inhibitors.

Nelson EM[1], Philbrick AM.

Author information

Abstract

OBJECTIVE: To investigate the nature of the interaction between selective serotonin reuptake inhibitors (SSRIs) and tramadol to mitigate or avoid serotonin syndrome.

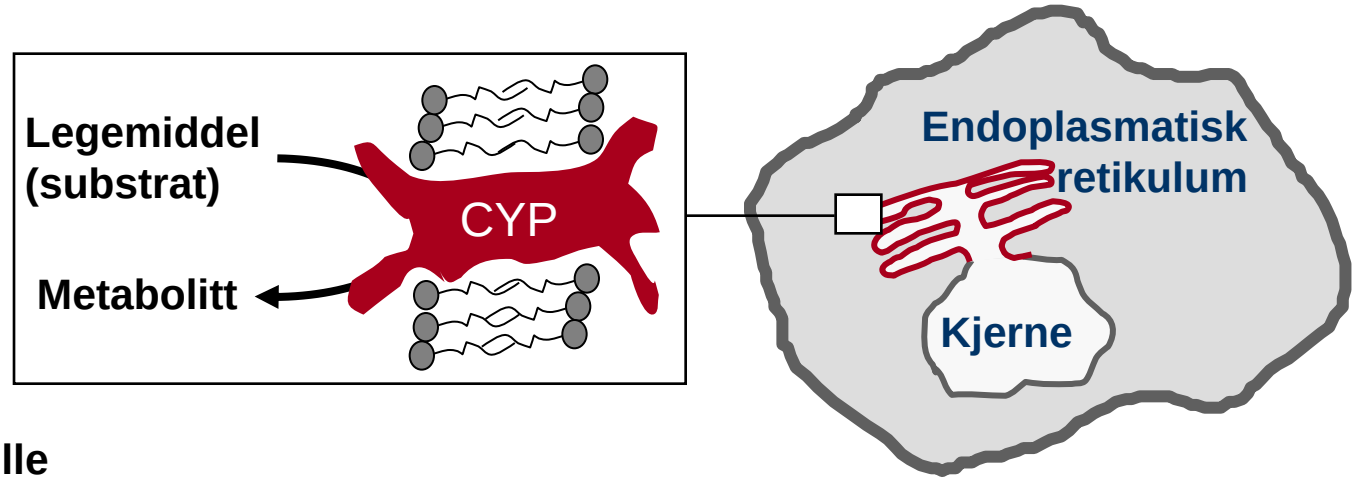
DATA SOURCES: PubMed, Ovid MEDLINE, and International Pharmaceutical Abstracts from January 1990 to August 2012 were searched. Key words used were tramadol, antidepressive agents, antidepressants, drug interactions, selective serotonin uptake inhibitors, and serotonin syndrome.

STUDY SELECTION AND DATA EXTRACTION: Only English-language studies were included. No randomized controlled trials were identified. Review articles, case reports, and 1 case series that identified the scope of interaction between tramadol and SSRIs were evaluated. Review articles evaluating the role of pharmacogenetics in the use of tramadol, SSRIs, and serotonin syndrome were also reviewed.

DATA SYNTHESIS: Published documentation describing the interaction between tramadol and SSRIs and its relevance to serotonin syndrome is limited to a few case reports and 1 case series. While both tramadol and SSRIs increase the amount of serotonin in the brain, the interaction is much more complicated. Tramadol is metabolized through CYP2D6 enzymes and all SSRIs are inhibitors of these enzymes. Inhibitors of CYP2D6 can increase the concentration of tramadol in the blood and thus increase its effects on serotonin in the brain, contributing to the development of serotonin syndrome. CYP2D6 poor metabolizers are at a greater risk of serotonin syndrome and an inadequate analgesic effect.

CONCLUSIONS: Coadministration of tramadol and SSRIs has caused serotonin syndrome. An attempt should be made to identify individuals who are poor metabolizers of CYP2D6 and avoid this combination in those patients. When SSRIs and tramadol must be used in combination, it is critical that patients be aware of the signs and symptoms of serotonin syndrome, should they occur.

Cytokrom P450 (CYP)



cyto	celle
krom	farge
P450	enzymer (proteiner) som har maks ("peak") absorpsjon ved bølgelengde 450 nm

- **Enzymene CYP1A2, CYP2C9, CYP2C19, CYP2D6 og CYP3A4 generelt viktigst i human legemiddelmetabolisme (>70 %)**
- **Individuelle variasjoner i enzymaktiviteter:**

INTERAKSJONER

-> **hemmere (reduserer metabolisme)**

-> **indusere (øker metabolisme)**

GENETIKK (CYP2D6, CYP2C9, CYP2C19)

-> **medfødte variasjon (livslang)**

CYP-interaksjoner – noen aktuelle kombinasjoner

Enzym	Hemmere	Indusere	Påvirkes av hemmere/indusere (↑↓ effekt/bivirk.)
CYP3A4	Amiodaron (Cordarone) Diltiazem (Cardizem) Erytromycin (Ery-Max) Flukonazol (Diflucan) *Grapefruktjuice* Itrakonazol (Sporanox) Ketokonazol (Fungoral) Klaritromycin (Klacid) Nelfinavir (Viracept) Ritonavir (Norvir) Verapamil (Ispotin)	Bosentan (Tracleer) Fenytoin (Epinat) Fenobarbital (Fenemal) *Johannesurt* Karbamazepin (Tegretol) Rifampicin (Rimactan)	Alfentanil (Rapifen), Alprazolam (Xanor), Apixaban (Eliquis), Atorvastatin (Lipitor), Buspiron (Buspar), Buprenforfin (Norspan), Ciklosporin (Sandimmun), Eletriptan (Relpax), Eplerenon (Inspra), Ergotamin (Anervan), Etinylestradiol (P-piller), Felodipin (Plendil), Fentanyl (Durogesic), Kabergolin (Cabaser), Klonazepam (Rivotril), Kodein (P Forte), Larkanidin (Zanidip), *Metadon*, Nifedipin (Adalat), Oksykodon (Oxycontin), Quetiapin (Seroquel), Repaglinid (Actos), Risperidon (Risperdal), Rivaroksaban (Xarelto), Sildenafil (Viagra), Saxagliptin (Onglyza), Simvastatin, Sitagliptin (Januvia)[1], Sirolimus, Solifenacin (Vesicare), Tadalafil (Cialis), Takrolimus, Ticagrelor (Brilique), Vardenafil (Levitra)
CYP2D6	Bupropion (Wellbutrin) Fluoksetin (Fontex) *Metadon* Paroksetin (Seroxat) Terbinafin (Lamisil)	[ingen kjente]	Amitriptylin (Sarotex), Atomoxetin (Strattera), Haloperidol (Haldol), Klomipramin (Anafranil), Kodein* (P. Forte), Metoprolol (SeloZok), Mianserin (Tolvon), Nortriptylin (Noritren), Perfenazin (Trilafon), Risperidon (Risperdal), Tamoxifen* (Nolvadex), Tramadol* (Nobligan), Venlafaksin (Efexor)
CYP2C19	Fluoksetin (Fontex) Fluvoksamin (Fevarin) Omeprazol (Losec) Vorikonazol (Vfend)	Fenytoin (Epinat) *Johannesurt* Rifampicin (Rimactan)	Amitriptylin (Sarotex), Citalopram (Cipramil), Escitalopram (Cipralex), Diazapam (Valium), Klomipramin (Anafranil), Klopidogrel* (Plavix), Moklobemid (Aurorix)
CYP2C9	Amiodaron (Cordarone) Flukonazol (Diflucan) Metronidazol (Flagyl) Trimetoprim/sulfa	Bosentan (Tracleer) *Johannesurt* Rifampicin (Rimactan)	Fluvastatin (Lescol), Fenytoin (Epinat), Glibenklamid, Glimeperid (Amaryl), Glipizid (Mindiab), Irbesartan (Aprovel), Losartan* (Cozaar), Nateglinid (Starlix), NSAIDs, Warfarin (Marevan)
CYP1A2	Ciprofloxacin (Ciproxin) Fluvoksamin (Fevarin)	*Tobakksrøyking* Rifampicin (Rimactan)	Duloksetin (Zymbalta), Klozapin (Leponex), Olanzapin (Zyprexa), Propranolol (Inderal), Teofyllin (Theo-Dur), Warfarin (Marevan)

Omdannes til aktiv form via det aktuelle enzymet

CYP3A4-induksjon: *quetiapin (Seroquel)* + *karbamazepin*

J Opioid Manag. 2015 Jul-Aug;11(4):357-61. doi: 10.5055/jom.2015.0284.

Decreased responsiveness to oxycodone: A case of a pharmacokinetic drug interaction?

Pon D[1], Hwang J[2], Lo T[2], Zyl CV[3].

Author inf

Abstract

Concurrent ac
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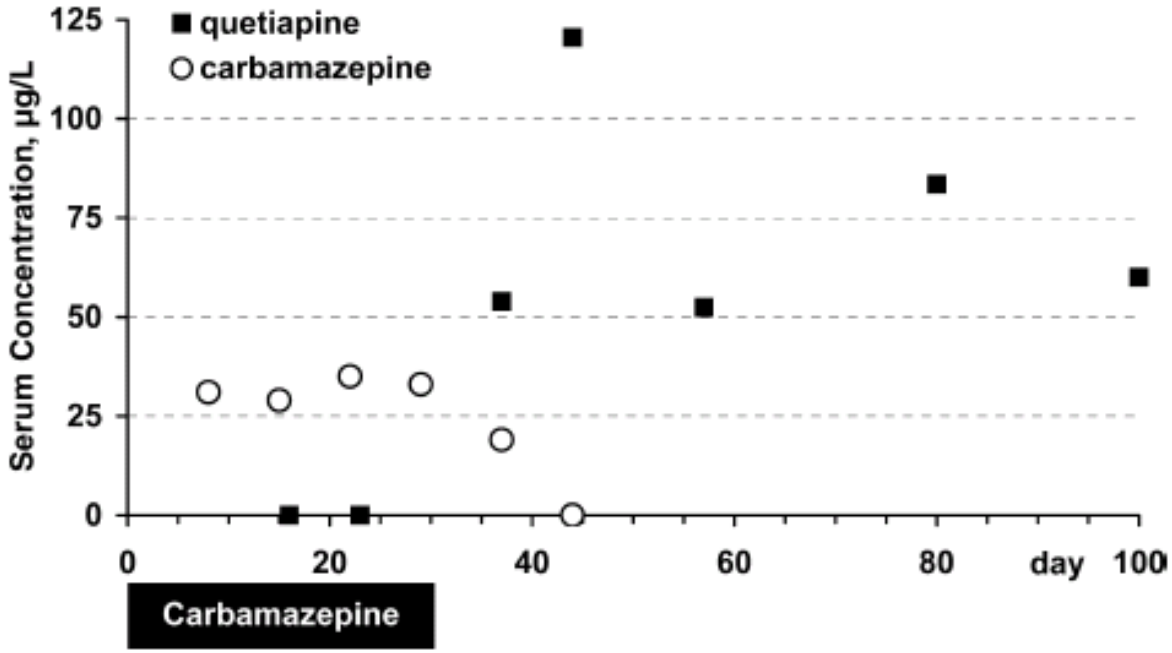
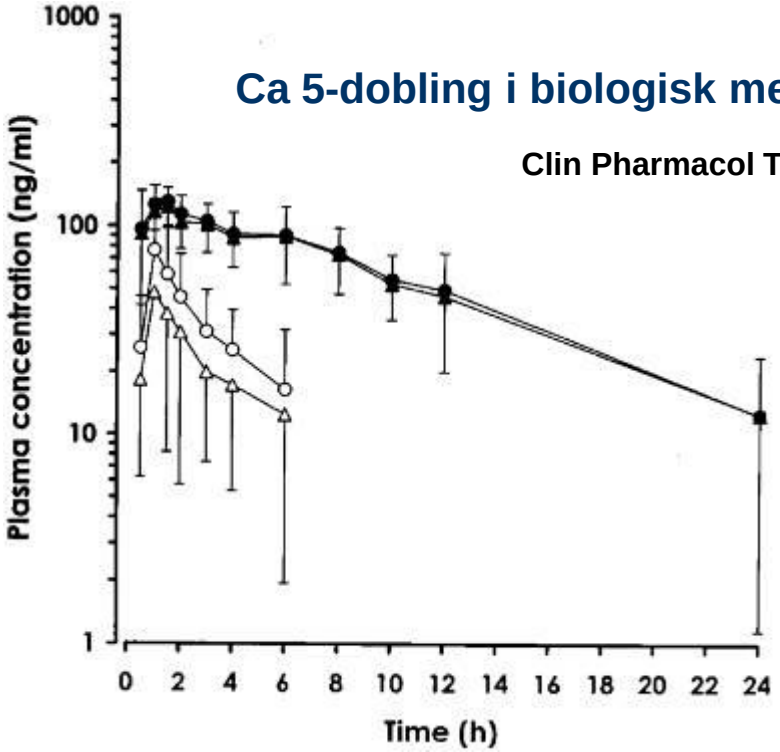


FIGURE 1. Serum concentrations of carbamazepine (empty circles) and quetiapine (filled dots) after the beginning of the quetiapine treatment. Carbamazepine had already been given for several weeks and was discontinued on day 31 of the chart. There is a quick and overshooting buildup of the quetiapine concentration afterward.

Clinical Neuropharmacology • Volume 32, Number 1, January/February 2009

CYP2D6-interaksjon: *metoprolol (Selo Zok)* + *paroksetin (Seroxat)*



Ca 5-dobling i biologisk metoprololdose

Clin Pharmacol Ther 2000;67:283-91

- Tilsvarende med fluoksetin (Fontex) og bupropion (Wellbutrin/Zyban), men mindre med citalopram (Cipralex/Cipramil)

- Sertralin (Zoloft) "snillest" mot metoprolol

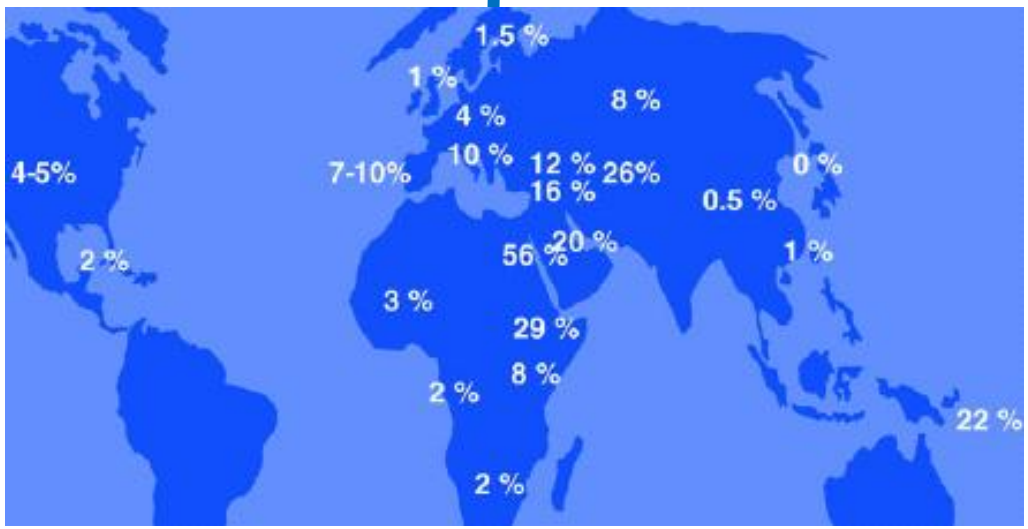
5-10% av pasientene født med like dårlig metoprololmetabolisme som Seroxat, Wellbutrin/Zyban eller Fontex medfører (!!)

Mayo Clin Proc. 2008;83(5):595-599

Medfødt treg eller ultrarask legemiddelnedbrytning

[diploid genkode; 1 allel far + 1 allel far]

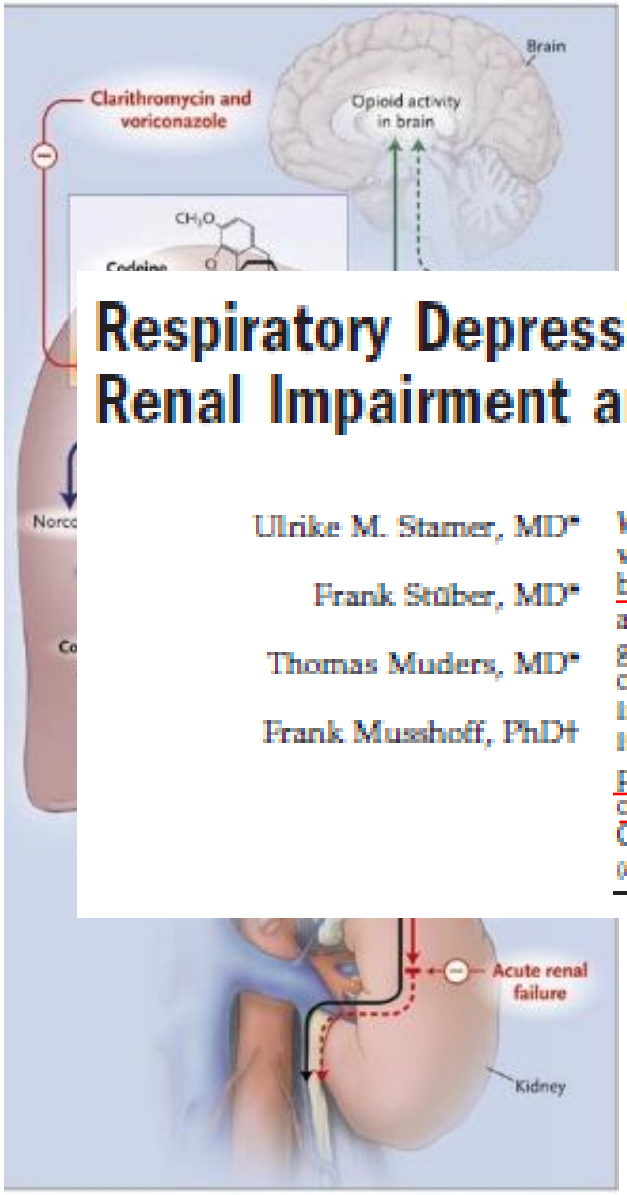
- **CYP2D6**
  - **5-10 % homozygot trege omsettere ('poor metabolizers', PMs)**
  - **1-2 % ultraraske omsettere ('ultrarapid metabolizers', UMs)**
  - **Hjertemedisiner + *psykofarmaka*, kodein*, tramadol*, tamoksifen*++**



- **CYP2C19**
  - **3-5 % PMs (15-20%; Øst-Asia)**
  - **3-5 % UMs**
  - **Antidepressiva (bl.a. Cipralex), klopidogrel* (Plavix) ++**

- **CYP2C9**
  - **1-3 % PMs**
  - **Warfarin (Marevan), diabetesmidler, Ibux ++**

***prodrugs (må aktiveres)**



Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism

Yvan Gasche, M.D., Youssef Daali, Pharm.D., Ph.D., Marc Fathi, Ph.D., Alberto Chiappe, Silvia Cottini, M.D., Pierre Dayer, M.D., and Jules Desmeules, M.D.

Respiratory Depression with Tramadol in a Patient with Renal Impairment and CYP2D6 Gene Duplication

Ulrike M. Stamer, MD*
Frank Stüber, MD*
Thomas Muders, MD*
Frank Musshoff, PhD†

We observed opioid-related respiratory depression in a patient receiving tramadol via patient-controlled analgesia. Predisposing factors were the patient's genetic background and renal impairment. Complete recovery occurred after naloxone administration, thus confirming opioid intoxication. Analysis of the patient's genotype revealed a CYP2D6 gene duplication resulting in ultra-rapid metabolism of tramadol to its active metabolite (+)O-desmethyltramadol. Concomitant renal impairment resulting in decreased metabolite clearance enhanced opioid toxicity. This genetic CYP2D6 variant is particularly common in specific ethnic populations and should be a future diagnostic target whenever administration of tramadol or codeine is anticipated, as both drugs are subject to a comparable CYP2D6-dependent metabolism.

(Anesth Analg 2008;107:526–9)

- **CYP3A4-hemmere: Klacid + soppmiddel**
  [mer kodein via CYP2D6 (-> morfin) enn CYP3A4]
- **Akutt nyresvikt**
  [akkumulering av aktiv morfinmetabolitt]

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

Lancet 2006; 368: 704

Motherisk Program, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8,

In April, 2005, a full-term healthy r
vaginally, showed intermittent per
breastfeeding and lethargy starting
well-baby paediatric visit on day 11, t
that the baby had regained his birt

Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death

TO THE EDITOR: Obstructive sleep apnea is not rare in children with hypertrophic tonsils, and the common curative procedure is adenotonsillectomy.[1] Codeine is commonly prescribed for pain after adenotonsillectomy.[2] The respiratory depressant effects of opioids may influence the occurrence of respiratory complications.[3] An estimated one third of cases of apnea in children are not resolved after adenotonsillectomy.[4]

We report on the case of a healthy 2-year-old boy weighing 13 kg, with a history of snoring and sleep-study–confirmed sleep apnea, who underwent elective adenotonsillectomy. The outpatient surgery was uncomplicated, and 6 hours after surgery the boy received 10 mg of meperidine and 12.5 mg of dimenhydrinate intramuscularly and was sent home with instructions for 10 to 12.5 mg of codeine and 120 mg of acetaminophen syrup to be administered orally every 4 to 6 hours as needed. On the second evening after surgery, fever and wheezing developed in the child. At 9 a.m. the next day, the child's vital signs were absent, and resuscitation efforts failed.

Postmortem examination showed evidence of chronic tracheitis, aspiration of food particles, and bilateral consolidation in the lungs that was consistent with bronchopneumonia. Codeine (0.70 mg per liter) and morphine (32 ng per milliliter) were detected in the femoral blood by means of gas chromatography–mass spectrometry; there was no evidence of other drugs or metabolites. Cytochrome P-450 2D6 (CYP2D6) genotyping revealed functional duplication of the *CYP2D6* allele, resulting in the ultrarapid-metabolizer phenotype.

In this case, the prescribed and administered dose of codeine was within the recommended range of 1 to 3 mg per kilogram of body weight per day.[1,2] Increased conversion of codeine to morphine due to ultrarapid metabolism resulted in toxic accumulation of morphine. The concentration of 32 ng per milliliter of morphine at autopsy exceeded therapeutic levels and may have contributed to respiratory depression and death. Respiratory depression has been shown in young children with serum morphine concentrations exceeding 20 ng per milliliter.[3]

The boy had other contributing factors that should be considered. Autopsy results indicated evidence of bronchopneumonia, further enhancing the risk of hypoxemia. As many as a third of young children with obstructive sleep apnea remain symptomatic after adenotonsillectomy,[4] showing decreased responsiveness to increases in the partial pressure of carbon dioxide.[5] Recurrent episodes of hypoxemia may lead to alterations in the μ-opioid receptor and increased sensitiv-

Kasuistikk – hjerte/kar

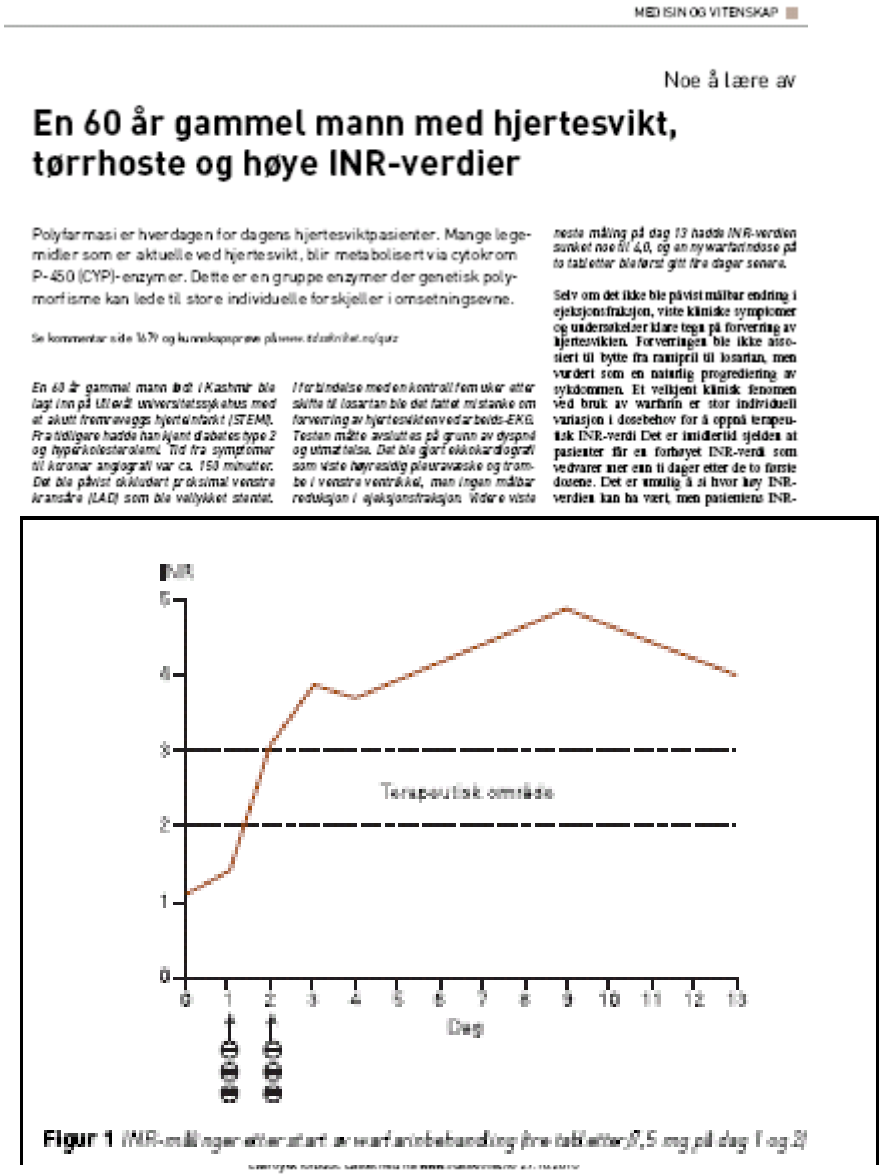
- **Type 2 diabetes, hyperkolesterolemi, infarkt -> *postinfarkt hjertesvikt***

- **Legemidler**
  - **Amaryl (glimeperid); 4 mg daglig [CYP2C9]**
  - **Simvastatin; 40 mg daglig**
  - **Plavix (klopidogrel); 75 mg daglig [CYP2C19]**
  - **Diural (furosemid); 20 mg daglig**
  - **Cozaar (losartan)*; 50 mg daglig [CYP2C9]**
  - **Selo Zok (metoprolol); 25 mg daglig [CYP2D6]**
  - **Marevan (warfarin); etter skjema [CYP2C9]**

  ***byttet fra ramipril (Triatec) p.g.a. tørrhoste**

- **CYP-test**
  - ***2C9*3* homozygot (defekt metabolisme, PM)**
  - ***2D6*4* homozygot (defekt metabolisme, PM)**
  - ***2C19* normal [-> god aktivering/effekt Plavix]**

Framtidig bruk…



MEDISIN OG VITENSKAP

Noe å lære av

En 60 år gammel mann med hjertesvikt, tørrhoste og høye INR-verdier

Polyfarmasi er hverdagen for dagens hjertesviktpasienter. Mange legemidler som er aktuelle ved hjertesvikt, blir metabolisert via cytokrom P-450 (CYP)-enzymer. Dette er en gruppe enzymer der genetisk polymorfisme kan lede til store individuelle forskjeller i omsetningsevne.

Se kommentar side 1679 og kunnskapsprøve på www.tidsskriftet.no/quiz

En 60 år gammel mann født i Kashmir ble lagt inn på Ullevål universitetssykehus med et akutt fremreveggs hjerteinfarkt (STEMI). Fra tidligere hadde han kjent diabetes type 2 og hyperkolesterolemi. Tid fra symptomer til koronar angiografi var ca. 150 minutter. Det ble påvist okkludert proksimal venstre kransåre (LAD) som ble vellykket stentet.

I forbindelse med en kontroll fem uker etter skifte til losartan ble det tatt mistanke om forverring av hjertesviktenved arbeids-EKG. Testen måtte avsluttes på grunn av dyspné og utmattelse. Det ble gjort ekkokardiografi som viste høyresidig pleuravæske og trombe i venstre ventrikkel, men ingen målbar reduksjon i ejeksjonsfraksjon. Videre viste neste måling på dag 13 hadde INR-verdien sunket noe til 4,0, og en ny warfarindose på to tabletter ble først gitt fire dager senere.

Selv om det ikke ble påvist målbar endring i ejeksjonsfraksjon, viste kliniske symptomer og undersøkelser klare tegn på forverring av hjertesvikten. Forverringen ble ikke assosiert til bytte fra ramipril til losartan, men vurdert som en naturlig progrediering av sykdommen. Et velkjent klinisk fenomen ved bruk av warfarin er stor individuell variasjon i dosebehov for å oppnå terapeutisk INR-verdi. Det er imidlertid sjelden at pasienter får en forhøyet INR-verdi som vedvarer mer enn ti dager etter de to første dosene. Det er umulig å si hvor høy INR-verdien kan ha vært, men pasientens INR-

Figur 1 *INR-målinger etter start av warfarinbehandling (tre tabletter 2,5 mg på dag 1 og 2)*

Kamal, Norstad & Molden. Tidsskr Nor Legeforen 2008; 128: 1677–9

Pharmacogenet Genomics. 2014 Feb;24(2):113-7. doi: 10.1097/FPC.0000000000000025.

Strongly increased exposure of meloxicam in CYP2C9*3/*3 individuals.

Lee HI[1], Bae JW, Choi CI, Lee YJ, Byeon JY, Jang CG, Lee SY.

⊕ Author information

Abstract

OBJECTIVE: The effects of CYP2C9*1/*3 and *3/*3 genotypes on the pharmacokinetics and pharmacodynamics of meloxicam were evaluated in healthy Korean subjects.

METHODS: After oral administration of 15 mg meloxicam, the plasma concentrations of meloxicam were assessed in 11 CYP2C9*1/*1 individuals, eight CYP2C9*1/*3 individuals, and three CYP2C9*3/*3 individuals. The pharmacodynamic effects were determined by measuring thromboxane B2 generated in blood.

RESULTS: A nine-fold lower apparent oral clearance and an eight-fold higher AUC0-∞ of single-dose meloxicam were observed in CYP2C9*3/*3 individuals when compared with CYP2C9*1/*1 individuals. CYP2C9*3/*3 individuals also showed markedly increased inhibition of thromboxane B2 generation by meloxicam.

Gastroenterology. 2007 Aug;133(2):465-71. Epub 2007 May 21.

Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9 polymorphisms.

Pilotto A[1], Seripa D, Franceschi M, Scarcelli C, Colaizzo D, Grandone E, Niro V, Andriulli A, Leandro G, Di Mario F, Dallapiccola B.

⊕ Author information

Abstract

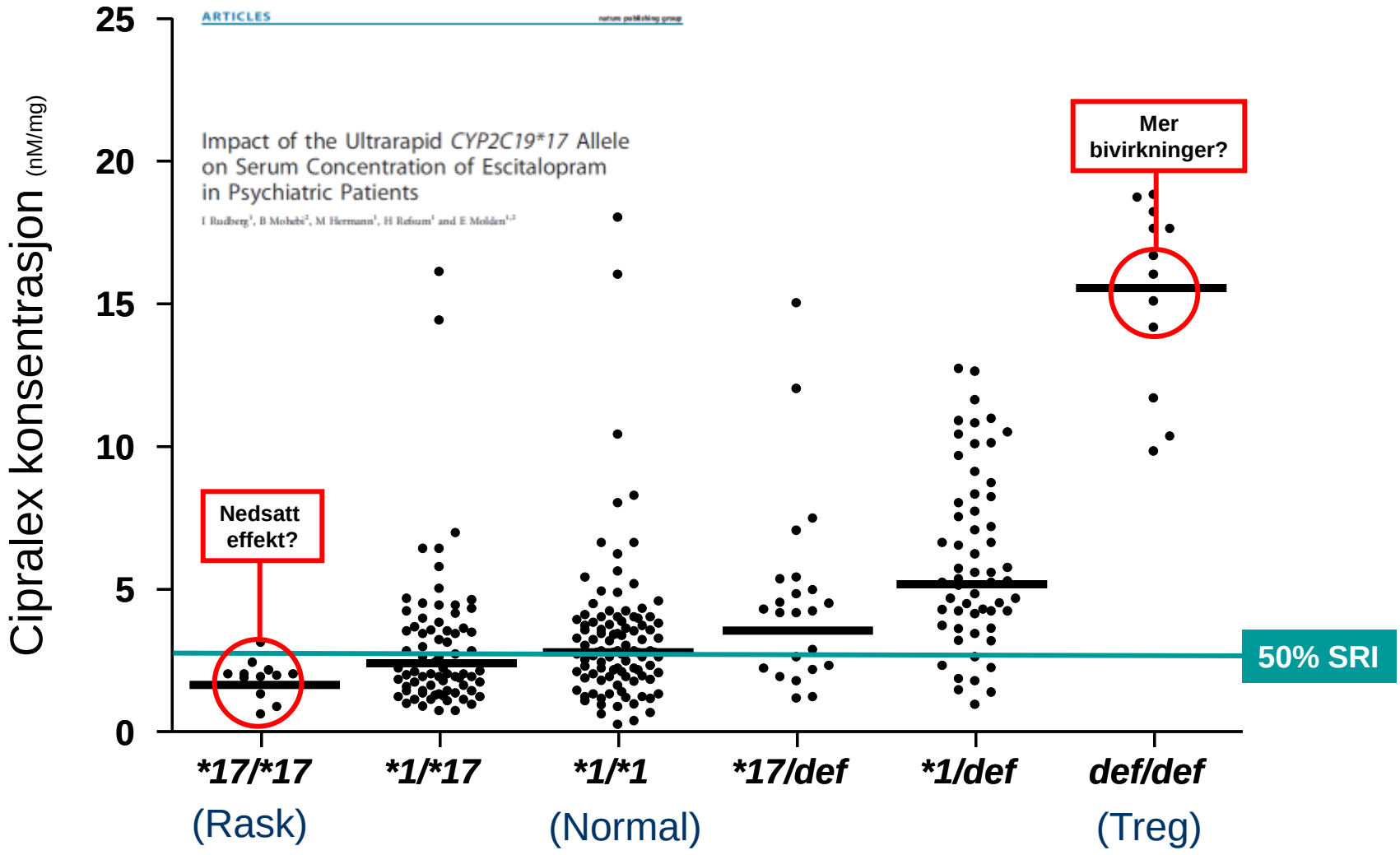
BACKGROUND AND AIMS: Several nonsteroidal anti-inflammatory drugs (NSAIDs) are metabolized by the cytochrome P450 2C9 (CYP2C9). Two common variants of the CYP2C9 gene (CYP2C9*2 and *3) were reported to significantly affect the activity of the CYP2C9 enzyme. The aim of this study was to evaluate the impact of CYP2C9 polymorphisms on the risk of gastroduodenal bleeding in acute NSAID users.

METHODS: This case-control study included 26 patients with endoscopically documented NSAID-related gastroduodenal bleeding lesions and 52 age-, sex- and NSAID use-matched controls with no lesions at endoscopy. Both cases and controls were Helicobacter pylori negative and acute users of an NSAID or cyclooxygenase-2 inhibitor that undergoes CYP2C9 metabolism (ie, celecoxib, diclofenac, ibuprofen, naproxen, or piroxicam). Two marker single nucleotide polymorphisms in the CYP2C9 gene, identifying the CYP2C9 *2 and *3 allele, were evaluated in all subjects.

RESULTS: Setting the CYP2C9*1/*1 wild type as reference, significantly higher frequencies of CYP2C9*1/*3 (34.6% vs 5.8%; P < .001; odds ratio [OR], 12.9; 95% confidence interval [CI], 2.917-57.922) and CYP2C9*1/*2 (26.9% vs 15.4%; P = .036; OR, 3.8; 95% CI, 1.090-13.190) were identified in bleeding versus control patients, whereas no differences between bleeding and controls were observed in the distribution of CYP2C9*2/*3 heterozygotes. Considering allele carriers, the presence of CYP2C9*3 allele was associated with a significant high risk of bleeding (adjusted OR, 7.3; 95% CI, 2.058-26.004).

CONCLUSIONS: CYP2C9 genotyping may identify subgroups of persons who potentially are at increased risk of gastroduodenal bleeding when treated with NSAIDs metabolized by CYP2C9. Further studies that evaluate the effectiveness of a strategy using CYP2C9 genotyping in NSAID users are needed before genotyping is introduced into clinical practice.

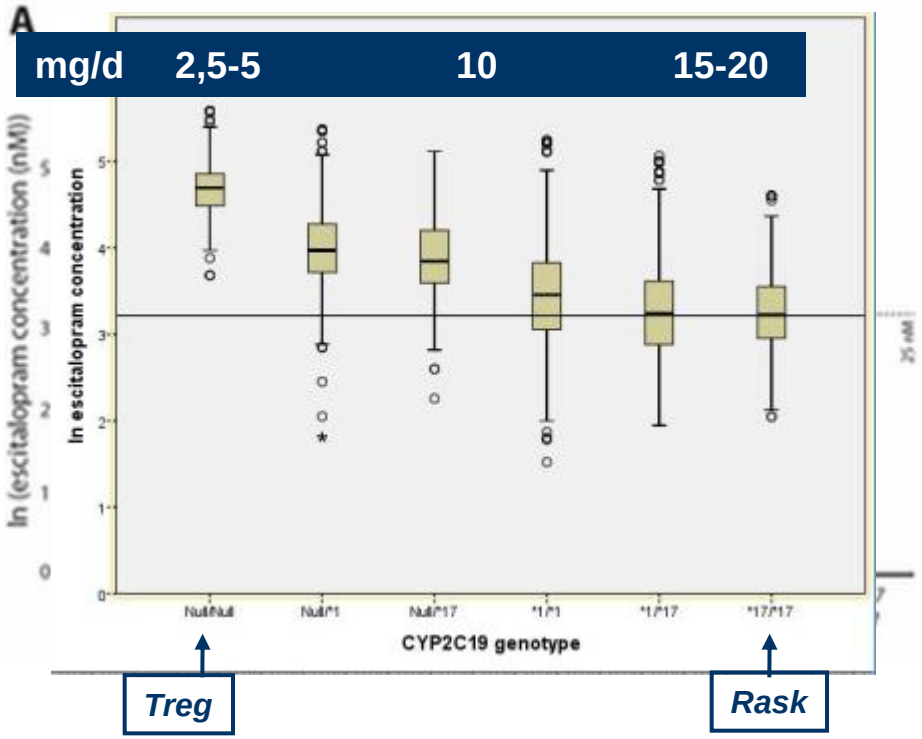
CYP2C19-genetikk: betydning for konsentrasjon/nivå av Cipralex

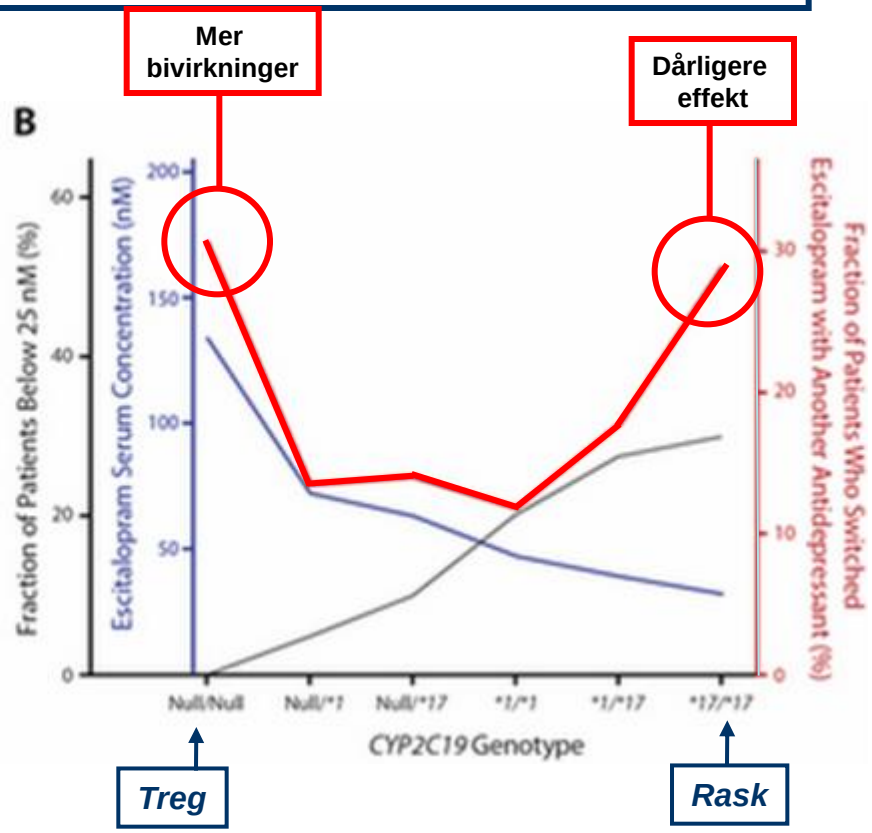


Rudberg I, Mohebi B, Hermann M, Refsum H, Molden E. Clin Pharmacol Ther. 2008 Feb;83(2):322-7.

CYP2C19-genetikk: betydning for terapisvikt av Cipralex

- **2 087 pasienter med Cipralex-analyser, analysehistorikk av antidepressiva og CYP-genotype**
  - ***Primært endepunkt: Bytte (switch) til andre antidepressiva <1 år etter siste Cipralex-måling***





Based on data from Center for Psychopharmacology, Diakonhjemmet

Am J Psychiatry (*IF 14.2*), 2018 May 1;175(5):463-470.

Reseptor-genetikk og klinisk respons – *OPRM1*

The Pharmacogenomics Journal **15**, 255-262 (June 2015) | doi:10.1038/tpj.2014.59

Association of OPRM1 A118G variant with risk of morphine-induced respiratory depression following spine fusion in adolescents

V Chidambaran, J Mavi, H Esslinger, V Pilipenko, L J Martin, K Zhang and S Sadhasivam

The μ1 opioid receptor (OPRM1) genetic variant A118G results in decreased μ-receptor binding potential in the brain and increases morphine requirement. We hypothesized that OPRM1 A118G polymorphism will affect morphine-induced respiratory depression (MIRD) risk in children receiving morphine. A prospective genotype-blinded study was conducted in 88 healthy adolescents (11–18 years; 67% female, 85% Caucasian) who underwent spine fusion for scoliosis. They were followed for 48 h postoperatively for MIRD, pain scores, morphine consumption and use of analgesic adjuvants. Patients were genotyped for OPRM1 A118G variant—76% were wild type (AA) and 24% heterozygous/homozygous for variant (AG/GG). Multivariable logistic regression showed that the risk of MIRD in patients with AA genotype was significantly higher (odds ratio 5.6, 95% CI: 1.4–37.2, P=0.030). Presence of G allele was associated with higher pain scores (effect size 0.73, P=0.045). This novel association is an important step toward predicting MIRD susceptibility and personalizing morphine use.

- ***118 A>G* gir aminosyrebytte fra asparagin til aspartat**
- **Endret følsomhet av reseptor**
- ***G*-bærere større dosebehov**
- **Hyppighet *G*-variant:**
  - **10-15 % blant kaukasere,**
  - **3-4 % blant afro-afrikanere**

Hovedpoenger

- **Farmakogenetisk variasjon viktig årsak til forskjeller i legemiddelrespons innad og mellom etniske grupper**

  [andre faktorer kan disponere for alvorlighetsgrad; eks. nedsatt nyrefunksjon]

- **Praktiske tips**

  - Benytte *CYP*-genotyping/smertepanel på aktuelle pasienter for å optimalisere og persontilpasse behandlingen

  - NB! Også sjekke legemiddel/legemiddel-interaksjoner, særlig ved ved oppstart/seponering (www.interaksjoner.no)

- **Utfordringer**

  - Kompetanse + bruk/overføring av informasjon i helsevesenet

  [informasjon om genotype kan brukes på tvers av terapiområder]