Regional smertesamling 2019,

29.11-2o19. Store Aud, Ullevål

Regional Kompetansetjeneste for Smerte -ReKS

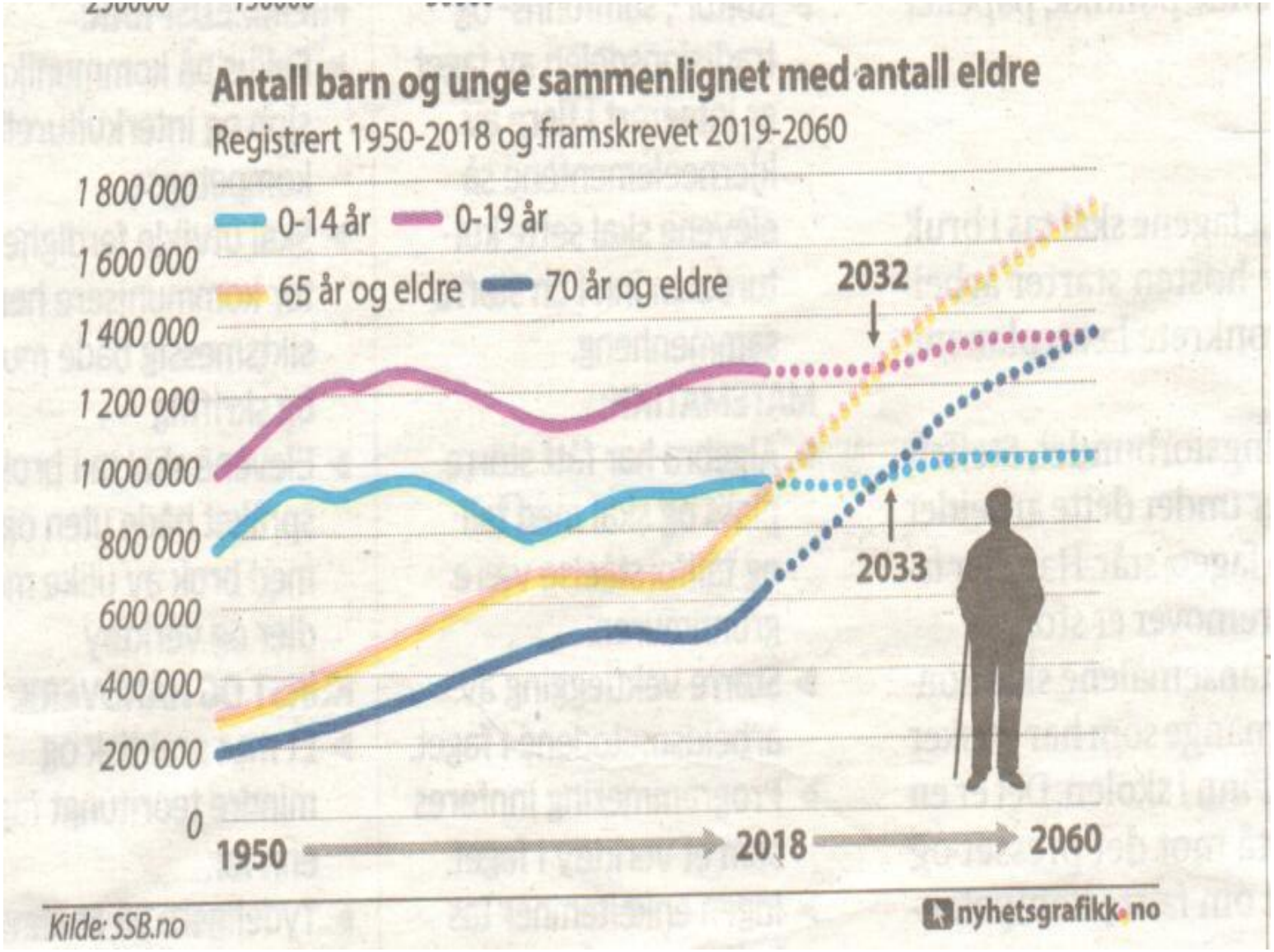
Smerte hos eldre er vanlig og vanskelig -- lærerike pasienthistorier 12.45-13.15

Harald Breivik

Nå forfremmet til **Sjuende far i Bygg 37B**

Eldrebølgen er her

Aftenposten 27.06-2o18



Eldrebølgen er her og følges av en **tsunami**

Eldrebølgen er her og følges av en **tsunami**

..en **tsunami** **av eldre som trenger behandling for smerter**

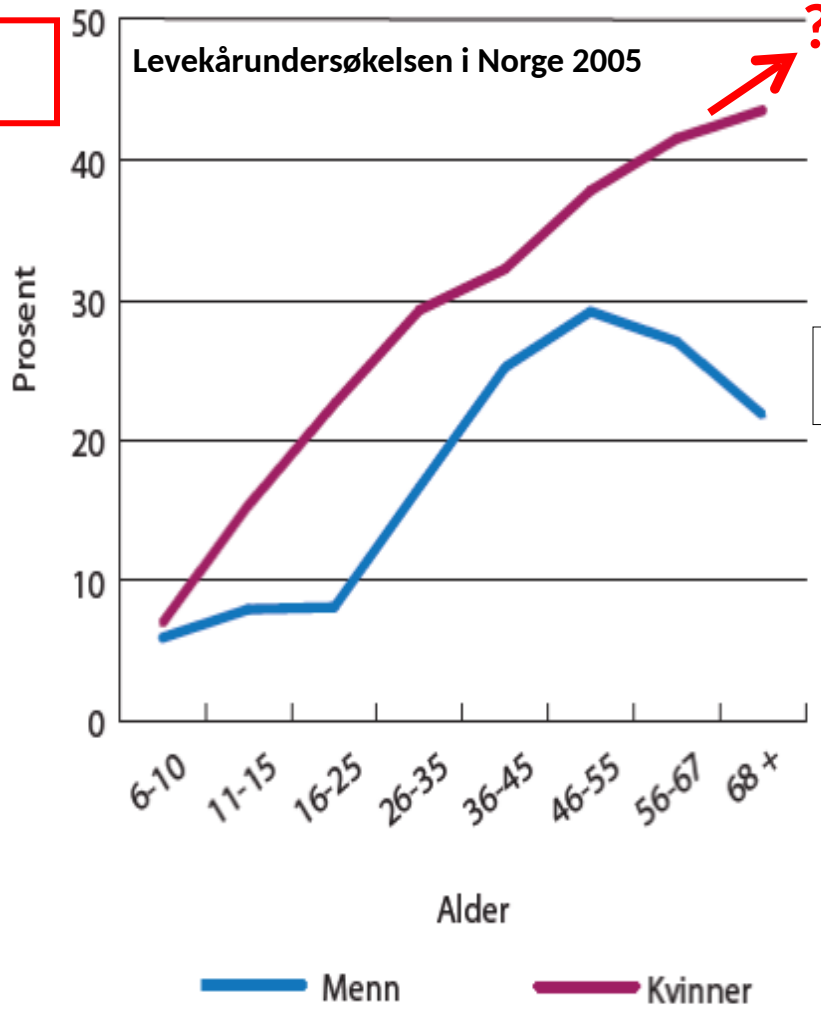
Arthur Schopenhauer (1788 - 1860)

Pessimismens filosof:

“Å leve er å lide”

Kronisk smerte i prosent av befolkningen

Intervju av 3373 hjemmeboende personer i alder 16-95 år



Enkene lever og lider!

Gjennomsnitt for alle over 18 år = 29,3%

Nielsen CS, Folkehelserapporten 2010,kapt16.

Figur 1. Forekomsten av kroniske smerter i prosent av befolkningen etter alder og kjønn.

Kilde: Data fra Levekårsundersøkelsen 2005. Analysen er basert på besvarelse fra 3371 hjemmeboende personer i alder fra 16–95 år. Data for barn 6–15 år er rapportert av deres foreldre. Kroniske smerter er definert som smerter med varighet på seks måneder eller

Hvorfor **lider** eldre av mer smerter enn yngre?

Smerte er oftere et symptom på en (eller flere) sykdommer hos eldre – f.eks.: Artrose;diabetes, **cancer-survivors**.

THE GERONTOLOGICAL SOCIETY OF AMERICA
The Gerontologist
cite as: Gerontologist, 2016, Vol. 56, No. S2, S243–S255
doi:10.1093/geront/gnw002
OXFORD

Literature Review

Musculoskeletal Health Conditions Represent a Global Threat to Healthy Aging: A Report for the 2015 World Health Organization World Report on Ageing and Health

Andrew M. Briggs, BSc(Physio)Hons, PhD,[*,1,2] Marita J. Cross, BSc (Hons), MPH (Hons), PhD,[3] Damian G. Hoy, BAppSc(Physio), MPH, PhD,[4,5] Lídia Sànchez-Riera, MD, PhD,[6] Fiona M. Blyth, BSc (Med), MBBS (Hons), MPH, PhD, FAFPHM,[7] Anthony D. Woolf, BSc, MBBS, FRCP,[8] and Lyn March, MBBS, MSc, PhD, FAFPHM, FRACP[3]

Table 3. Global Prevalence (%) (Lower, Upper 95% Uncertainty Intervals) of Activity-Limiting Low Back Pain and Neck Pain That Had Lasted for At Least 1 Day, Knee Osteoarthritis, Hip Osteoarthritis, Rheumatoid Arthritis, and Other Musculoskeletal Conditions, by Age Group

Age group	Low back pain	Neck pain	Knee osteoarthritis	Hip osteoarthritis	Rheumatoid arthritis	Other musculoskeletal conditions
All ages	9.4 (9.0, 9.8)	4.9 (4.6, 5.3)	3.7 (3.5, 4.0)	0.9 (0.7, 1.0)	0.24 (0.23, 0.25)	8.2 (8.0, 8.5)
55–64 years	16.9 (16.0, 17.9)	8.2 (7.6, 8.8)	13.1 (12.3, 14.0)	2.8 (2.4, 3.3)	0.53 (0.51, 0.55)	16.5 (16.0, 17.2)
65–74 years	20.0 (19.0, 21.1)	8.0 (7.5, 8.6)	14.2 (13.4, 15.2)	4.1 (3.6, 4.9)	0.78 (0.75, 0.82)	22.4 (21.4, 23.4)
75–84 years	22.9 (21.8, 24.2)	7.8 (7.2, 8.4)	14.9 (14.1, 15.9)	5.8 (5.1, 6.9)	1.06 (1.01, 1.11)	24.8 (23.7, 26.0)
85+ years	23.3 (22.3, 24.6)	7.3 (6.8, 7.8)	15.4 (14.5, 16.4)	7.9 (6.9, 9.3)	1.35 (1.28, 1.43)	24.9 (23.7, 26.3)

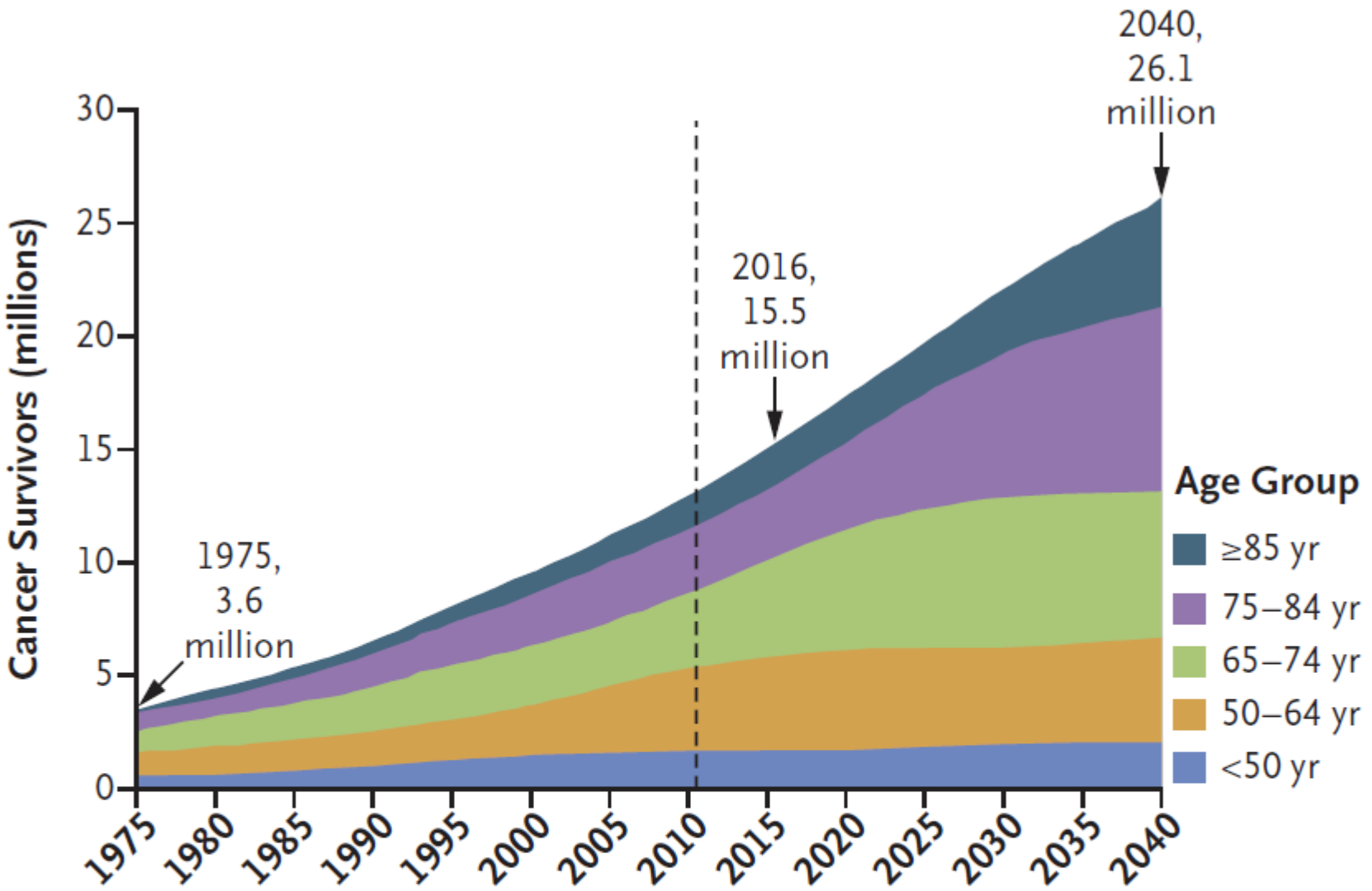


Figure 1. Changing Demographic Characteristics of Cancer Survivors in the United States.

Shown is the number of cancer survivors according to age group, starting

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cancer Survivorship

Charles L. Shapiro, M.D.

ADVANCES IN CANCER SCREENING AND EARLY DETECTION, IMPROVEMENTS in therapeutics, and supportive care all contribute to decreasing cancer mortality. Figure 1 shows the changing demographic characteristics of the

Bedre screening, tidlig diagnose, bedre kurativ terapi, bedre oppfølging

→**Flere overlever** som **kurerte kreft-pasienter** – **cancer-survivors**

→Cytostatika, stråler, kirurgi →**nerveskadesmerter**

→Bio-**psyko-sosiale** komponenter ofte betydelige

i cancer-survivors med smerter

From the Icahn School of Medicine at Mount Sinai Uptown, New York. Address reprint requests to Dr. Shapiro at the Icahn School of Medicine, 1 Gustave L. Levy Pl., Box 1079, New York, NY 10029, or at charles.shapiro@mssm.edu.

N Engl J Med 2018;379:2438-50.
DOI: 10.1056/NEJMra1712502

WHO: “Numbers and proportion of elderly increase globally & rapidly”

<u>WHO, Geneva, 2015:</u>

«The proportion of those **above 65 years** is soon larger than those **5 years and younger** »

Pain is often part of the diseases of the elderly…..

Burden of diseases is much aggravated by pain..

Aging in good health is **NOT** the rule….

Advice from WHO (2015) to secure healthy aging…

WHO(2o15):Healthy aging – what can we **all** do?

- Skaff deg en god utdanning
- Ikke røke tobakk
- Bruk svært lite alkohol
- Sunn livsstil senest fra 30-års alder
- Behandle høgt blodtrykk allerede i “middle age”
- Diet med fisk og grønnsaker (“Mediterranean diet”)
- **Vær fysisk aktiv, mentalt aktiv, og sosialt aktiv**
- Høre-apparat er viktig
- **Hold din partner sunn og glad.**

Så noen lærerike pasienthistorier

En frisk cancer-coli survivor (10 år etter operasjon)**, nå 72-år:**

Hun venter på kirurgi for humerus-fractur **etter fall**.

Sterke akutte smerter (10/10 ved bevegelse; 7/10 i ro)

Forslag til smerte-lindring?

Diclofenak (=det globalt mest brukte NSAID(=Voltaren))
Diklofenak til en **frisk** cancer-survivor **72 år**
Hun venter på kirurgi for humerus-fractur etter **fall**

Diclofenak 50 mg tbl x3 dgl→ lindret **smerte i ro**-2/10

Smerte ved **bevegelse** fortsatt sterke (7-8/10)

Etter 4-5 dager føler hun seg veldig uvell og svimmel,

Ingen andre symptom!

Hva kan dette være?

Diclofenak (=det globalt mest brukte NSAID(=Voltaren))
Diklofenak til en **frisk** cancer-survivor **72 år**
Hun venter på kirurgi for humerus-fractur etter **fall**

Diclofenak 50 mg tbl x3 dgl→ lindret **smerte i ro**-2/10
Smerte ved **bevegelse** fortsatt sterke (8-9/10)

Etter 4-5 dager føler hun seg veldig uvell og svimmel,
Ingen andre symptom!
Hva kan dette være?

Men så....

Tilfeldig oppdaget: **Svart avføring.**

Hgb fra 15 g/dL til 7 g/dL

Gastroscopi: Blødende ulcus.

OBS: INGEN ulcus smerter

Flere problem med NSAID til eldre?

NSAID (diclofenak, ibuprofen, naproxen,++) er effektive til akutt-smerte lindring hos elder, men **risiko-fyllte**

NSAID gir gastrointestinale **ulcus** uten ulcus-**smerter**

NSAID hemmer **blodplatene** og øker **blødning**-risiko

NSAID øker risiko for slag, infarkt, nyresvikt

NSAIDs skal **IKKE** forskrives til eldre (over 65 + år) for **kroniske** smerter

Gir:

Smertefrie GI-sår→blødning

Cardiovaskulære katastrofer (MI/Slag)

Forverrer allerede redusert nyrefunksjon

Gjelder:

Ibuprofen, naproksen, ketoprofen, diklofenak, ketorolak, piroksikam,meloksikam

Celekoksib og etorikosib (Arcoxia) har samme effekt på nyrer og cardiovaskulære system

Journal of American Geriatric Society 2009

Risiko for cardiovaskulære komplikasjoner øker med dosen og med varigheten av behandlingen med NSAIDs/ COXibs

Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, Brophy JM.

"Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of (almost 450 000) individual patient data".

BMJ 2017;357:j1909.

"With use for **one to seven days** the probability of myocardial infarction **risk** was increased for **celecoxib**, for **ibuprofen**, and **highest for diclofenac, naproxen**, and **rofecoxib**"

Risk of myocardial infarction increased with time up to one month.

Risk of myocardial infarction increased with dose.

Take-home message:

(1) **Risk of myocardial infarction increases from first dose of traditional NSAIDs and COX-2 inhibitors.**

(2) No practical difference in risk between traditional NSAIDs and the more COX-2 selective inhibitors.

(3) Do not prescribe NSAIDs to patients who already have cardiovascular risk-factors

NSAIDs* must be used with caution in:

- Age > 65 years (renal impairment)
- Diabetes (renal impairment)
- Widespread vascular disease
- Patients on **ACE-inhibitors, diuretics**, betablockers, cyclosporin, methotrexate
- Major surgery (risk of decreased renal function)

(Rowbotham et al: Royal College of Anaesthetists - **1998**)

*(also COX2-inhibitors)

Åndsfrisk 86 år: 12 år etter ca coli(coecum-nær) og 8 år etter operasjon for ca coli sigmoideum – nå **akutt lumbago** (NRS 5-7/10)

Han har nå moderat **hjertesvikt** med bevart ejeksjons-fraksjon

og **nyresvikt** (eGFR$_{CystatinC}$ 22ml/min/1.74m2)

Behandles med ACE-hemmer: Ramipril 1,25 mg x 2, Burinex 1 mg x 2.

Han prøver paracetamol 1 g →litt/lite smertelindring

Får beskjed om å ta Ibux 400 mg x 3 i tillegg

→ 2 dager etter: **Uttalt ankel-legg-ødem…..**

Hva nå??

Fordeler med steroider for lindring av akutte smerter

- Rask og lengevarende analgesi
- Antiemetisk
- Ingen blødning
- Ingen effekt på nyrene/lever
- Ikke økt risiko for sårinfeksjon
- Ikke allergi

Romundstad, L et al. Acta Anaesth Scand (2004)

Romundstad et al. Anesth Analg (2006)

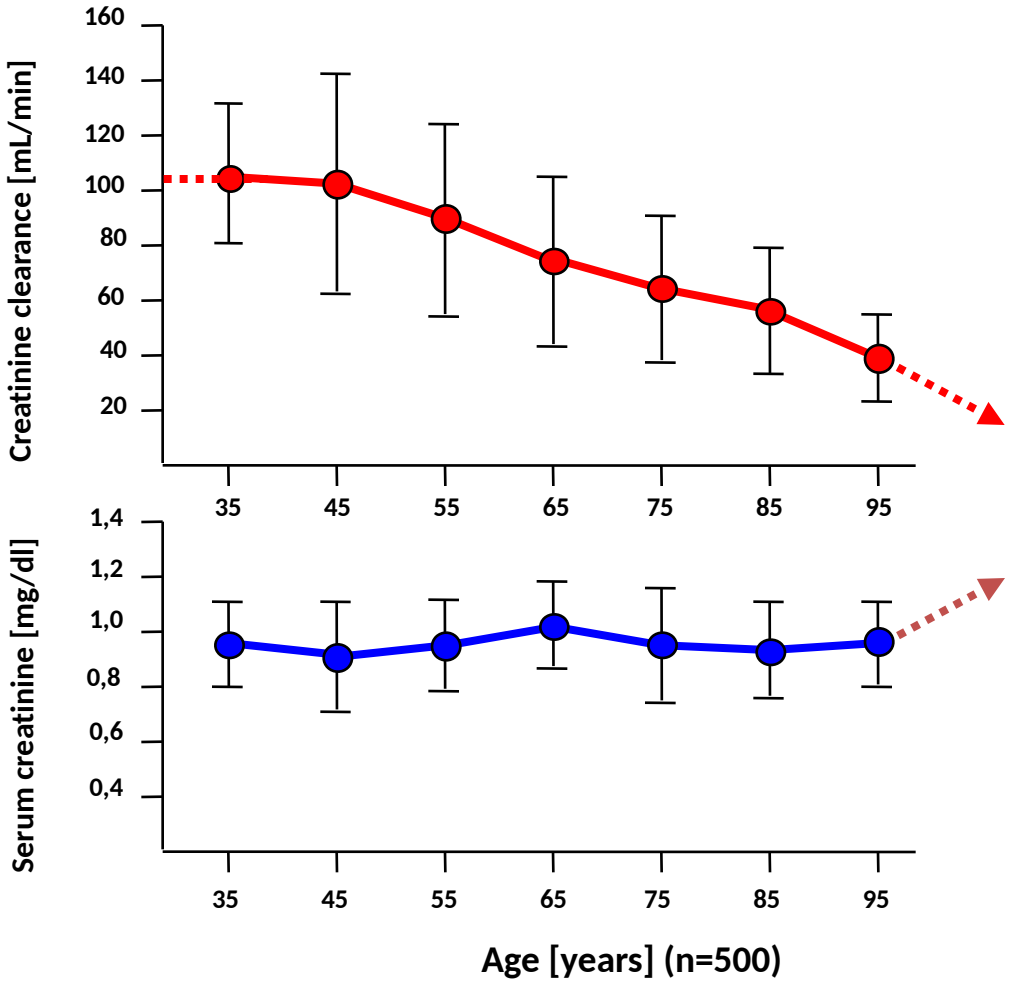
NSAIDs and "Triple whammy" acute renal failure

Complex interplay among the effects of

1. NSAIDs,
2. Angiotensin-converting enzyme inhibitors(**ACE**) or angiotensin receptor antagonists (ARA),
3. and diuretics

whammy = (ond) trussel

Age-dependent renal impairment not well estimated from serum creatinine



Rate of decline:

1 mL/min per year of life after the 40th year of age

"Creatinine-blind range"

Mühlberg W et al. Gerontology 1999;45:243-53.

NSAIDs and Triple whammy acute renal failure

Kollinius-Bringland M, Affas F, Wretenberg P. Acute renal failure after local infiltration anesthesia. Two cases related to orthopedic surgery described. Lakartidningen 2013;110:284–5.

Prieto-García L, Pericacho M, Sancho-Martínez SM, Sánchez Á, Martínez-Salgado C, López-Novoa JM, López-Hernández FJ. Mechanisms of triple whammy acute kidney injury. Pharmacol Ther 2016, http://dx.doi.org/10.1016/j.pharmthera.2016.07.011. Aug 1. [Epub ahead of print]. pii: S0163-7258(16)30136-X.

NSAIDs should **not** be prescribed for elderly (>65 + years) for **chronic pain**

Occasional, short term use for acute pain may be **OK?**

Never more than 3 (- 5) **days?**

“NSAIDs bring on cardiac diseases in osteoarthritis patients”

- **NSAID use for osteoarthritis may bring on cardiovascular disease**
- Published: Aug. 7, 2019 at 12:51 PM

Tauren Dyson

Aug. 7 (UPI) -- Nonsteroidal anti-inflammatory drugs that treat inflammation and pain raise the risk of congenital heart disease, heart attack and other conditions for people with osteoarthritis, new findings show.

- In fact, people with osteoarthritis who take NSAIDs have a 23 percent higher likelihood of developing cardiac disease compared to people without the condition, according to a study published in August in Arthritis Rheumatology.
- In addition, they have a 42 percent higher risk of developing congestive heart failure, 17 percent of ischemic heart disease and 14 percent risk of stroke.
- "To the best of our knowledge, this is the first longitudinal study to evaluate the mediating role of NSAID use in the relationship between osteoarthritis and cardiovascular disease in a large population-based sample," senior study author Aslam Anis, a researcher at the University of British Columbia and study senior author, said in a news release.
- For this longitudinal study, the researchers examined data for 7,743 osteoarthritis patients from British Columbia, Canada, comparing them with 23,229 people who did not have osteoarthritis. They found about 41 percent of the cardiovascular risk within this group came from NSAID use.
- "Our results indicate that osteoarthritis is an independent risk factor for cardiovascular disease and suggest a substantial proportion of the increased risk is due to the use of NSAIDs," Anis said. "This is highly relevant because NSAIDs are some of the most commonly used drugs to manage pain in patients with osteoarthritis. It's important for people with OA to talk to their care providers and discuss the risks and benefits of NSAIDs."

Uheldige—farlige komplikasjoner til NSAIDs (COX-1 og/eller COX-2 hemmere)

COX-1 hemmere (ibuprofen, naproxen,diklofenak,piroksikam; ketorolak (bare til intravenøs i Norge)

Hemmer produksjon av **pro-**inflammatoriske prostaglandiner, spesielt **thromboxane A**

(1)COX-1 hemming gir den **N**on**S**teroide**A**ntiinflammatoriske **D**roge (**NSAID**) - effekten

(2) Hemmer blodplate-aggregasjon

→**plate-proppen** dannes ikke

→ **Øket** risiko for **blødning**

COX-2 hemmere (celekoksib,etorikoksib, parekoksib (bare til intravenøs)

Hemmer produksjonen av **anti-**inflammatoriske prostaglandiner, spesielt **prostacyklin** som fører til

→**hypertensjon, nyresvikt;**

→**aterosklerotiske plaque vokser**→ **myocard-infarkt;** →**plutselig hjerte-død**

cerebrale infarkt →**slag**

Ingen øket blødningsrisiko

NSAIDs kan hemme **både** COX-1 **og** COX-2

Ketorolak har nesten bare COX-1 hemming

Etorikoksib har nesten bare COX-2 hemming

De øvrige har både COX-1 og COX-2 i ulike fraksjoner

Diklofenak og meloksikam hemmer COX-2 **mer** enn COX-1

De cardiovaskulære komplikasjoner like uttalte for diklofenak, ibuprofen og naproksen

som for celekoksib.

Pasienter med cardiovaskulære sykdommer bør
ikke bruke traditionelle NSAIDs, heller **ikke Arcoxia** (etorikoksib) for smertelindring.
Bruk **paracetamol,** evt med kodein

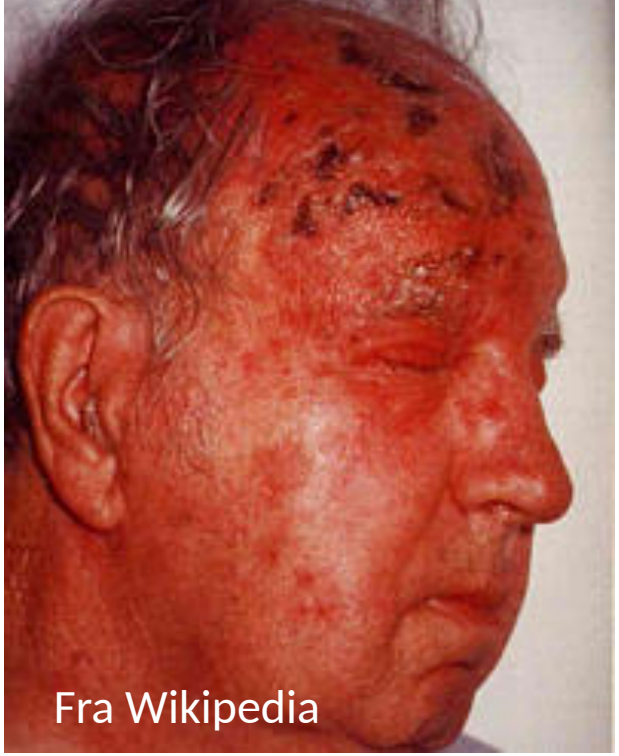
Mann 76 år-- kommer til sin tannlege med sterke smerter i h. overkjeve – opp til pannen

Ingen endringer i munnslimhinne, tannkjøtt, rtg av tanngarden—

Kan hende litt rødmusset høgre kinn?

Hva er dette?

Primær orofacial smerte?


Fra Wikipedia

4 uker senere – hva er dette?

Akutt herpes zoster i n.trig V1 og V2

Akutt herpes zoster

Akutt HZ og Postherpes-nevralgi

Ved tilfeldig immunforsvar svekkelse→Reaktivering av varicella-zoster virus (VZV)

etter vannkopper (varicella) som barn.

Reaktiverte VZV i dorsale ganglier→akutt herpes zoster (HZ)

omlag 1-4 av 100 eldre personer hvert år

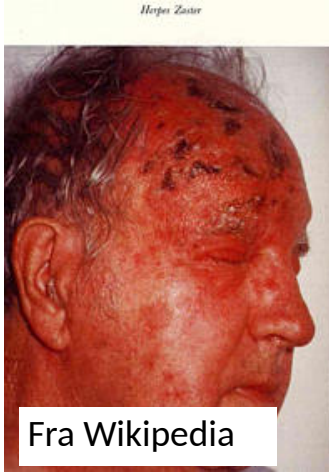
Livslang postherpes nevralgi etter akutt HZ i ca. **20**%

En 76 år, tidligere frisk, mann med HZ

Akutt HZ, V1 + V2; voldsomme smerter **8-10**/10

- ➢innlagt kommunal akutt overvåkingsavdeling
  - ➢fikk aciklovir(Tbl. Zovirax 800 mg x 5 dgl)
  - ➢og amitriptylin (Sarotex) 25 mg dgl,
- ➢Pforte+Ibux hjalp bare litt (ansvarlig lege ikke tilgjengelig!).
- ➢Skrev seg ut pga u-utholdelige smerter:
  - ➢Fikk hjelp av fast(?)-lege: OxyContin 10 mg x 3 (++?) dgl
- ➢Obstipasjon! Urinretensjon! →Urosepsis
- ➢→ Intensivavdeling: Diverse komplikasjoner.

Overlevde, men med **post-herpes nevralgi**



Fra Wikipedia

Hva kunne vært gjort bedre?

Forebygge med vaksine mot herpes zoster!

Forebygge opioid-obstipasjon (Movendig/Targiniq)!

Eldre menn har **risiko for urinretensjon** av opioid!

Ikke forskriv amitriptylin (Sarotex) →svimmel/sedert+fall-risiko

Amitriptylin (Sarotex) skal **IKKE** forskrives til eldre (over 65 + år)

→trett, ortostase, svimmel→fare for →fall

Dworkin et al. Pain 2007

Varicella-Zosta Virus (VZV)-vaksine (**Zostavax**) **til alle over 60-år?**

Zostavax (levende,svekket virus) vaksinasjon reduserer insidensen av akutt HZ med over 50% og postherpes nevralgi med mer enn 60%

In **Scotland** HZ-vaccine (Zostavax) is **offered free**
and persons >60 y are urged to accept the vaccine,
→ Health care system saves a large amount compared with a unvaccinated population

New Herpes Zoster vaccine (Shingrix) should be offered to elderly adults

Neuzil KM, Griffin MR. **Preventing Shingles and Its Complications in Older Persons** (Editorial)N ENGL J MED 2016;375:1079-80.

A.L. Cunningham et al. Efficacy of the Herpes Zoster **Subunit Vaccine** in Adults,70 Years of Age or Older. NEJM 2016;376:1019 (**Shingrix**)

Persons > 50 years: 97% protection against acute HZ

Persons > 70 years: **91% protection** against acute HZ

(n=139 009)

88% protection against postherpetic nevralgic pain among the few who did have acute HZ.

(I Norge: Må søke om registrerings-fritak)

Bare få utvalgte med innsikt og god økonomi tar HZ-vaksine i Norge

- Ingen regner med å få HZ
- men opp til 4% (økende med alder) får HZ
- HZ-vaksine lite kjent
- HZ-vaksine er dyr (Shingrix er2500 NOK x 2)

(Kjenner bare 4 personer som er vaksinert)

68 years man with chronic low back pain

His GP prescribed paracetamol and tramadol

Tramadol dose gradually increased to 500(++?)mg daily

Pain as before, complained of severe constipation,

not sleeping well, dysphoric/anxious, poor memory.

Tramadol was tapered and discontinued after 6 months

(+clonidine 25 mcg x 1-3d- but dizzy!):

Back-pain as before.

Feeling better, socially active, libido returned.

"I have my head back and my wife has her husband back"

Opioid-abstinens og Antidepressiva-abstinens når tramadol seponeres

Opioid-abstinens

- Motorisk urolig/myoclone rykninger
- Akathisia
- Engstelig, panikk
- Nedstemt
- Søvnproblem
- Svette-hyperhidrose
- Nesedrypp, tåreflod
- Diare, mageknip
- Kvalme
- Mydriasis

Antidepressiva-abstinens

- "Rest leg syndrom"
- Parestesier
- Engstelig
- Panikk-angst
- Forvirring
- Delusions/Hallusinasjoner
- Paranoia

Miotto K et al. Trends in tramadol. AnesthAnalg Dec 1st, 2016

NEWS

NICE updates antidepressant guidelines to reflect severity and length of withdrawal symptoms

Gareth Iacobucci

The BMJ

The National Institute for Health and Care Excellence has amended its guidelines[1] on depression to recognise the severity and length of antidepressant withdrawal symptoms.

press ahead with withdrawal services and a helpline for those who have become dependent on these and other prescribed drugs."

Hovedproblem ved medikamentell behandling av eldre med smerter

Smalt terapeutisk vindu av

- analgetika (morfin/kodein/oksykodon)og
- antihyperalgetika (amitriptylin**!**, gabapentin)

Smertelindring begrenses av bivirkninger som

sedasjon og svimmelhet → farlig hos eldre

→ snubler i gulvteppe→ fallskader,

typisk er collum-fractur

(en katastrofe → "begynnelsen på slutten")

Hvorfor er smertebehandling vanskeligere hos eldre ?

Egentlig samme prinsipp som for yngre voksne, men co-morbiditeter og polyfarmaci til disse gjør farmakologisk behandling "krevende"

Noen vanlige problem:

1. Alder-relaterte nyre-problem hos alle eldre og gamle

   →**akumulering av medikament som skilles ut renalt: pregabalin (Lyrica)**

2. Efflux-transporteren, Permeability-Para-glycoprotein (**P**gp) i BBB er mindre effektiv hos eldre og særlig hos gamle

3. →**Perifert active droger slipper inn i CNS, e.g. naloxegol, loperamide**

4. Multiple medikament-interaksjoner, noen velkjente og mange vi ikke var klar over (pga for lite kunnskap!)

Flere eksempler:

PPIgruppen (lanzoprazol) øker Moventig (naloxegol) inne i CNS og utløser opioid-abstinens

Imodium (loperamide – et potent opioid) slipper gjennom BBB hos eldre og gir typiske subjektive morfin-effekter

Ukjent for mange at NSAID-interaksjoner kan gi akutt nyresvikt: **"Triple-whammy acute renal failure"**

Complex interplay among the effects of

1. NSAIDs,
2. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor antagonists (ARAs),
3. and diuretics

Enda ett lærerikt tilfelle av feilbehandlet kronisk smerte hos en **eldre kvinne**

og et eksempel på en økende gruppe pasienter til Avd for smertebehandling, OUS:

Rydde opp i feilbehandla smertepasienter……

75yo rullestol-bundet **lady** med uttalte ryggsmerter og neuropatisk legg-smerter

Medisinering:

- Transdermal fentanyl 100 µg/h (=720 mg oral morphine/24 h)
- Diclofenac (Voltaren) 150 mg daily.
- Pregabalin (Lyrica) 450 mg/daily
- PPI (lanzoprazol) 60 mg/daily
- Amitriptylin 50 mg
- Acetylsalicylic acid 75 mg/daily
- Atorvastatin (Lipitor)40 mg/daily
- Bumetanid (Burinex) 1 mg/daily

➢ **To store problem**:

1. Uttalt opioid-indusert mage- og tarm-dysfunksjon(**OiBD)** med uttalt **cardialgi** og **obstipasjon** (PPI & laxatives –ineffective)
2. **Uttalt sedation**, **sover** (“nodding”)mesteparten av 24 hrs, og **sosialt isolert**.

Behandling av hennes OiBD – obstipasjon og cardialgi:

Forskrevet **naloxegol** –(Moventig)

som er en **p**erifert **a**ktiv **m**y-**o**pioid **r**eceptor **a**ntagonist (**PAMORA**):

Advart om at hun måtte være i nærheten av do når hun tok første Moventig (naloxegol) tabletten på 25 mg.

→Hun hadde en "voldsom" **tarm-tømming** (not all in WC)

Men,

Hun fikk også uttalt **opioid-abstinens symptom, og mer smerte:**

Hvordan kan det forklares?

Why is naloxegol a PAMORA?

Naloxegol is a PEGylated **naloxone** molecule where a polyethylene-glycol moiety is attached to make a **very large molecule** that should ensure that it does not get into the brain.

Not a good explanation……

Permeability glycoprotein= **Pgp**

is an **efflux transporter – transports "toxins"** out of cells against concentration gradients

A protein of the cell membrane that pumps toxins out of cells.

It is a defence mechanism against harmful substances.

Pgp is extensively distributed and expressed:

- **in the capillary endothelial cells of the blood–brain barrier where it pumps "toxins" out of CNS back into the capillaries.**

- in the intestinal epithelium where it pumps xenobiotics (such as toxins or drugs) back into the intestinal lumen,
- in liver cells where it pumps them into bile ducts,
- in the cells of the proximal tubule of the kidney where it pumps them into urine-conducting ducts,

P-glycoprotein = **Permeability** glycoprotein= **Pgp** = Multidrug resistance protein 1 (MDR1)

An important protein of the cell membrane that pumps many foreign substances out of cells.

It is an ATP-dependent efflux pump with broad substrate specificity.

It exists in animals, fungi and bacteria and likely evolved as a defence mechanism against harmful substances.

Pgp is extensively distributed and expressed:

- in the intestinal epithelium where it pumps xenobiotics (such as toxins or drugs) back into the intestinal lumen,
- in liver cells where it pumps them into bile ducts,
- in the cells of the proximal tubule of the kidney where it pumps them into urine-conducting ducts,
- **in the capillary endothelial cells composing the blood–brain barrier where it pumps "toxins" back into the capillaries**.

Why is naloxegol a PAMORA?

Naloxegol is a substrate for Permeability$_{glycoprotein}$-(P$_{gp}$)

- P$_{gp}$ keeps naloxegol outside the BBB

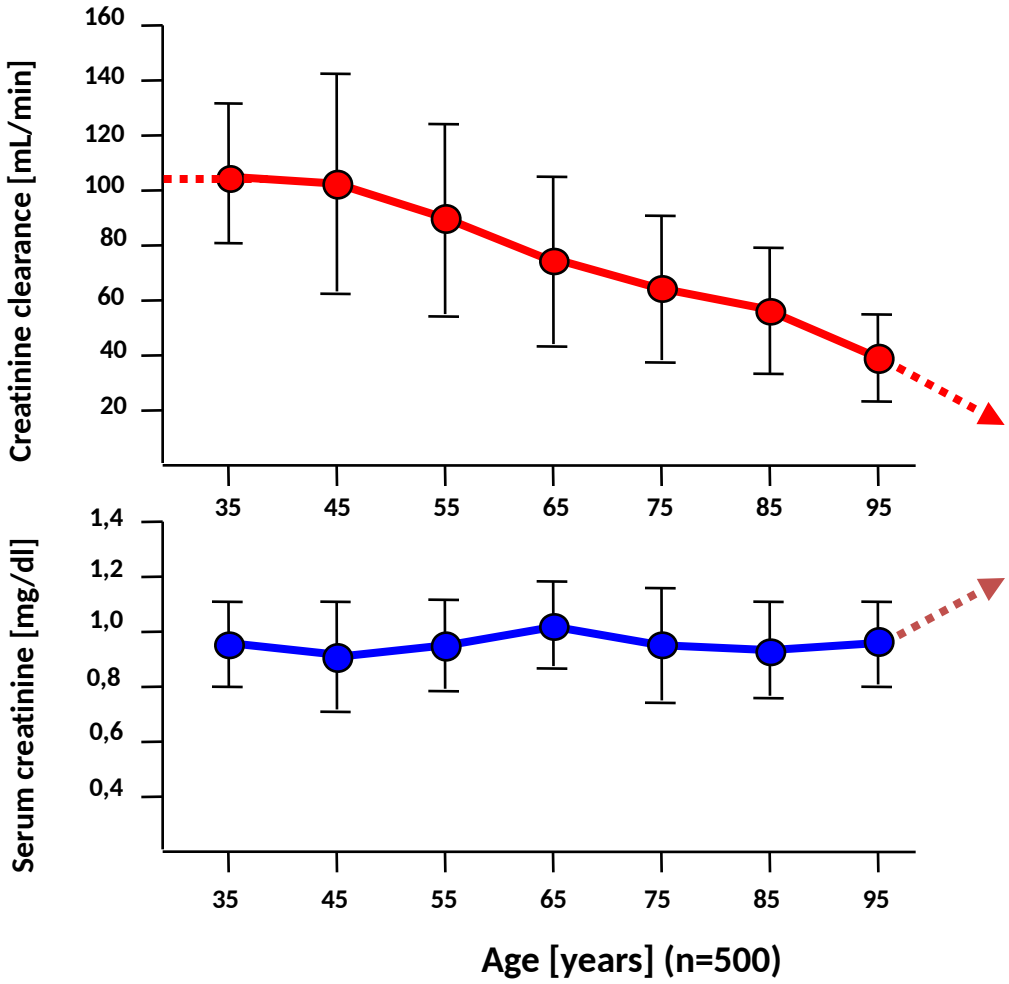
<u>Some reasons Ppg is not able to keep naloxegol outside the BBB</u>

- **P$_{gp}$** is reduced in **elderly** persons
- **Renal** failure down-regulates **P$_{gp}$**
- Co-medications may be **inhibitors** of Pgp

Elderly patients with reduced renal function:

Not enough P$_{gp}$ to keep all naloxegol molecules outside the BBB – the Blood Brain Barrier

Age-dependent renal impairment not well estimated from serum creatinine



Rate of decline:

1 mL/min per year of life after the 40th year of age

"Creatinine-blind range"

Mühlberg W et al. Gerontology 1999;45:243-53.

Common pharmacological inhibitors of Permeability-glycoprotein (P_{gp})

lansoprazole, omeprazole and other proton-pump inhibitors

amiodarone, azithromycin, captopril,

clarithromycin, cyclosporin, colchicine, diltiazem, erythromycin, felodipine,

nifedipine, paroxetine, piperine,

quercetin, **quinidine**, quinine, reserpine, ritonavir, sertraline, tariquidar, tamoxifen and verapamil.

(**Imodium** (loperamide) and quinidine → strong opioid-agonist effect in the CNS)

Solhaug V, Molden E. Individual variability in clinical effect and tolerability of opioid analgesics. Importance of drug interactions and pharmacogenetics. **Scand J Pain** 2017

Was she taking any inhibitors of Pgp's pumping of naloxegol to outside of BBB?

- Fentanyl patch 100 µg/h
- Pregabalin (Lyrica) 450 mg/daily
- Diclofenac (Voltaren) 150 mg daily (for several years)
- **Lanzoprazol** 60 mg/daily
- Burinex (bumetanid) 1 mg for leg-oedema
- Atorvastatin (Lipitor)40 mg/daily
- Acetylsalicylic acid 75 mg/daily

Several problems with her co-medications!

- Renal failure (?caused by diclofenac 150 mg/d for years)

  But: her eGFR creatinine = 58 ml/min/1.73m2

This 75 yrs wheelchair-bond lady had a low muscle mass – and creatinine was not an appropriate measurement for kidney function

Renal failure (aggravated by diclofenac 150 mg/d for years)

eGFR creatinine = 58 ml/min/1.73m2

eGFR cystatin C = 32 ml/min/1.73m2

Cystatin C estimate of GFR in elderly: www.egfr.se

Cystatin C is a peptide from all nucleated cells.

The **musle-mass independent** **cystatin C** serum concentrations for estimating renal function in **children and** **frail elderly patients** developed by Anders Grub, University of Lund, Sweden.

See www.egfr.se

Stevens LA et al. Estimating GFR using Serum **Cystatin C** Alone and in Combination with Serum Creatinine. Am J Kidney Dis. 2008;51:395-406.

Lyrica **450 mg**/day and **renal** impairment caused the extreme sedation in this 75 y patient

Diclofenac 150 mg/d taken for several years contributed to her severe renal impairment.

Lyrica was reduced to 150 mg/day, serum concentration of pregabalin reduced from **75** to **15** micromol/L

and she **“woke up”**

Buprenorphine not excreted by the kidneys and causes less endocrine disturbances

Converted to **transmucosal buprenorphine**

Temgesic sublingual tablets 0.4 mg, 2 x 4 = 3.2 mg/day

She is now **awake** with good **pain relief** and less **OiBD**

According to **CDC** (Centers for Disease Control and Prevention, Atlanta, GA, USA, Ma 2014 (email: Mbohm @cdc.gov)

3.2 mg buprenorphine sublingual = 32?/90? mg morphine orally →with better effect on her back-pain.

Buprenorphine has less effect on **androgen** hormone

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- Burinex (bumetanid) 1 mg for leg-oedema?

- Renal failure (aggravated by diclofenac 150 mg/d for years)

  eGFR creatinine = 58 ml/min/1.73m2

  eGFR cystatin c = 32 ml/min/1.73m2

  Several problems with her co-medications!

She had been on several drugs that caused adverse effects

Fentanyl transcutaneous patch 100 µg/h (=720 mg oral morphine/d) converted to

sublingual buprenorphine 3.2 mg/d (=32/90?mg oral morphine/d)

Pregabalin 450 mg/daily (reduced to 150 mg)

Diclofenac (Voltaren) 150 mg daily (discontinued)

Lanzoprazol 60 mg/daily (reduced to 15 mg/d)

Atorvastatin (Lipitor)40 mg/d (causes muscle pain--discontinued)

Amitriptylin 50 mg (anticholinergic and sedative--discontinued)

Enda et «interessant» tilfelle

Loperamid (Immodium) kept out of CNS by effluxtransporter Pgp

70 yrs patient with LBP and PPP (persisten pelvic pain)

On OxyContin 10 mg bid (+?)→OiGIDF

Complained of cardialgia→ on a PPI

Complained of diarea (?) («**obstipasjons-diare**»)

Used Immodium several days/wk to stop «diarea»

This stopped «diarea» and relieved her LBP, but not her PersistentPelvicPain

On exam: Massive content in rectum, «full» colon

What to do?

98 yrs man with **severe claudiactio intermit**, and acute L2-3 **prolapsed disc** with radicular pain, reduced strength in thigh muscles of left leg: Rx.: paracetamol + oxycodone + prednisolon + **amitriptylin 10 mg (dizzy!).**

He had been on dabigatran (**Pradaxa**) after a minor stroke a few years ago

$eGFR_{creatinine}$ about **50 ml**/min (he is not using his legs much)

$eGFR_{cystatinC}$ only **22 ml**/min

Dabigatran excreted by kidneys; is contraindicated if eGFR< 30 ml/min/1.7m2

He fell, hit the front of his scull and right shoulder → profuse bleeding

Dabigatran was changed to apixaban (Eliquis)

Atorvastatin (Lipitor) that causes muscle-pain was **discontinued** (LDL =1.2)

In small children and elderly (>75yrs): cystatin C in serum→ correct estimates of renal function (eGFR)

For his LBP: Prednisolon 20 mg → Tapered and DC I løpet av 14 dager.

Alvorlige bivirkninger av antikolinerge medikament til eldre og gamle

AntiCholinergic drugs cause unpleasant sedation; cognitive dysfunction; muscle-dysfunction; aggravate pain

Strong anticholinergic drugs

Atropine

Scopolamine

Alimemazine (Valergan)

Amitriptylin (Sarotex)

Clozapin (Leponex)

Doksepin (Sinequan)

Moderate anticholinergic drugs

Klorpromazine

Nortriptylin (Noritren)

Kvetiapin (Seroquel)

Benzodiazepines

Z-hypnotica

All **sedative antihistamines**

Some opioids, e.g. fentanyl

The Burden of Anticholinergic drugs→ increased risk of dementia

Memory-loss; hallucinations; agitation; unclear; agitated; delirium

Sedation→”sleep”→ not-refreshing sleep

Mydriasis (bella-donna)**, accommodation-paresis** → **unclear vision**

Motoric restless→myoclonic twitching → misdiagnosed as”epileptic”

Cardiac effects: Tachyarrhythmia's

Xerostomia

Urinary retention

OBS: Increased risk of dementia

(Gray SL, Hanlon JT. *BMJ* 2018;361:k1722)

Anticholinergic drugs and increased risk of dementia in older adults

Should we be concerned?

Gray SL, Hanlon JT. *BMJ* 2018;361:k1722 (Published 25 April 2018)

Anticholinergic drugs prevent acetylcholine from binding to muscarinic and nicotinic receptors, have numerous **adverse** effects, **especially in older adults**.

Anticholinergics, **used by 10-27% of older adults**, for overactive bladder, seasonal allergies, and depression.

They can cause temporary **impairment in cognition**, reduced attention and memory, longer reaction time.

Evidence now show that they **increase risk of dementia**, especially

- **anticholinergic antidepressants,**
- **antiparkinsonian drugs,**
- **drugs to treat urinary incontinence.**

Richardson K et al: Anticholinergic drugs and risk of dementia. BMJ 2018;361:k1315

Richardson K et al:
Anticholinergic drugs and risk of dementia; a case control study.
BMJ 2018;361:k1315
15 000 cases and 86 000 controls

WHAT THIS STUDY ADDS

Antidepressant, urological, and antiparkinson drugs with definite anticholinergic activity are linked to future dementia incidence, with associations persisting up to 20 years after exposure

Gastrointestinal and cardiovascular anticholinergic drugs are not positively associated with later dementia incidence

Amitriptylin (Sarotex) should **NOT** be prescribed for those > 65 + years

→ **sedated, orthostatic, dizziness**

→ **risk of →fall**

Elderly who fall→increased mortality

(Nortriptylin a bit better?)

Dworkin et al. Pain 2007

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In small children and elderly (>75yrs): cystatin C in serum→ correct estimates of renal function (eGFR)

Viktigste «take home message»

WHO(2o15):Healthy aging – what can we do?

- Skaff deg en god utdanning
- Ikke røke tobakk
- Bruk svært lite alkohol
- Sunn livsstil senest fra 30-års alder
- Behandle høgt blodtrykk allerede i “middle age”
- Diet med fisk og grønnsaker (“Mediterranean diet”)
- **Vær fysisk aktiv, mentalt aktiv, og sosialt aktiv**
- Høre-apparat er viktig
- **Hold din partner sunn og glad.**
- Keep your partner healthy and happy.

Stor takk!