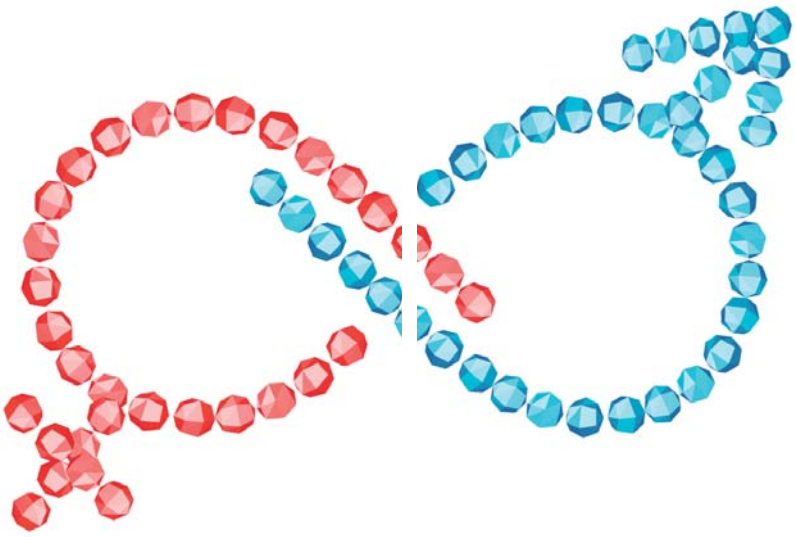

2016

Kjønnsforskjeller i effekter og bivirkninger av legemidler

Systematisk litteratursøk med sortering

folkehelseinstituttet

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Key messages

The Norwegian Directorate of Health commissioned The Knowledge Centre in the Norwegian Institute of Public Health to do a systematic search for systematic reviews and sorting of any possibly relevant abstracts on gender differences in effects and adverse events of drugs.

Methods

We searched for published and ongoing systematic reviews in several electronic databases from 2011 until June 2016. Two researchers independently identified possibly relevant references and evaluated relevance according to the inclusion criteria.

Results

- We identified 4415 references. Of these, 103 were possibly relevant.
- We sorted the references according to diagnosis and type of medication. We sorted the references into these groups:
    - Diabetes (5)
    - Cardiovascular diseases (33)
        - Antithrombotics (8)
        - Antiplatelet drugs (9)
        - Lipid-lowering medications (11)
        - Other drugs for cardiovascular diseases (5)
    - Cancer (14)
    - Psychological diseases and addiction (20)
        - Antidepressants (10)
        - Other psychiatric medication (10)
    - Pain/sedation (4)
    - Nicotine addiction (9)
    - Other diseases (18)

Title:
Gender differences in effects and adverse events of drugs

Type of publication:

Systematic reference list

A systematic reference list is the result of a search for relevant literature according to a specific search strategy. The references resulting from the search are then grouped and presented with their abstracts.

Doesn't answer everything:

- No critical evaluation of study quality
- No analysis or synthesis of the studies
- No recommendations

Publisher:

Norwegian Knowledge Centre for the Health Services

Updated:

Last search for studies:
June 2016.

Hovedfunn

Kunnskapssenteret i Folkehelseinstituttet fikk i oppdrag av Helsedirektoratet å utføre et systematisk litteratursøk med påfølgende sortering av mulig relevante publikasjoner om kjønnsforskjeller i effekter og bivirkninger av legemidler.

Metode

Vi søkte etter publiserte og pågående systematiske oversikter i flere elektroniske databaser fra 2011 til juni 2016. To forskere gikk uavhengig av hverandre gjennom identifiserte referanser og vurderte relevans med tanke på inklusjonskriteriene.

Resultater

- Vi identifiserte totalt 4415 referanser. Av disse var 103 mulig relevante.
- Vi sorterte referansene etter diagnoser og medikamentgrupper. Vi sorterte referansene i disse gruppene:
  - Diabetes (5)
  - Hjerte-/karsykdommer (33)
    - Antitrobotiske legemidler (8)
    - Blodplatehemmere (9)
    - Serum-lipidsenkende midler (11)
    - Andre legemidler ved hjerte-/karsykdommer (5)
  - Kreftsykdommer (14)
  - Psykiske lidelser (20)
    - Antidepressiver (10)
    - Andre psykofarmaka (10)
  - Smerte/sedasjon (4)
  - Nikotinavhengighet (9)
  - Andre sykdommer/tilstander (18)

Tittel:

Kjønnsforskjeller i effekt og bivirkninger av legemidler

Publikasjonstype:

Systematisk litteratursøk med sortering

Systematisk litteratursøk med sortering er resultatet av å
- søke etter relevant litteratur ifølge en søkestrategi og
- eventuelt sortere denne litteraturen i grupper presentert med referanser og vanligvis sammendrag

---

Svarer ikke på alt:

- Ingen kritisk vurdering av studienes kvalitet
- Ingen analyse eller sammenfatning av studiene
- Ingen anbefalinger

Hvem står bak denne publikasjonen?

Kunnskapssenteret har gjennomført oppdraget etter forespørsel fra Helsedirektoratet.

Når ble litteratursøket utført?

Søk etter studier ble avsluttet juni 2016.

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Forord

Nasjonalt kunnskapssenter for helsetjenesten i Folkehelseinstituttet fikk i oppdrag fra Helsedirektoratet v/Hege Wang å finne litteratur om kjønnsforskjeller i effekter og bivirkninger av legemidler.

Prosjektgruppen har bestått av:

- Hilde H. Holte, seniorforsker, Kunnskapssenteret
- Vigdis Underlang, forsker, Kunnskapssenteret
- Gyri Hval Straumann, bibliotekar, Kunnskapssenteret

Signe Flottorp	Gunn E. Vist	Hilde H. Holte
Avdelingsdirektør	*Seksjonsleder*	*Prosjektleder*

Innledning

Bakgrunn

Helsedirektoratet skal, på oppdrag av Helse- og omsorgsdepartementet, sette i gang arbeidet med en kunnskapsoppsummering med fokus på kvinnehelse som vil kunne bidra til å belyse kjønnsrelaterte forskjeller med hensyn til effekter og bivirkninger av legemidler.

Helsedirektoratet ønsket å bruke ulike datakilder for å belyse problemstillingen. Et systematisk litteratursøk ville være et godt utgangspunkt for dette arbeidet.

Produktet skal benyttes i en rapport til Helse- og omsorgsdepartementet som vil sette fokus på kvinnehelse og bidra til å belyse kjønnsrelaterte forskjeller i effekter og bivirkninger av legemidler.

Metode

Litteratursøking

Vi søkte systematisk etter litteratur i følgende databaser:

- Embase
- Medline
- PsycINFO
- Cochrane Library (CDSR, DARE, HTA)
- Epistemonikos

Vi har også sett gjennom pågående prosjekter hos SBU, og søkt etter pågående systematiske oversikter i PROSPERO og POP-databasen.

Forskningsbibliotekar Gyri Hval Straumann planla og utførte samtlige søk. Den fullstendige søkestrategiene er presentert i vedlegg til denne rapporten. Søk etter studier ble avsluttet 7. juni 2016.

Inklusjonskriterier

Populasjon:	Kvinner og menn, uavhengig av alder
Tiltak:	Legemidler
Sammenlikning:	Ikke aktuelt
Utfall:	Kjønnsspesifikke effekter og bivirkninger
Studiedesign	Systematiske oversikter
Språk:	Alle

Artikkelutvelging

To forskere (Hilde H. Holte og Vigdis Underland) gikk gjennom alle titler og sammendrag for å vurdere relevans i henhold til inklusjonskriteriene. Vurderingene gjorde vi uavhengig av hverandre og sammenlignet i etterkant. Vi diskuterte oss fram til enighet.

Utvelging av litteratur ble kun gjort basert på tittel og sammendrag. Vi bestilte ikke fulltekst av oversiktene.

Sortering

Til grunnlaget for sorteringen valgte vi å først sortere etter diagnosegruppe. Hvis det var flere enn tre referanser for en diagnosegruppe ble disse samlet under en felles overskrift. For diagnosegruppene hjerte/karsykdommer og psykiske lidelser var referansene mange, og vi sortere disse i undergrupper. Vi brukte Norsk Legemiddelhåndbok som grunnlag for å inndele i ulike medikamentklasser.

Styrker og svakheter ved litteratursøk med sortering

Ved litteratursøk gjennomfører vi systematiske litteratursøk for en gitt problemstilling. Resultatene fra søket blir i sin helhet overlevert oppdragsgiver, eller vi kan gjennomgå søkeresultatet før overleveringen og sortere ut ikke-relevante artikler. Dette gjøres basert på tittel og eventuelt sammendrag. Artiklene innhentes ikke i fulltekst. Det gjør at vi kan ha inkludert titler som ville vist seg ikke å være relevante ved gjennomlesning av fulltekst. Vi benytter kun databaser for identifisering av litteratur og kan derfor ha gått glipp av potensielt relevante studier. Andre måter å identifisere studier på, som søk i referanselister, kontakt med eksperter på fagfeltet og upublisert litteratur, er ikke utført i dette oppdraget. Vi gjennomfører ingen kvalitetsvurdering av artiklene.

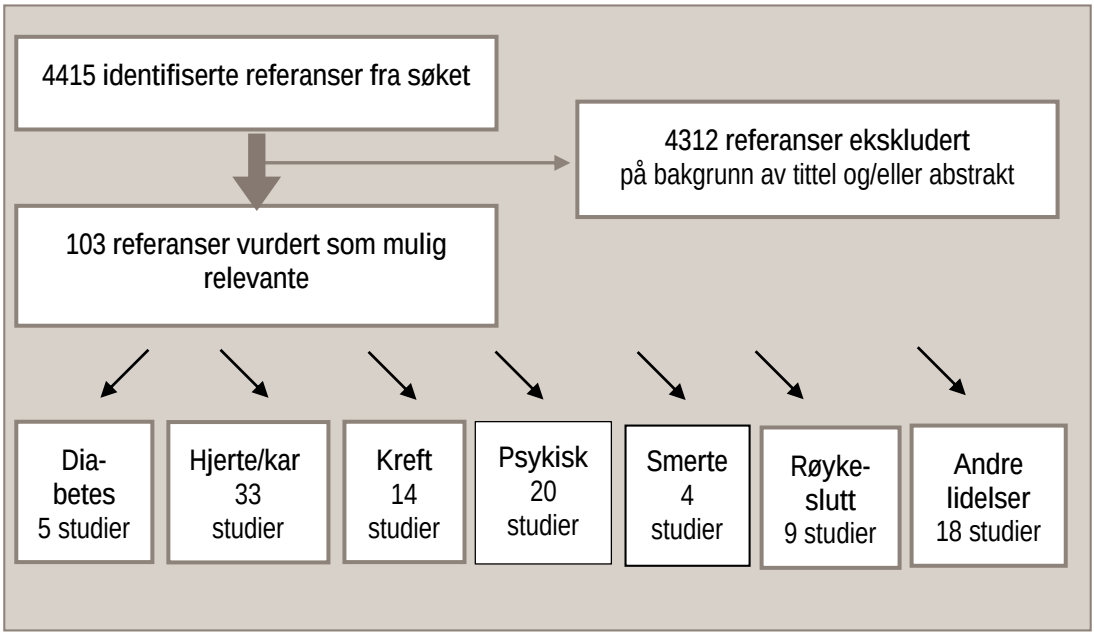
Ved en full forskningsoppsummering ville vi ha innhentet artiklene i fulltekst for endelig vurdering opp mot inklusjonskritene. Vi ville så ha kvalitetsvurdert inkluderte studier i henhold til våre sjekklister, og sammenstilt og diskutert resultatene.

Resultat

Resultat av søk

Søket resulterte i 4415 referanser. Vi vurderte 103 av de identifiserte referansene til å være mulig relevante i henhold til inklusjonskriteriene.

Hovedårsaken til eksklusjon var at publikasjonene, vurdert på grunnlag av sammendragene, ikke belyste kjønnsforskjeller i effekt av legemidler eller at sammendragene i oversiktsartiklene ikke redegjorde for en systematisk metode for identifisering av litteratur.



Figur 1. Flytskjema over identifisert litteratur

Resultat av sorteringen

De mulig relevante referansene ble sortert i syv kategorier ut fra diagnosegruppe (se figur 1). Vi presenterer referansene fordelt i kategoriene og alfabetisk etter førsteforfatter. Vi oppgir forfattere, tittel på publikasjonen, publikasjonssted og sammendrag av artikkelen slik de fremkom i de elektroniske databasene.

Diabetes

I alt identifiserte vi fem relevante referanser.

Arnetz L, Ekberg NR, Alvarsson M. **Sex differences in type 2 diabetes: focus on disease course and outcomes**. Diabetes Metab Syndr Obes 2014;7:409-420.

Abstract: BACKGROUND: Women with type 2 diabetes (T2D) are less likely to reach the goals for hemoglobin A1c compared with men, and have higher all-cause mortality. The risk of cardiovascular disease is elevated among both men and women with T2D, however, the risk has declined among men over recent years while it remains stationary in women. Reasons for these sex differences remain unclear, and guidelines for diabetes treatment do not differentiate between sexes. Possible causes for varying outcome include differences in physiology, treatment response, and psychological factors. This review briefly outlines sex differences in hormonal pathophysiology, and thereafter summarizes the literature to date on sex differences in disease course and outcome.
METHODS: Systematic searches were performed on PubMed using "sex", "gender", and various glucose-lowering therapies as keywords. Earlier reviews are summarized and results from individual studies are reported. Reference lists from studies were used to augment the search.
RESULTS: There is an increased risk of missing the diagnosis of T2D when screening women with only fasting plasma glucose instead of with an oral glucose tolerance test. The impact of various risk factors for complications may differ by sex. Efficacy and side effects of some glucose-lowering drugs differ between men and women. Men with T2D appear to suffer more microvascular complications, while women have higher morbidity and mortality in cardiovascular disease and also fare worse psychologically.
CONCLUSION: Few studies to date have focused on sex differences in T2D. Several questions demand further study, such as whether risk factors and treatment guidelines should be sex-specific. There is a need for clinical trials designed specifically to evaluate sex differences in efficacy and outcome of the available treatments.

Kautzky-Willer A, Kosi L, Lin J, Mihaljevic R. **Gender-based differences in glycaemic control and hypoglycaemia prevalence in patients with type 2 diabetes: results from patient-level pooled data of six randomized controlled trials**. Diabetes, Obesity & Metabolism 2015;17(6):533-540.

Abstract: AIMS: To determine the impact of gender on glycaemic control and hypoglycaemia in insulin-naive patients with type 2 diabetes (T2DM).
METHODS: Data were pooled from six randomized clinical trials of insulin glargine or NPH insulin in insulin-naive, inadequately controlled patients. Female [n=1251; mean glycated haemoglobin (HbA1c) level 8.99%, age 56.91years, diabetes duration 9.84years] and male patients (n=1349; mean HbA1c 8.9%, age 57.47years, diabetes duration 10.13years) were started on and treated with insulin glargine or NPH insulin for 24-36weeks. HbA1c and fasting blood glucose levels, percent achieving HbA1c target of <7% and insulin dose change were recorded.
RESULTS: For both men and women, HbA1c levels were significantly reduced over time (p<0.001); a significantly greater HbA1c reduction was observed in men than in women (-1.36 vs. -1.22; p=0.002). Significantly fewer women achieved target HbA1c of <7% (p<0.001). At the study end, women had a significantly higher insulin dose/kg than men (0.47 vs. 0.42U/kg; p<0.001). The incidence rates of severe and severe nocturnal hypoglycaemia were significantly higher in women (3.28% vs. 1.85%; p<0.05 and 2.24% vs. 0.59%; p<0.001, respectively). Women were more likely to experience severe hypoglycaemia [odds ratio (OR) 1.80; 95% confidence interval (CI) 1.08, 3.00; p=0.02] and severe nocturnal hypoglycaemia (OR: 3.80; 95% CI 1.72, 8.42; p=0.001).
CONCLUSIONS: These observations confirm studies that found a smaller improvement in HbA1c and greater hypoglycaemia in women during insulin treatment. Physicians should be aware of the need to determine and closely monitor dosing, particularly in women, to optimize the balance between glycaemic control and hypoglycaemia

risk.Copyright © 2015 The Authors. Diabetes, Obesity and Metabolism published by John Wiley & Sons Ltd.

Saberi S, Esfandiari NH, MacEachern MP, Tan MH. **Detemir plus aspart and glulisine induced lipoatrophy: 2015 literature review and report of a new case**. Clinical Diabetes and Endocrinology 2015;1 (1) (no pagination)(10).

Abstract: Background: In the first and only literature review, conducted in 2009, of human insulin analog- induced lipoatrophy, there were 12 published cases, including 1 with aspart, 1 with detemir, 1 with NovoMix 30 and none with detemir plus aspart. It is perceived that insulin analog induced-lipoatrophy is increasing. We conducted a 2015 literature review of published reports of lipoatrophy induced by aspart, detemir, detemir plus aspart, and NovoMix30. We also report a new case of detemir plus aspart and glulisine induced lipoatrophy.
Methods: Our focused literature searches (limited to 1995-2014) in PubMed, Embase, and Web of Science, using a combination of insulin analog and lipoatrophy terminology, was conducted in early January 2015.
Results: From the 520 unique citations there were 33 (from 13 papers and 9 abstracts) lipoatrophy cases induced by detemir (n=5), aspart (n=21), detemir plus aspart (n=4) and NovoMix 30 (n=3), representing 30 new cases since 2009. Many of these reported cases were females (76%), had type 1 diabetes mellitus (T1DM) (94%) and were in young persons (61%). A 41-year-old T1DM woman developed lipoatrophy on her upper thighs, arms and abdomen 14months after injecting detemir plus aspart at the same sites. Later on, after a year on continuous subcutaneous insulin infusion (CSII) using aspart and then glulisine, she developed lipoatrophy at the infusion sites. When CSII insulin was switched to lispro she did not develop lipoatrophy after 10months. Meanwhile, the original lipoatrophy sites significantly improved.
Conclusions: Our literature review uncovered 30 new published cases of aspart, detemir, aspart plus detemir and NovoMix 30-induced lipoatrophy since 2009. The largest increase in cases was in aspart- induced lipoatrophy. Recent surveys showed most rapid acting insulin analog-induced lipoatrophy were associated with CSII. In our review of the reported cases, 85.7% cases of aspart-induced lipoatrophy were associated with CSII. As in previous reports, we showed lipoatrophy was more common in females, T1DM and young persons. Our patient may be the 5th published case of detemir plus aspart-induced lipoatrophy and possibly the first case report of glulisine induced lipoatrophy. She believed both detemir plus aspart and glulisine induced the lipoatrophy.

Shemesh E, Rudich A, Harman-Boehm I, Cukierman-Yaffe T. **Effect of intranasal insulin on cognitive function: A systematic review**. Journal of Clinical Endocrinology and Metabolism 2012;97(2):366-376.

Abstract: Aim: Epidemiological and mechanistic studies raised the possibility that cognitive function may be affected by brain responses to insulin. We systematically reviewed and analyzed existing clinical trials thatassessedthepotential beneficial effectsofintranasal insulinadministrationoncognitive functions. Methods: Interventional studies measuring changes in cognitive functions in response to intranasal insulin were retrieved and included if they were in English and assessed cognitive functions before and after treatment. Cohen's effect size was calculated to allow comparison between studies. Results: Eight studies (328 participants) were analyzed. No significant side effects of intranasal insulin administration were reported. Seven studies included healthy subjects' response to intranasal insulin, and three evaluated the cognitive effect among patients with minimal cognitive impairment or overt Alzheimer's disease. In healthy people, Cohen's effect size calculations suggest that only 160 IU/d intranasal insulin induced potential beneficial effects. Although females, when compared head-to-head, exhibited greater improvements in cognitive tests than men, the composite analysis of all included studies did not support this trend. Among cognitively impaired patients, only lower doses of insulin were assessed, and 20 IU revealed potential beneficial effects on cognitive functions. This was significant in a single study assessing long-term

intranasal insulin administration, whereas acute administration of 20 IU intranasal insulin tended to show a beneficial effect on immediate recall in Apo epsilon4(-), but not Apo epsilon4(+), patients.
Conclusions: The current limited clinical experience suggests potential beneficial cognitive effects of intranasal insulin. Analyses provide clinical considerations for future research aimed at elucidating whether intranasal insulin may be used to improve cognitive functions. Copyright © 2012 by The Endocrine Society.

Zhu ZN, Jiang YF, Ding T. **Risk of fracture with thiazolidinediones: An updated meta-analysis of randomized clinical trials**. Bone 2014;68:115-123.

Abstract: Objective: The use of thiazolidinediones (TZDs) has been associated with increased fracture risk. We performed a comprehensive literature review and meta-analysis to estimate the risk of fractures with TZDs.
Methods: We searched MEDLINE, Embase and the Cochrane Database, from inception to May 2014. We included all randomized trials that described the risk of fractures or changes in bone mineral density (BMD) with TZDs. We pooled data with odds ratios (ORs) for fractures and the weighted mean difference in BMD. To assess heterogeneity in results of individual studies, we used Cochran's Q statistic and the I² statistic.
Results: We included 24,544 participants with 896 fracture cases from 22 randomized controlled trials. Meta-analysis showed that the significantly increased incidence of fracture was found in women (OR. =. 1.94; 95%CI: 1.60-2.35; P<. 0.001), but not in men (OR. =. 1.02; 95%CI: 0.83-1.27; P=. 0.83). For women, the fracture risk was similar in rosiglitazone (OR. =. 2.01; 95%CI: 1.61-2.51; P<. 0.001) and pioglitazone (OR. =. 1.73; 95%CI: 1.18-2.55; P=. 0.005) treatment and appeared to be similar for participants aged <. 60. years old (OR. =. 1.89; 95%CI: 1.51-2.36; P<. 0.001) and aged >. 60. years old (OR. =. 2.07; 95%CI: 1.51-2.36; P<. 0.001). There was a non-significant trend towards increased risk of fractures in different cumulative durations of TZD exposure. TZD treatment was also associated with significant changes in BMD among women at the lumbar spine(weighted mean difference: -. 0.49%, 95%CI: -. 0.66% to -. 0.32%; P<. 0.001), the femoral neck (weighted mean difference: -. 0.34%, 95%CI: -. 0.51% to -. 0.16%; P<. 0.001) and the hip(weighted mean difference: -. 0.33%, 95%CI: -. 0.52% to -. 0.14%; P<. 0.001).
Conclusions: Our results suggest that TZD treatment is associated with an increased risk of fractures in women, effects of rosiglitazone and pioglitazone are similar, fracture risk is independent of age and fracture risk has no clear association with duration of TZD exposure.

Hjerte-/karsykdommer

I alt identifiserte vi 33 relevante referanser.

Tabell 1: *Antall oversiktsartikler sortert etter medikamentklasse*

Tiltak	Antall referanser: 33
Antitrombotiske legemidler	8
Blodplatehemmere	9
Serum-lipidsenkende midler	11
Andre legemidler ved hjerte/karsykdommer	5

Antitrombotiske legemidler

Ahmad Y, Lip GY, Apostolakis S**. New oral anticoagulants for stroke prevention in atrial fibrillation: impact of gender, heart failure, diabetes mellitus and paroxysmal atrial fibrillation.** Expert Review of Cardiovascular Therapy 2012;10(12):1471-1480.

Abstract: The emergence of new oral anticoagulants is a major development in cardiovascular medicine. In this overview, we sought to evaluate the impact of gender, heart failure, paroxysmal atrial fibrillation (AF) and diabetes on stroke prevention with warfarin and the new oral anticoagulants by conducting a semisystematic review and meta-analysis including 44,563 patients in recent contemporary Phase III trials. The new oral anticoagulants were superior to warfarin irrespective of gender or the presence of diabetes. For nonparoxysmal AF, event rates are similar with warfarin and new anticoagulants. There is some suggestion of the benefit of new oral anticoagulants in patients with paroxysmal AF. For patients without heart failure, the new drugs are superior, whereas in patients with evidence of heart failure the new drugs were similar to warfarin. In conclusion, new oral anticoagulants are better than warfarin irrespective of gender or the presence of diabetes mellitus. Patients with heart failure and nonparoxysmal AF seem not to gain additional prognostic benefit from new anticoagulants.

Alotaibi GS, Almodaimegh H, McMurtry MS, Wu C**. Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism?** A sex-based meta-analysis. Thrombosis Research 2013;132(2):185-189.

Abstract: INTRODUCTION: Bleeding complications occur more frequently in women than men in clinical trials of warfarin and thrombolytics. It is unknown whether these sex-related differences exist for new oral anticoagulants, including dabigatran, rivaroxaban, and apixaban. To determine whether women suffer more bleeding complications with these agents, we conducted a systematic review and meta-analysis of randomized controlled trials on new oral anticoagulants for venous thromboembolism (VTE).
MATERIALS AND METHODS: Medline, Embase, and the Cochrane-controlled trial register on the Cochrane library were searched to identify studies that evaluated novel oral anticoagulants versus any comparator, and reported outcomes, including major bleeding and recurrent VTE, stratified by sex. No language restrictions were applied. Studies were evaluated according to a priori inclusion criteria and critically appraised using established internal validity criteria. Pooled relative risk was estimated using a random effects model.
RESULTS: Eight studies were eligible, comprising 9417 patients. There was no difference in the primary efficacy outcome of recurrent VTE between men and women [Relative Risk (RR) 1.02, 95% confidence interval (CI) 0.74-1.39]. However, men had less major bleeding with novel oral anticoagulants compared to women [RR 0.79, 95% CI 0.66-0.97, p=0.03]. All-cause mortality was not reported by sex in any of the studies.
CONCLUSION: Women suffer more bleeding complications than men when receiving novel oral anticoagulants for VTE. Future clinical trials should report outcomes stratified by sex, and further studies are needed to investigate the clinical impact of this sex-related safety difference.Copyright © 2013.

Dentali F, Sironi AP, Gianni M, Orlandini F, Guasti L, Grandi AM, et al. Gender Difference in Efficacy and Safety of Nonvitamin K **Antagonist Oral Anticoagulants in Patients with Nonvalvular Atrial Fibrillation or Venous Thromboembolism: A Systematic Review and a Meta-Analysis of the Literature**. Seminars in Thrombosis and Hemostasis 2015;41(7):774-787.

Abstract: Introduction Limited information exists on gender-related differences in the safety and efficacy of non-vitamin K antagonist oral anticoagulants (NOACs). Aim of

the StudyTo assess the safety and efficacy of direct oral anticoagulants (DOACs)/NOACs in men and women pooling data from randomized controlled trials on the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF) and on the acute and extended treatment of venous thromboembolism (VTE). Methods: MEDLINE and EMBASE databases were searched up to June 2014. The efficacy outcome was defined as the prevention of stroke and systemic embolism (AF studies), or as the prevention of recurrent VTE or VTE-related death (VTE studies). The safety outcome was defined as the occurrence of major and/or clinically relevant nonmajor bleeding. Differences in the efficacy and safety outcomes were expressed as risk ratio (RR) with pertinent 95% confidence intervals (95% CI).
Results: A total of 13 studies (> 100,000 patients) were included. DOACs appeared to have a similar efficacy and safety compared with vitamin K antagonists in female and male patients treated for nonvalvular AF and acute VTE. In the extended treatment of VTE NOACs had a RR of bleeding of 4.97 (95% CI 1.06, 23.41) in males and 1.33 (95% CI 0.63, 2.83) in females compared with placebo (subgroup difference chi-square test: 2.25, p=0.13).
Conclusions: No gender-related difference in the efficacy and safety of NOACs in patients with AF or acute VTE was found. A trend toward an increased risk of bleeding in male patients as compared with female patients was detected in the extended treatment of VTE.

Fabbian F, De Giorgi A, Tiseo R, Zucchi B, Manfredini R. **Reducing the risk of venous thromboembolism using apixaban - Patient perspectives and considerations. Should more attention be given to females?** Patient Preference and Adherence 2016;10:73-80.

Abstract: Background: New oral anticoagulant agents, such as apixaban, rivaroxaban, dabigatran, or endoxaban, have recently become for patients an alternative option to conventional treatment in the therapy of venous thromboembolism (VTE). Thus, we aimed to review the available information on adverse events (AEs) of apixaban compared to conventional therapy (heparin or vitamin K antagonists) in randomized controlled trials (RCTs) on patients treated for VTE, with a particular attention to sex subgroups.
Methods: An electronic search in MEDLINE and Embase was performed by using the keywords "apixaban" and "venous thromboembolism". All RCTs focused on apixaban in the treatment and prevention of VTE were evaluated for the presence of AEs. AEs were classified as serious, bleeding, and cause of discontinuation. Moreover, we also searched by using the keywords "gender" and "venous thromboembolism" and "anticoagulants".
Results: Considering all subjects enrolled in the eleven RCTs as a whole to investigate the occurrence of AEs, we extrapolated an events/subjects rate of 57.8% for AEs (6,445/11,144), 7.7% for serious AEs (975/12,647), 9.1% for bleeding events (1,229/13,454), and 3.2% for discontinuation of apixaban (421/13,039). The percentage of AEs was lower in subjects treated with apixaban than in those treated with conventional VTE therapy (53% vs 56.3%, respectively). However, only one study provided data on separate analysis by sex of either efficacy or safety of apixaban.
Conclusion: Under the patient's perspective, apixaban could represent a good choice in the treatment of VTE, due to its pharmacological, economical, and safety profile. These positive aspects are certainly present in both sexes, since the available studies include a correct percentage of women, but data with separate analyses by sex are extremely limited. Future clinical trials should include in their results on clinical impact and outcomes a stratification by sex, and studies aimed to evaluate possible sex-related differences for these drugs should be strongly encouraged.

Lapner S, Cohen N, Kearon C. **Influence of sex on risk of bleeding in anticoagulated patients: a systematic review and meta-analysis**. Journal of Thrombosis & Haemostasis 2014;12(5):595-605.

Abstract: BACKGROUND: The risk of bleeding on anticoagulation varies between patients. It is uncertain whether sex influences this risk.

OBJECTIVES: To determine if the risk of major bleeding differs between men and women receiving anticoagulation for atrial fibrillation or venous thromboembolism(VTE).
METHODS: We searched MEDLINE, EMBASE, and Cochrane databases, and relevant conference proceedings, until February 2013. We included randomized controlled trials and prospective cohort studies of patients on therapeutic anticoagulation for atrial fibrillation or VTE. Two reviewers independently extracted data. The relative risk of bleeding in men compared to women was pooled using a random-effects model.
RESULTS: Forty-two studies including 94 293 patients were eligible; 78 044 patients (83%) had atrial fibrillation; 16 156 patients (17%) had VTE; 37 250 patients were women (40%); and there were 4147 major bleeds. The relative risk of major bleeding for men vs. women was 1.02(95% CI 0.95-1.10; P = 0.27 for heterogeneity). The relative risk was 1.02 (95% CI 0.95-1.09) in patients with atrial fibrillation and 0.80 (95% CI 0.65-0.98) in patients with VTE (P = 0.03 for subgroup effect). Type of anticoagulant,intensity of anticoagulation, and whether patients began or were already established on anticoagulants at enrollment did not influence the relative risk of major bleeding in men compared to women.
CONCLUSIONS: The risk of major bleeding on anticoagulation appears to be the same in men and women, particularly if patients have atrial fibrillation. This finding is less certain for patients with VTE, in whom the risk of bleeding may be marginally lower in men compared to in women.

Loffredo L, Violi F, Perri L. **Sex related differences in patients with acute venous thromboembolism treated with new oral anticoagulants.** A meta-analysis of the interventional trials. Int J Cardiol 2016;212:255-258.

Abstract: BACKGROUND: Gender differences have been reported in patients with acute VTE treated with antithrombotic drugs.
OBJECTIVE: To address the relationship between gender and new oral anticoagulants (NOACs), we performed a meta-analysis to evaluate the incidence of recurrent VTE and major plus clinically relevant non-major bleedings in males and females, with acute VTE, treated with NOACs over the treatment period.
DESIGN: Systematic review and meta-analysis of double blind randomized controlled trials (RCTs). DATA SOURCES: MEDLINE, Cochrane Library of Clinical Trials (up to September 2015). STUDY SELECTION: RCTs that compared the beneficial and harmful effects of NOAC drugs (apixaban, dabigatran, edoxaban and rivaroxaban).
DATA EXTRACTION: Three authors abstracted data. Study-specific risk ratios (RR) were combined using random-effects model.
RESULTS: Nine studies including 16,372 patients were selected. No significant difference for the incidence of recurrent VTE was found between men and women. Compared to men, women had a higher incidence of major bleedings plus clinically relevant minor bleedings (5.3% and 7.9% respectively; RR: 0.635; 95% CI: 0.54-0.74; p<0.001). The subgroup analysis showed a significant gender difference in incidence of major bleedings and clinically relevant minor bleedings only for Edoxaban (RR: 0.52; 95% CI: 0.42-0.64; p<0.001).
CONCLUSIONS: This meta-analysis showed, compared to men, a higher risk of bleeding in women with acute VTE treated with NOACs. Future trials should evaluate the effect of gender on bleeding in patients with acute VTE treated with NOACs.

Meseguer E, Mazighi M, Labreuche J, Arnaiz C, Cabrejo L, Slaoui T, et al. **Outcomes of intravenous recombinant tissue plasminogen activator therapy according to gender: a clinical registry study and systematic review.** Stroke 2009;40(6):2104-2110.

Abstract: BACKGROUND AND PURPOSE: The natural history of stroke is worse in women than in men. Controversial data have been published on the efficacy of thrombolysis with recombinant tissue plasminogen activator (rtPA) according to gender. We evaluated gender differences in the efficacy and safety outcomes of intravenous rtPA using a clinical registry and systematic review.

METHODS: Since January 2002, we collected baseline characteristics and efficacy and safety outcomes for patients who received intravenous rtPA in our center. We performed a systematic PubMed literature search for previous observational studies that examined gender effects on outcomes after intravenous rtPA treatment.
RESULTS: No gender difference in good outcome at 3 months (adjusted OR for women, 1.41; 95% CI, 0.76 to 2.60) and in 90-day mortality (adjusted OR, 1.38; 95% CI, 0.59 to 3.19) was found in our registry. We identified 16 studies that evaluated the gender effect among intravenous rtPA-treated patients. None of these studies supported a gender difference in favorable outcome, and one suggested an increased risk of mortality in men. In unadjusted partial meta-analysis in 4074 women and 5840 men including our registry data, we found a trend toward a lower risk of symptomatic intracranial hemorrhage in women (crude OR, 0.87; 95% CI, 0.68 to 1.10).
CONCLUSIONS: These results suggest no gender difference in outcome among patients treated with intravenous rtPA.

Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. **Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants**. Am J Cardiol 2014;113(3):485-490.

Abstract: Studies comparing gender-specific outcomes in patients with atrial fibrillation (AF) have reported conflicting results. Gender differences in cerebrovascular accident/systemic embolism (CVA/SE) or major bleeding outcomes with novel oral anticoagulant (NOAC) use are not known. The goal of this analysis was to perform a systematic review and meta-analysis evaluating gender differences in residual risk of CVA/SE and major bleeding outcomes in patients with nonvalvular AF treated with either warfarin or NOAC. Sixty-four randomized studies were identified using keywords "gender," "AF," and "CVA." Using the Preferred Reporting Items for Systemic Reviews and Meta-analysis method, 6 studies met criteria for inclusion in this meta-analysis. CVA/SE and major bleeding outcomes were separately analyzed in cohorts receiving warfarin and NOAC agents, comparing men with women. Women with AF taking warfarin were at a significantly greater residual risk of CVA/SE compared with men (odds ratio 1.279, 95% confidence interval 1.111 to 1.473, Z = -3.428, p = 0.001). No gender difference in residual risk of CVA/SE was noted in patients with AF receiving NOAC agents (odds ratio 1.146, 95% confidence interval 0.97 to 1.354, p = 0.109). Major bleeding was less frequent in women with AF treated with NOAC. In conclusion, women with AF treated with warfarin have a greater residual risk of CVA/SE and an equivalent major bleeding risk, whereas those treated with NOAC agents deemed superior to warfarin are at equivalent residual risk of CVA/SE and less major bleeding risk compared with men. These results suggest an increased net clinical benefit of NOAC agents compared with warfarin in treating women with AF.

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Adelman EE, Lisabeth L, Brown DL. **Gender differences in the primary prevention of stroke with aspirin**. Women's Health 2011;7(3):341-353.

Abstract: Aspirin is used to prevent ischemic stroke and other types of cardiovascular disease. Seven trials of aspirin focusing on the effectiveness of primary prevention of stroke and other cardiovascular events have been performed, but three of these did not include women. Data from these trials, and one meta-analysis, suggest that aspirin prevents myocardial infarction in men and stroke in women, although the findings in women were driven by the results of a single large study, and a subsequent meta-analysis did not find a gender difference. The reasons for the possible gender differences in aspirin's effectiveness are not entirely clear. © 2011 Future Medicine Ltd.

Berger JS, Bhatt DL, Cannon CP, Chen Z, Jiang L, Jones JB, et al. **The relative efficacy and safety of clopidogrel in women and men a sex-specific collaborative meta-analysis**. J Am Coll Cardiol 2009;54(21):1935-1945.

Abstract: OBJECTIVES: This study sought to investigate the efficacy and safety of clopidogrel in women and men.
BACKGROUND: Previous analyses have shown sex-based differences in response to several antiplatelet medications. Little is known about the efficacy and safety of clopidogrel in women and men.
METHODS: This study performed a meta-analysis of all blinded randomized clinical trials comparing clopidogrel and placebo (CURE [Clopidogrel in Unstable Angina to Prevent Recurrent Events], CREDO [Clopidogrel for the Reduction of Events During Observation], CLARITY-TIMI 28 [Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction 28], COMMIT [Clopidogrel and Metoprolol in Myocardial Infarction Trial], and CHARISMA [Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance] trials), involving a total of 79,613 patients, of whom 30% were women. The relative efficacy and safety of clopidogrel at reducing cardiovascular events (cardiovascular death, myocardial infarction [MI], or stroke) in women and men was estimated using random-effects modeling.
RESULTS: Overall, clopidogrel was associated with a highly significant 14% proportional reduction in the risk of cardiovascular events (odds ratio [OR]: 0.86; 95% confidence interval [CI]: 0.80 to 0.93), with no significant differences in treatment effect between women and men. Among the 23,533 women enrolled, there were fewer cardiovascular events in the clopidogrel group compared with the placebo group (11.0% vs. 11.8%; OR: 0.93; 95% CI: 0.86 to 1.01). In women the risk reduction with clopidogrel seemed to be greatest for MI (OR: 0.81; 95% CI: 0.70 to 0.93), with the effects on stroke (OR: 0.91; 95% CI: 0.69 to 1.21) or total death (OR: 0.99; 95% CI: 0.90 to 1.08) not statistically significant. Among the 56,091 men enrolled, there were fewer cardiovascular events in those receiving clopidogrel compared with placebo (7.8% vs. 9.0%; OR: 0.84; 95% CI: 0.78 to 0.91), and the risk reduction was significant for MI (OR: 0.83; 95% CI: 0.76 to 0.92), stroke (OR: 0.83; 95% CI: 0.71 to 0.96), and total death (OR: 0.91; 95% CI: 0.84 to 0.97). Clopidogrel increased the risk of major bleeding in both women (OR: 1.43; 95% CI: 1.15 to 1.79) and men (OR: 1.22; 95% CI: 1.05 to 1.42).
CONCLUSIONS: Clopidogrel reduces the risk of cardiovascular events in both women and men.

Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. **Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials**. Jama 2006;295(3):306-313.

Abstract: CONTEXT: Aspirin therapy reduces the risk of cardiovascular disease in adults who are at increased risk. However, it is unclear if women derive the same benefit as men. OBJECTIVE: To determine if the benefits and risks of aspirin treatment in the primary prevention of cardiovascular disease vary by sex.
DATA SOURCES AND STUDY SELECTION: MEDLINE and the Cochrane Central Register of Controlled Trials databases (1966 to March 2005), bibliographies of retrieved trials, and reports presented at major scientific meetings. Eligible studies were prospective, randomized controlled trials of aspirin therapy in participants without cardiovascular disease that reported data on myocardial infarction (MI), stroke, and cardiovascular mortality. Six trials with a total of 95 456 individuals were identified; 3 trials included only men, 1 included only women, and 2 included both sexes.
DATA EXTRACTION: Studies were reviewed to determine the number of patients randomized, mean duration of follow-up, and end points (a composite of cardiovascular events [nonfatal MI, nonfatal stroke, and cardiovascular mortality], each of these individual components separately, and major bleeding).
DATA SYNTHESIS: Among 51,342 women, there were 1285 major cardiovascular events: 625 strokes, 469 MIs, and 364 cardiovascular deaths. Aspirin therapy was associated with a significant 12% reduction in cardiovascular events (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.79-0.99; P = .03) and a 17% reduction in stroke (OR, 0.83; 95% CI, 0.70-0.97; P = .02), which was a reflection of reduced rates of ischemic stroke (OR, 0.76; 95% CI, 0.63-0.93; P = .008). There was no significant effect on MI or cardiovascular mortality. Among 44,114 men, there were 2047 major cardiovascular events: 597 strokes, 1023 MIs, and 776 cardiovascular deaths. Aspirin therapy was associated with a significant 14% reduction in cardiovascular events (OR, 0.86; 95% CI,

0.78-0.94; P = .01) and a 32% reduction in MI (OR, 0.68; 95% CI, 0.54-0.86; P = .001). There was no significant effect on stroke or cardiovascular mortality. Aspirin treatment increased the risk of bleeding in women (OR, 1.68; 95% CI, 1.13-2.52; P = .01) and in men (OR, 1.72; 95% CI, 1.35-2.20; P<.001). CONCLUSIONS: For women and men, aspirin therapy reduced the risk of a composite of cardiovascular events due to its effect on reducing the risk of ischemic stroke in women and MI in men. Aspirin significantly increased the risk of bleeding to a similar degree among women and men.

Boersma E, Harrington RA, Moliterno DJ, White H, Théroux P, Van de Werf F, et al. **Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials**. Lancet 2002;359(9302):189-198.

Abstract: BACKGROUND: Platelet glycoprotein IIb/IIIa inhibitors have been shown to reduce cardiac complications in patients undergoing percutaneous coronary intervention. The clinical efficacy of these drugs in acute coronary syndromes, however, is still unclear. We did a meta-analysis of all large randomised trials designed to study the clinical efficacy and safety of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes who were not routinely scheduled to undergo early coronary revascularisation.
METHODS: Inclusion criteria were: randomisation of patients with acute coronary syndromes but without persistent ST elevation; comparison of a glycoprotein IIb/IIIa inhibitor with placebo or control therapy; non-recommendation of early coronary revascularisation during study-drug infusion; and enrollment of at least 1000 patients. Data on individual patients were obtained from all participants in these trials.
FINDINGS: Six trials, enrolling 31402 patients, fulfilled the inclusion criteria. 30 days after randomisation, 3530 (11.2%) patients died or developed a myocardial infarction. At 30 days, a 9% reduction in the odds of death or myocardial infarction was seen with glycoprotein IIb/IIIa inhibitors compared with placebo or control (10.8% [1980/18297] vs 11.8% [1550/13105] events; odds ratio 0.91 [95% CI 0.84-0.98]; p=0.015). The relative treatment benefit was similar in subgroups of patients according to important clinical baseline characteristics; hence, the absolute treatment benefit was largest in high-risk patients. An unexpected and significant interaction was seen between sex and allocated treatment, with a treatment benefit in men (0.81 [0.75-0.89] but not in women (1.15 [1.01-1.30]). However, once patients were stratified according to troponin concentration, there was no evidence of a sex difference in treatment response, and a risk reduction was seen in men and women with raised troponin concentrations. Major bleeding complications were increased by glycoprotein IIb/IIIa inhibitors (2.4% [445/18297] vs 1.4% [180/13105]; p<0.0001), but intracranial bleeding was not (16 [0.09%] vs 8 [0.06%]; p=0.40).
INTERPRETATION: Glycoprotein IIb/IIIa inhibitors reduce the occurrence of death or myocardial infarction in patients with acute coronary syndromes not routinely scheduled for early revascularisation. The event reduction is greatest in patients at high risk of thrombotic complications. Treatment with a glycoprotein IIb/IIIa inhibitor might therefore be considered especially in such patients early after admission, and continued until a decision about early coronary revascularisation has been made.

Cuzick J, Thorat MA, Bosetti C, Brown PH, Burn J, Cook NR, et al. **Estimates of benefits and harms of prophylactic use of aspirin in the general population**. Annals of Oncology 2015;26(1):47-57.

Abstract: Background: Accumulating evidence supports an effect of aspirin in reducing overall cancer incidence and mortality in the general population. We reviewed current data and assessed the benefits and harms of prophylactic use of aspirin in the general population. Methods: The effect of aspirin for site-specific cancer incidence and mortality, cardiovascular events was collated from the most recent systematic reviews. Studies identified through systematic Medline search provided data regarding harmful effects of aspirin and baseline rates of harms like gastrointestinal bleeding and peptic ulcer. Results: The effects of aspirin on cancer are not apparent until at least 3 years after the start of use, and some benefits are sustained for several years after cessation in

long-term users. No differences between low and standard doses of aspirin are observed, but there were no direct comparisons. Higher doses do not appear to confer additional benefit but increase toxicities. Excess bleeding is the most important harm associated with aspirin use, and its risk and fatality rate increases with age. For average-risk individuals aged 50-65 years taking aspirin for 10 years, there would be a relative reduction of between 7% (women) and 9% (men) in the number of cancer, myocardial infarction or stroke events over a 15-year period and an overall 4% relative reduction in all deaths over a 20-year period. Conclusions: Prophylactic aspirin use for a minimum of 5 years at doses between 75 and 325 mg/day appears to have favourable benefit-harm profile; longer use is likely to have greater benefits. Further research is needed to determine the optimum dose and duration of use, to identify individuals at increased risk of bleeding, and to test effectiveness of Helicobacter pylori screening-eradication before starting aspirin prophylaxis.

Sutcliffe P, Connock M, Gurung T, Freeman K, Johnson S, Kandala NB, et al. **Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: A systematic review and overview of reviews**. Health Technology Assessment 2013;17(43):V-252.

Abstract: Background: Prophylactic aspirin has been considered to be beneficial in reducing the risks of heart disease and cancer. However, potential benefits must be balanced against the possible harm from side effects, such as bleeding and gastrointestinal (GI) symptoms. It is particularly important to know the risk of side effects when aspirin is used as primary prevention - that is when used by people as yet free of, but at risk of developing, cardiovascular disease (CVD) or cancer. In this report we aim to identify and re-analyse randomised controlled trials (RCTs), systematic reviews and meta-analyses to summarise the current scientific evidence with a focus on possible harms of prophylactic aspirin in primary prevention of CVD and cancer.
Objectives: To identify RCTs, systematic reviews and meta-analyses of RCTs of the prophylactic use of aspirin in primary prevention of CVD or cancer. To undertake a quality assessment of identified systematic reviews and meta-analyses using meta-analysis to investigate study-level effects on estimates of benefits and risks of adverse events; cumulative meta-analysis; exploratory multivariable meta-regression; and to quantify relative and absolute risks and benefits.
Methods: We identified RCTs, meta-analyses and systematic reviews, and searched electronic bibliographic databases (from 2008 September 2012) including MEDLINE, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, NHS Centre for Reviews and Dissemination, and Science Citation Index. We limited searches to publications since 2008, based on timing of the most recent comprehensive systematic reviews.
Results: In total, 2572 potentially relevant papers were identified and 27 met the inclusion criteria. Benefits of aspirin ranged from 6% reduction in relative risk (RR) for all-cause mortality [RR 0.94, 95% confidence interval (CI) 0.88 to 1.00] and 10% reduction in major cardiovascular events (MCEs) (RR 0.90, 95% CI 0.85 to 0.96) to a reduction in total coronary heart disease (CHD) of 15% (RR 0.85, 95% CI 0.69 to 1.06). Reported pooled odds ratios (ORs) for total cancer mortality ranged between 0.76 (95% CI 0.66 to 0.88) and 0.93 (95% CI 0.84 to 1.03). Inclusion of the Women's Health Study changed the estimated OR to 0.82 (95% CI 0.69 to 0.97). Aspirin reduced reported colorectal cancer (CRC) incidence (OR 0.66, 95% CI 0.90 to 1.02). However, including studies in which aspirin was given every other day raised the OR to 0.91 (95% CI 0.74 to 1.11). Reported cancer benefits appeared approximately 5 years from start of treatment. Calculation of absolute effects per 100,000 patient-years of follow-up showed reductions ranging from 33 to 46 deaths (all-cause mortality), 60-84 MCEs and 47-64 incidents of CHD and a possible avoidance of 34 deaths from CRC. Reported increased RRs of adverse events from aspirin use were 37% for GI bleeding (RR 1.37, 95% CI 1.15 to 1.62), between 54% (RR 1.54, 95% CI 1.30 to 1.82) and 62% (RR 1.62, 95% CI 1.31 to 2.00) for major bleeds, and between 32% (RR 1.32, 95% CI 1.00 to 1.74) and 38% (RR 1.38, 95% CI 1.01 to 1.82) for haemorrhagic stroke. Pooled estimates of increased RR for bleeding remained stable across trials conducted over several decades. Estimates of absolute rates of harm from aspirin use, per 100,000 patient-years of follow-up, were 99-178 for non-trivial bleeds, 46-49 for major bleeds, 68-117 for GI

bleeds and 8-10 for haemorrhagic stroke. Meta-analyses aimed at judging risk of bleed according to sex and in individuals with diabetes were insufficiently powered for firm conclusions to be drawn. Limitations: Searches were date limited to 2008 because of the intense interest that this subject has generated and the cataloguing of all primary research in so many previous systematic reviews. A further limitation was our potential over-reliance on study-level systematic reviews in which the person-years of follow-up were not accurately ascertainable. However, estimates of number of events averted or incurred through aspirin use calculated from data in stu y-level meta-analyses did not differ substantially from estimates based on individual patient data-level meta-analyses, for which person-years of follow-up were more accurate (although based on less-than-complete assemblies of currently available primary studies).
Conclusions: We have found that there is a fine balance between benefits and risks from regular aspirin use in primary prevention of CVD. Effects on cancer prevention have a long lead time and are at present reliant on post hoc analyses. All absolute effects are relatively small compared with the burden of these diseases. Several potentially relevant ongoing trials will be completed between 2013 and 2019, which may clarify the extent of benefit of aspirin in reducing cancer incidence and mortality. Future research considerations include expanding the use of IPD meta-analysis of RCTs by pooling data from available studies and investigating the impact of different dose regimens on cardiovascular and cancer outcomes. Funding: The National Institute for Health Research Health Technology Assessment programme.

Temizhan A. **[Aspirin in cardiovascular prevention: does the approach differ by gender?]**. Anadolu Kardiyol Derg 2007;7 Suppl 2:2-4.

Abstract: Although aspirin is effective in the treatment of acute coronary syndrome and in the secondary prevention of cardiovascular disease among both men and women, its use in primary prevention remains controversial. The gender-specific meta-analysis demonstrates that the specific types of benefit of aspirin therapy differ between women and men in primary prevention. For primary prevention of cardiovascular disease in women, aspirin therapy significantly reduced the risk of the composite of cardiovascular events primarily by its effect on reducing the risk of stroke. In contrast, in men; aspirin therapy significantly reduced the risk of the composite of cardiovascular events predominantly by reducing the risk of myocardial infarction. The reasons for any sex-based differences in the efficacy of aspirin for primary prevention are unclear and require further exploration.

Thorat MA, Cuzick J. **Prophylactic use of aspirin: systematic review of harms and approaches to mitigation in the general population**. Eur J Epidemiol 2015;30(1):5-18.

Abstract: A careful assessment of benefits and harms is required to assess suitability of aspirin as a prophylactic public health measure. However, comprehensive population-level data on harms are lacking. We collected and synthesized age and sex-specific data on harms relevant to aspirin use in average-risk individuals aged 50 years or older. We conducted systematic literature searches to identify baseline rates of gastrointestinal (GI) bleeding, peptic ulcer, major extra-cranial bleeding, and case-fatality rates due to GI bleeding or peptic ulcer in general population. The magnitude of aspirin-associated increase, the prevalence and attributable risk of Helicobacter pylori infection on these events in aspirin users was also assessed. Baseline rates of major extracranial bleeding events and GI complications increase with age; an almost threefold to fourfold increase is observed from age 50-54 to 70-74 years. Low or standard-dose aspirin use increases GI bleeding events by 60% leading to an annual excess of 0.45 and 0.79 GI bleeding events per 1,000 women and men aged 50-54 years respectively. 5-10% of major GI complications are fatal; a clear age dependence--higher fatality in older individuals, is seen. Eradication of H. pylori infection before aspirin use could reduce the incidence of upper GI complications by 25-30%. GI complications are increased by about 60% due to aspirin use but are fatal only in a very small proportion of individuals younger than 70 years of age. Major bleeding events that are comparable in severity to cancer or

CVD, are infrequent. Screening and eradication of H. pylori infection could substantially lower aspirin-related GI harms.

Zhang C, Sun A, Zhang P, Wu C, Zhang S, Fu M, et al. **Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis**. Diabetes Res Clin Pract 2010;87(2):211-218.

Abstract: BACKGROUND: To systematically review trials concerning the benefit and risk of aspirin therapy for primary prevention of cardiovascular events in patients with diabetes mellitus.
iazMETHODS: We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials. Eligible studies were prospective, randomized controlled trials of aspirin therapy for primary cardiovascular prevention in patients with diabetes with follow-up duration at least 12 months.
RESULTS: 7 trials included 11,618 individuals with diabetes. Aspirin therapy was not associated with a statistically significant reduction in major cardiovascular events (relative risk [RR] 0.92, 95% confidence interval [CI] 0.83-1.02, p=0.11). Aspirin use also did not significantly reduce all-cause mortality (0.95, 95% CI 0.85-1.06; p=0.33), cardiovascular mortality (0.95, 95% CI 0.71-1.27; p=0.71), stroke (0.83, 95% CI 0.63-1.10; p=0.20), or myocardial infarction (MI) (0.85, 95% CI 0.65-1.11; p=0.24). There was no significant increased risk of major bleeding in aspirin group (2.46, 95% CI 0.70-8.61; p=0.16). Meta-regression suggested that aspirin agent could reduce the risk of stroke in women and MI in men.
CONCLUSIONS: In patients with diabetes, aspirin therapy did not significantly reduce the risk of cardiovascular events without an increased risk of major bleeding, and showed sex-specific effects on MI and stroke.

Serum-lipidsenkende midler

Abramson BL, Benlian P, Hanson ME, Lin J, Shah A, Tershakovec AM. **Response by sex to statin plus ezetimibe or statin monotherapy: a pooled analysis of 22,231 hyperlipidemic patients**. Lipids in Health & Disease 2011;10:146.

Abstract: BACKGROUND: Despite documented benefits of lipid-lowering treatment in women, a considerable number are undertreated, and fewer achieve treatment targets vs. men.
METHODS: Data were combined from 27 double-blind, active or placebo-controlled studies that randomized adult hypercholesterolemic patients to statin or statin+ezetimibe. Consistency of treatment effect among men (n = 11,295) and women (n = 10,499) was assessed and percent of men and women was calculated to evaluate the between-treatment ability to achieve specified treatment levels between sexes.
RESULTS: Baseline lipids and hs-CRP were generally higher in women vs. men. Between-treatment differences were significant for both sexes (all p < 0.001 except apolipoprotein A-I in men = 0.0389). Men treated with ezetimibe+statin experienced significantly greater changes in LDL-C (p = 0.0066), non-HDL-C, total cholesterol, triglycerides, HDL-C, apolipoprotein A-I (all p < 0.0001) and apolipoprotein B (p = 0.0055) compared with women treated with ezetimibe+statin. The odds of achieving LDL-C < 100 mg/dL, apolipoprotein B < 90 mg/dL and the dual target [LDL-C < 100 mg/dL & apoliprotein B < 90 mg/dL] was significantly greater for women vs. men and the odds of achieving hs-CRP < 1 and < 2 mg/L and dual specified levels of [LDL-C < 100 mg/dL and hs-CRP < 2 mg/L] were significantly greater for men vs. women. Women reported significantly more gall-bladder-related, gastrointestinal-related, and allergic reaction or rash-related adverse events (AEs) vs. men (no differences between treatments). Men reported significantly more CK elevations (no differences between treatments) and hepatitis-related AEs vs. women (significantly more with ezetimibe+simvastatin vs. statin).
CONCLUSIONS: These results suggest that small sex-related differences may exist in response to lipid-lowering treatment and achievement of specified lipid and hs-CRP levels, which may have implications when managing hypercholesterolemia in women.

Adams SP, Tsang M, Wright JM. **Lipid-lowering efficacy of atorvastatin**. Cochrane Database of Systematic Reviews 2015;3:CD008226.

Abstract: BACKGROUND: This represents the first update of this review, which was published in 2012. Atorvastatin is one of the most widely prescribed drugs and the most widely prescribed statin in the world. It is therefore important to know the dose-related magnitude of effect of atorvastatin on blood lipids.
OBJECTIVES: Primary objective To quantify the effects of various doses of atorvastatin on serum total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides in individuals with and without evidence of cardiovascular disease. The primary focus of this review was determination of the mean per cent change from baseline of LDL-cholesterol. Secondary objectives * To quantify the variability of effects of various doses of atorvastatin.* To quantify withdrawals due to adverse effects (WDAEs) in placebo-controlled randomised controlled trials (RCTs).
SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 11, 2013), MEDLINE (1966 to December Week 2 2013), EMBASE (1980 to December Week 2 2013), Web of Science (1899 to December Week 2 2013) and BIOSIS Previews (1969 to December Week 2 2013). We applied no language restrictions.
SELECTION CRITERIA: Randomised controlled and uncontrolled before-and-after trials evaluating the dose response of different fixed doses of atorvastatin on blood lipids over a duration of three to 12 weeks.
DATA COLLECTION AND ANALYSIS: Two review authors independently assessed eligibility criteria for studies to be included and extracted data. We collected information on withdrawals due to adverse effects from placebo-controlled trials.
MAIN RESULTS: In this update, we found an additional 42 trials and added them to the original 254 studies. The update consists of 296 trials that evaluated dose-related efficacy of atorvastatin in 38,817 participants. Included are 242 before-and-after trials and 54 placebo-controlled RCTs. Log dose-response data from both trial designs revealed linear dose-related effects on blood total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. The Summary of findings table 1 documents the effect of atorvastatin on LDL-cholesterol over the dose range of 10 to 80 mg/d, which is the range for which this systematic review acquired the greatest quantity of data. Over this range, blood LDL-cholesterol is decreased by 37.1% to 51.7% (Summary of findings table 1). The slope of dose-related effects on cholesterol and LDL-cholesterol was similar for atorvastatin and rosuvastatin, but rosuvastatin is about three-fold more potent. Subgroup analyses suggested that the atorvastatin effect was greater in females than in males and was greater in non-familial than in familial hypercholesterolaemia. Risk of bias for the outcome of withdrawals due to adverse effects (WDAEs) was high, but the mostly unclear risk of bias was judged unlikely to affect lipid measurements. Withdrawals due to adverse effects were not statistically significantly different between atorvastatin and placebo groups in these short-term trials (risk ratio 0.98, 95% confidence interval 0.68 to 1.40).
AUTHORS' CONCLUSIONS: This update resulted in no change to the main conclusions of the review but significantly increases the strength of the evidence. Studies show that atorvastatin decreases blood total cholesterol and LDL-cholesterol in a linear dose-related manner over the commonly prescribed dose range. New findings include that atorvastatin is more than three-fold less potent than rosuvastatin, and that the cholesterol-lowering effects of atorvastatin are greater in females than in males and greater in non-familial than in familial hypercholesterolaemia. This review update does not provide a good estimate of the incidence of harms associated with atorvastatin because included trials were of short duration and adverse effects were not reported in 37% of placebo-controlled trials.

Bangalore S, Messerli FH. **Statin therapy for secondary prevention: Is there a gender difference? Test for interaction in meta-analysis revisited**. American Journal of Cardiology 2012;110(10):1553-1554.

Bushnell CD, Griffin J, Newby LK, Goldstein LB, Mahaffey KW, Graffagnino CA, et al. **Statin use and sex-specific stroke outcomes in patients with vascular disease**. Stroke 2006;37(6):1427-1431.

Abstract: BACKGROUND AND PURPOSE: Although statins reduce the risk of stroke in patients with coronary heart disease, possible differing effects of statins on stroke outcomes based on sex remain uncertain. We investigated the relationships between statin use and sex-specific stroke incidence, severity, and mortality.
METHODS: Data from 3 trials of oral glycoprotein IIb/IIIa inhibitors (first and second Sibrafiban versus aspirin to Yield Maximum Protection from ischemic Heart events postacute cOroNary sYndromes [SYMPHONY] and Blockade of the glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion [BRAVO]) were pooled and stroke outcomes compared among 8191 baseline statin users versus 14,752 nonusers. Time-to-event data were modeled with proportional hazards regression. Stroke severity was assessed retrospectively with the Canadian Neurological Scale (CNS) based on records with scoreable neurological examinations.
RESULTS: A total of 217 subjects had strokes (0.95%). Statin users had a lower risk of stroke in unadjusted (hazard ratio [HR], 0.69; 95% CI, 0.51 to 0.92) and risk-adjusted models (HR, 0.72; 95% CI, 0.53 to 0.97). There was no difference in stroke mortality with statin use (P=0.8). CNS scores could be assigned to 106 of the subjects, with no difference in severity among statin users and nonusers (median CNS=10.5 in users versus CNS=9.75 in nonusers; P=0.14). Women had more severe strokes than men (median CNS=10.5 in men versus 9.5 in women; Poisson regression P=0.035). Women had more severe strokes after adjustment for statin use (P=0.03) and the combination of statin use, atrial fibrillation, and age (P=0.03).
CONCLUSIONS: In patients included in these clinical trials of oral glycoprotein IIb/IIIa inhibitors, statin use is associated with a reduced risk of stroke but not severity or mortality. Women had more severe strokes than men, a difference that was not explained by baseline characteristics or statin use.

Dale KM, Coleman CI, Shah SA, Patel AA, Kluger J, White CM. **Impact of gender on statin efficacy**. Curr Med Res Opin 2007;23(3):565-574.

Abstract: OBJECTIVE: To determine the impact of statin therapy on the combined endpoint of cardiovascular events in women and men separately.
RESEARCH DESIGN AND METHODS: A systematic literature search through May 2006 was conducted to identify randomized, controlled statin trials evaluating the gender specific incidence of cardiovascular events. Weighted averages were reported as relative risks (RRs) with 95% confidence intervals (CI) calculated via random-effects model.
MAIN OUTCOME MEASURES: The primary outcome measured was a composite endpoint of all cardiovascular events. Secondary outcomes measured included death, myocardial infarction (MI), and stroke.
RESULTS: Fifteen trials were included in this meta-analysis. Cardiovascular events were reduced in men (RR 0.76 [95% CI 0.70, 0.81]) and women (RR 0.79 [95% CI 0.69, 0.90]). Reductions in mortality, MI, and stroke predominantly contributed to the reduction in cardiovascular events in men taking statins. Women did not have a reduction in mortality or stroke, suggesting that the reductions in cardiac events may have been predominantly due to reductions in need for revascularization and/or unstable angina.
CONCLUSIONS: Statins reduced the risk of cardiovascular events in men and women, but women on statins may not have reductions in mortality and stroke like their male counterparts.

Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. **Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials**. Lancet 2015;385(9976):1397-1405.

Abstract: BACKGROUND: Whether statin therapy is as effective in women as in men is debated, especially for primary prevention. We undertook a meta-analysis of statin trials in the Cholesterol Treatment Trialists' (CTT) Collaboration database to compare the effects of statin therapy between women and men.
METHODS: We performed meta-analyses on data from 22 trials of statin therapy versus control (n=134,537) and five trials of more-intensive versus less-intensive statin therapy (n=39,612). Effects on major vascular events, major coronary events, stroke, coronary revascularisation and mortality were weighted per 1.0 mmol/L reduction in LDL cholesterol and effects in men and women compared with a Cox model that adjusted for non-sex differences. For subgroup analyses, we used 99% CIs to make allowance for the multiplicity of comparisons.
FINDINGS: 46,675 (27%) of 174,149 randomly assigned participants were women. Allocation to a statin had similar absolute effects on 1 year lipid concentrations in both men and women (LDL cholesterol reduced by about 1.1 mmol/L in statin vs control trials and roughly 0.5 mmol/L for more-intensive vs less-intensive therapy). Women were generally at lower cardiovascular risk than were men in these trials. The proportional reductions per 1.0 mmol/L reduction in LDL cholesterol in major vascular events were similar overall for women (rate ratio [RR] 0.84, 99% CI 0.78-0.91) and men (RR 0.78, 99% CI 0.75-0.81, adjusted p value for heterogeneity by sex=0.33) and also for those women and men at less than 10% predicted 5 year absolute cardiovascular risk (adjusted heterogeneity p=0.11). Likewise, the proportional reductions in major coronary events, coronary revascularisation, and stroke did not differ significantly by sex. No adverse effect on rates of cancer incidence or non-cardiovascular mortality was noted for either sex. These net benefits translated into all-cause mortality reductions with statin therapy for both women (RR 0.91, 99% CI 0.84-0.99) and men (RR 0.90, 99% CI 0.86-0.95; adjusted heterogeneity p=0.43).
INTERPRETATION: In men and women at an equivalent risk of cardiovascular disease, statin therapy is of similar effectiveness for the prevention of major vascular events. FUNDING: UK Medical Research Council, British Heart Foundation, Australian National Health and Medical Research Council, European Community Biomed Program.

Gutierrez J, Ramirez G, Rundek T, Sacco RL. **Statin therapy in the prevention of recurrent cardiovascular events: a sex-based meta-analysis**. Archives of Internal Medicine 2012;172(12):909-919.

Abstract: BACKGROUND: The effect of statins on the prevention of cardiovascular events is well demonstrated. Whether this protective effect is equal for women and men remains less well established. Our objective was to evaluate if statin therapy is equally effective in decreasing recurrent cardiovascular events in women and men.
DATA SOURCES: Randomized clinical trials were searched in PubMed using as indexing terms (statins OR cholesterol lowering medications) AND (cardiovascular events OR stroke OR myocardial infarction OR cardiovascular death).
STUDY SELECTION: We included randomized, double-blinded, placebo-controlled trials evaluating statins for secondary prevention of cardiovascular events. Studies with an open-label design and observational studies were excluded.
DATA EXTRACTION: The earliest citation was used to determine the characteristic of the studied population and the methodology. All subsequent citations corresponding to the trial were evaluated for outcome rates by sex.
DATA SYNTHESIS: Eleven trials representing 43,193 patients were included in the analysis. Overall, statin therapy was associated with a reduced risk of cardiovascular events in all outcomes for women (relative risk [RR], 0.81 [95% CI, 0.74-0.89]) and men (RR, 0.82 [95% CI, 0.78-0.85]). However, they did not reduce all-cause mortality in women vs men (RR, 0.92 [95% CI, 0.76-1.13] vs RR, 0.79 [95% CI, 0.720.87]) or stroke (RR, 0.92 [95% CI, 0.76-1.10] vs RR, 0.81 [95% CI, 0.72-0.92]).
CONCLUSIONS: Statin therapy is an effective intervention in the secondary prevention of cardiovascular events in both sexes, but there is no benefit on stroke and all-cause mortality in women.

Kim BH, Cho KI, Jang JS, Park YH, Je HG. **Efficacy and safety of statins for primary prevention of cardiovascular events in women and men: Systemic review and up-to-date meta-analysis**. Experimental and Clinical Cardiology 2014;20(1):1222-1227.

Abstract: Background: The aim of this study was to perform a meta-analysis comparing by gender the cardiovascular outcomes related to statin therapy in primary prevention including recent large trials.
Methods: A systematic search of medical literatures was performed to identify randomized placebo and standard-care- controlled endpoint trials of statins with sex-specific outcome data, which were reported from 1994 to April 2012. Summary estimates of relative risks (RRs) of the therapy were calculated by using a random-effects model for women and men without CVD.
Results: Total eight studies with 59,744 participants were included (22,490 women, 37,254 men). Although statin treatment reduced the risk of total mortality (RR 0.70; 95% confidence interval [CI], 0.53 to 0.93), the risks of major coronary events (RR 0.62; 95% CI 0.37 to 1.04) and cerebrovascular events (RR 0.69; 95% CI 0.45 to 1.03) were not reduced by statin treatment in women without CVD. Although major adverse events and total cancer were not increased in both male and female patients taking statin, the stratified analysis by gender revealed higher risk of development of diabetes mellitus (DM) in female patients (RR 1.50; 95% CI 1.11 to 2.01).
Conclusions: Statin treatment was less beneficial in women without CVD with regard to lowering adverse clinical outcomes when compared to men.

Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. **Meta-analysis of statin effects in women versus men**. J Am Coll Cardiol 2012;59(6):572-582.

Abstract: OBJECTIVES: The aim of this study was to evaluate the effect of statins in decreasing cardiovascular events in women and men.
BACKGROUND: Published data reviews have suggested that statins might not be as effective in women as in men in decreasing cardiovascular events.
METHODS: Published data searches and contacts with investigators identified 18 randomized clinical trials of statins with sex-specific outcomes (N = 141,235, 40,275 women, 21,468 cardiovascular events). Odds ratios (ORs) and 95% confidence intervals (CIs) for cardiovascular events were calculated for women and men separately with random effects meta-analyses.
RESULTS: The cardiovascular event rate was lower among those randomized to statin intervention than in those randomized to control (low-dose statin in 4 studies, placebo in 11 studies, usual care in 3 studies) and similar in women and men (OR: 0.81, 95% CI: 0.75 to 0.89; $p < 0.0001$, and OR: 0.77, 95% CI: 0.71 to 0.83, $p < 0.0001$, respectively). The benefit of statins was statistically significant in both sexes, regardless of the type of control, baseline risk, or type of endpoint and in both primary and secondary prevention. All-cause mortality was also lower with statin therapy both in women and men without significant interaction by sex (p for interaction = 0.4457).
CONCLUSIONS: Statin therapy is associated with significant decreases in cardiovascular events and in all-cause mortality in women and men. Statin therapy should be used in appropriate patients without regard to sex.

Petretta M, Costanzo P, Perrone-Filardi P, Chiariello M. **Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis**. Int J Cardiol 2010;138(1):25-31.

Abstract: BACKGROUND: Evidence of lipid-lowering from clinical trials that included women is adequate to support their use in secondary prevention in women with known coronary disease. However the role of statin therapy in primary prevention is still controversial, in particular for female gender. The aim of our study is to perform a meta-analysis comparing by gender the cardiovascular outcomes related to statin therapy in primary prevention.
METHODS: We performed a meta-analysis including 8 randomized controlled trials (19,052 and 30,194 men, mean follow-up 3.9 years) that assessed the cardiovascular

outcomes related to statin therapy, including studies that provided sex-specific results. MEDLINE and the Cochrane Database, were searched for articles published in English and other languages up to March 2008.
RESULTS: Statins do not appear to have a beneficial effect on total mortality for both men and women in primary prevention over the 2.8- to 5.3 year study period (men: 95% Confidence Interval (CI) 0.83-1.04; comparison p = 0.22; women: 0.96; CI 0.81-1.13; p = 0.61). Statin therapy reduced the risk of coronary heart disease (CHD) events in men (0.59; CI 0.48-0.74; p = 0.0001), however in women this risk reduction was weakly significant (0.89 CI 0.79-1.00; p = 0.05) and disappeared when in sensitivity analysis, trials not entirely of primary prevention were excluded (HPS, PROSPER) (0.95 CI 0.78-1.16; comparison p = 0.562).
CONCLUSIONS: Our study showed that statin therapy reduced the risk of CHD events in men without prior cardiovascular disease, but not in women. Statins did not reduce the risk of total mortality both in men and women.

Wang D, Liu B, Tao W, Hao Z, Liu M. **Fibrates for secondary prevention of cardiovascular disease and stroke**. The Cochrane database of systematic reviews 2015;10:CD009580.

Abstract: BACKGROUND: Fibrates are a class of drugs characterised by mainly lowering high triglyceride, raising high-density lipoprotein (HDL) cholesterol, and lowering the small dense fraction of low-density lipoprotein (LDL) cholesterol. Their efficacy for secondary prevention of serious vascular events is unclear, and to date no systematic review focusing on secondary prevention has been undertaken.
OBJECTIVES: To assess the efficacy and safety of fibrates for the prevention of serious vascular events in people with previous cardiovascular disease (CVD), including coronary heart disease and stroke.
SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 9, 2014) on the Cochrane Library, MEDLINE (OVID, 1946 to October week 1 2014), EMBASE (OVID, 1980 to 2014 week 41), the China Biological Medicine Database (CBM) (1978 to 2014), the Chinese National Knowledge Infrastructure (CNKI) (1979 to 2014), Chinese Science and Technique Journals Database (VIP) (1989 to 2014). We also searched other resources, such as ongoing trials registers and databases of conference abstracts, to identify further published, unpublished, and ongoing studies.
SELECTION CRITERIA: We included randomised controlled trials (RCTs) in which a fibrate (for example gemfibrozil, fenofibrate) was compared with placebo or no treatment. We excluded RCTs with only laboratory outcomes. We also excluded trials comparing two different fibrates without a placebo or no-treatment control.
DATA COLLECTION AND ANALYSIS: Two review authors independently selected trials for inclusion, assessed risk of bias, and extracted the data. We contacted authors of trials for missing data.
MAIN RESULTS: We included 13 trials involving a total of 16,112 participants. Eleven trials recruited participants with history of coronary heart disease, two trials recruited participants with history of stroke, and one trial recruited participants with a mix of people with CVD. We judged overall risk of bias to be moderate. The meta-analysis (including all fibrate trials) showed evidence for a protective effect of fibrates primarily compared to placebo for the primary composite outcome of non-fatal stroke, non-fatal myocardial infarction (MI), and vascular death (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.83 to 0.94; participants = 16,064; studies = 12; I(2) = 45%, fixed effect). Fibrates were moderately effective for preventing MI occurrence (RR 0.86, 95% CI 0.80 to 0.93; participants = 13,942; studies = 10; I(2) = 24%, fixed effect). Fibrates were not effective against all-cause mortality (RR 0.98, 95% CI 0.91 to 1.06; participants = 13,653; studies = 10; I(2) = 23%), death from vascular causes (RR 0.95, 95% CI 0.86 to 1.05; participants = 13,653; studies = 10; I(2) = 11%, fixed effect), and stroke events (RR 1.03, 95% CI 0.91 to 1.16; participants = 11,719; studies = 6; I(2) = 11%, fixed effect). Excluding clofibrate trials, as the use of clofibrate was discontinued in 2012 due to safety concerns, the remaining class of fibrates were no longer effective in preventing the primary composite outcome (RR 0.90, 95% CI 0.79 to 1.03; participants = 10,320; studies = 7; I(2) = 50%, random effects). However, without clofibrate data,

fibrates remained effective in preventing MI (RR 0.85, 95% CI 0.76 to 0.94; participants = 8304; studies = 6; I(2) = 47%, fixed effect). There was no increase in adverse events with fibrates compared to control. Subgroup analyses showed the benefit of fibrates on the primary composite outcome to be consistent irrespective of age, gender, and diabetes mellitus.
AUTHORS' CONCLUSIONS: Moderate evidence showed that the fibrate class can be effective in the secondary prevention of composite outcome of non-fatal stroke, non-fatal MI, and vascular death. However, this beneficial effect relies on the inclusion of clofibrate data, a drug that was discontinued in 2002 due to its unacceptably large adverse effects. Further trials of the use of fibrates in populations with previous stroke and also against a background treatment with statins (standard of care) are required.

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Agarwal R, Weir MR. **Blood pressure response with fixed-dose combination therapy: comparing hydrochlorothiazide with amlodipine through individual-level meta-analysis.** Journal of hypertension 2013;31(8):1692-1701.

Abstract: BACKGROUND: Although fixed-dose combination drug therapy is commonly used to treat hypertension, the efficacy of head-to-head comparisons of dual fixed-dose combinations has not been well described. We hypothesized that when used in combination with an angiotensin receptor blocker (ARB) olmesartan medoxomil, hydrochlorothiazide (HCTZ) will be as effective as the dihydropyridine calcium channel blocker (CCB) amlodipine to lower both clinic and 24-h ambulatory blood pressure (BP). Furthermore, we hypothesized that response to ARB along with HCTZ or ARB along with CCB may be heterogeneous depending on clinical characteristics.
METHODS: An individual-level meta-analysis was performed among 559 individuals treated with dual combination therapy in five trials. A forced titration scheme was used in each of these trials and blood BP was measured both in the clinic and outside using 24-h ambulatory BP monitors.
RESULTS: The mean age was 62 years, 55% were men, 46% had diabetes mellitus, 17% were black, clinic BP averaged 159.5/89.5 mmHg and 24-h ambulatory BP 145.0/82.5 mmHg. Overall, baseline-adjusted lowering of mean 24-h ambulatory BP was 22.0/11.7 mmHg. BP reductions were similar between ARB along with HCTZ and ARB along with CCB groups. However, clinic BP was lowered 4.3/1.8 mmHg more with ARB along with CCB combination (28.4/13.0 mmHg drop) than with ARB along with HCTZ combination (24.1/11.2 mmHg drop). The white coat effect (WCE) was therefore mitigated 3.8/1.7 mmHg more with ARB along with CCB combination. Heterogeneity in ambulatory BP response was noted. Compared with men, women had a greater ambulatory and clinic BP lowering with either combination. ARB along with HCTZ produced a greater BP-lowering effect among men, elderly, nonobese and nondiabetic. On the contrary, ARB along with CCB produced a greater BP-lowering effect among women, young, obese and diabetic individuals. This heterogeneity in response was often undetectable with clinic BP measurements. In multivariable analysis, sex and diabetes mellitus remained independent measures of heterogeneity.
CONCLUSION: Overall, the combination of olmesartan and HCTZ is as effective as olmesartan and CCB in lowering 24-h, daytime, and night-time ambulatory BP. However, greater lowering is noted with the olmesartan and CCB combination for clinic BP. Thus, out-of-office BP monitoring is necessary to provide better assessment of overall BP and response to treatment. Women and diabetic individuals may have slightly better 24-h ambulatory BP response with the olmesartan and CCB combination therapy.

Brown RA, Williams M, Barker CM, Mauri L, Meredith IT, Fajadet J, et al. **Sex-specific outcomes following revascularization with zotarolimus-eluting stents: comparison of angiographic and late-term clinical results.** Catheter Cardiovasc Interv 2010;76(6):804-813.

Abstract: OBJECTIVES: We examined angiographic and late-term clinical outcomes according to sex in recent percutaneous coronary intervention (PCI) trials involving zotarolimus-eluting stents (ZES).
BACKGROUND: Differences in outcome between men and women undergoing PCI have been inconsistently described with bare metal and first-generation drug-eluting stents.
METHODS: Clinical and angiographic outcomes among ZES-treated patients were evaluated by sex using propensity score modeling in a patient-level systematic overview of six trials and were also compared to patients receiving bare metal stents (BMS).
RESULTS: Among 2,132 patients, 608 were female (28.5%). Compared to men, women were older and more frequently had diabetes, hypertension, and a smaller reference vessel diameter ($P < 0.05$ for all). For both sexes, the relative reductions in 8-month angiographic binary restenosis and late lumen loss were statistically significant and of similar extent with ZES compared to BMS. By 2 years, treatment with ZES resulted in significantly lower target vessel revascularization (TVR) and target vessel failure (TVF; 10.0% vs. 21.5%, $P = 0.0003$) among women that paralleled risk reductions for men. However, among ZES-treated patients, 2-year rates of TVR (8.2% vs. 10.4%, $P = 0.005$) and TVF (9.9% vs. 12.8%, $P = 0.004$) were significantly lower among women, although rates of death and myocardial infarction were similar.
CONCLUSIONS: Despite greater baseline clinical and angiographic risk than men, women undergoing PCI with ZES compared to BMS experienced significant reductions in angiographic restenosis and repeat revascularization yet similar safety. Among all patients treated with ZES, late-term safety and efficacy outcomes are similar, if not lower, among women compared to men.

He YM, Yang XJ, Zhao X, Cheng XJ, Xu HF, Qian YX, et al. **beta-Blockers in heart failure: Benefits of beta-blockers according to varying male proportions of study patients**. Clinical Cardiology 2012;35(8):505-511.

Abstract: Background: In patients with heart failure (HF), b-blockers reduce mortality. It's not known whether the beneficial effects of the b-blockers were associated with the differing male proportions of study patients. It also remains to be clarified regarding the true beneficial effects of the 3 b-blockers recommended by the guideline on mortality in the real world. Hypothesis: The benefits of b-blockers in HF patients were sex-related different.
Methods: Randomized, placebo controlled clinical trials were included if they evaluated the beneficial effects of the three b-blockers on mortality and on hospital admissions on an intention-to-treat basis, and lasted at least 3 months.
Results: Twenty-eighty trials with 14,829 patients were included. The b-blockers significantly reduced all cause mortality by 29.6%, cardiac death by 29.8%, sudden death by 49.4%, respectively. The magnitude of benefits of b-blockers in HF patients was increased with the increased male proportion. A similar magnitude of reduction in all cause mortality was observed among the three b blockers. A trend toward to reduced cardiac death was observed among the three b blockers, but only in bisoprolol was this statistically different (RR, 0.72; 95%CI, [0.59-0.87]). Metoprolol was significantly superior to carvedilol ($P = 0.008$) or bisoprolol ($P = 0.034$) in reduced sudden death.
Conclusions: In patients with HF, the 3 commonly used b-blockers significantly reduced mortality. Greater benefits of b-blockers were observed in the higher male proportion studies. The metoprolol was significantly superior to carvedilol or bisoprolol in reduced sudden death. Additional trials are required to determine whether the benefits of b-blockers will be observed in female HF patients.

Olde Engberink RH, Frenkel WJ, van den Bogaard B, Brewster LM, Vogt L, van den Born BJ. **Effects of Thiazide-Type and Thiazide-Like Diuretics on Cardiovascular Events and Mortality: Systematic Review and Meta-Analysis.** Hypertension 2015;65(5):1033-1040.

Abstract: Thiazide diuretics are recommended as first-line therapy for hypertension and are among the most commonly prescribed drugs worldwide. According to their

molecular structure, thiazide diuretics can be divided in thiazide-type (TT) and thiazide-like (TL) diuretics. TL diuretics have a longer elimination half-life compared with TT diuretics and have been shown to exert additional pharmacological effects, which may differently affect cardiovascular risk. In this meta-analysis, we compared the effects of TT and TL diuretics on cardiovascular events and mortality. Randomized, controlled studies in adult hypertensive patients that compared TT or TL diuretics with placebo or antihypertensive drugs and had ≥1 year follow-up were included. Primary outcome was cardiovascular events; secondary outcomes included coronary events, heart failure, cerebrovascular events, and all-cause mortality. Meta-regression analysis was used to identify confounders and correct for the achieved blood pressure reductions. Twenty-one studies with >480 000 patient-years were included. Outcomes were not affected by heterogeneity in age, sex, and ethnicity among included studies, whereas larger blood pressure reductions were significantly associated with increased risk reductions for all outcomes (P<0.001). Corrected for differences in office blood pressure reductions among trials, TL diuretics resulted in a 12% additional risk reduction for cardiovascular events (P=0.049) and a 21% additional risk reduction for heart failure (P=0.023) when compared with TT diuretics. The incidence of adverse events was comparable among TT, TL diuretics, and other antihypertensive therapy. Our data suggest that the best available evidence seems to favor TL diuretics as the drug of choice when thiazide treatment is considered for hypertension.

Rabi DM, Khan N, Vallee M, Hladunewich MA, Tobe SW, Pilote L. **Reporting on sex-based analysis in clinical trials of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker efficacy.** Can J Cardiol 2008;24(6):491-496.

Abstract: BACKGROUND: Clinical practice recommendations for hypertension do not make recommendations specific to men or women. However, the sex hormones appear to modulate differently the renin-angiotensin system (RAS), which plays a central role in the regulation of blood pressure. Today, little is known about the effects of sex on the efficacy of therapies that antagonize the RAS, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).
OBJECTIVE: To identify randomized controlled trials evaluating the efficacy of ACEIs and ARBs in preventing major cardiovascular outcomes, determine what proportion of the trial participants were female, and evaluate whether there was any evidence of a sex difference in the efficacy of these agents.
METHODS: A systematic review of the literature was conducted to identify randomized controlled trials that used either ACEIs or ARBs for the treatment of hypertension.
RESULTS: Thirteen ACEI trials and nine ARB trials were identified. Sex-specific outcome data were available in six of the ACEI trials and three of the ARB trials. These trials enrolled 74,105 patients; 39.1% were women. Seven of the nine trials indicated that ACEIs or ARBs may be slightly more beneficial in men. The magnitude of these differences, in most trials, was small.
CONCLUSIONS: Sex-specific data are reported in 43% of large hypertension clinical trials. Review of the trials reporting sex-specific effect sizes indicates that ACEIs and ARBs may be more effective in men.

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Chemotherapy for non-small cell lung cancer. Cochrane Database of Systematic Reviews 2000 (2):CD002139.

Abstract: BACKGROUND: The role of chemotherapy in the treatment of patients with non-small cell lung cancer was not clear. A systematic review and quantitative meta-analysis was therefore undertaken to evaluate the available evidence from all relevant

randomised trials. OBJECTIVES: To evaluate the effect of cytotoxic chemotherapy on survival in patients with non-small cell lung cancer. To investigate whether or not predefined patient sub-groups benefit more or less from chemotherapy.
SEARCH STRATEGY: MEDLINE and CANCERLIT searches (1963-june 1992) were supplemented by information from trial registers and by hand searching relevant meeting proceedings and by discussion with relevant trialists and organisations.
SELECTION CRITERIA: Trials comparing primary treatments of surgery, surgery + radiotherapy, radical radiotherapy or supportive care versus the same primary treatment, plus chemotherapy were eligible for inclusion provided that they randomised non-small cell lung cancer patients using a method which precluded prior knowledge of treatment assignment.
DATA COLLECTION AND ANALYSIS: A quantitative meta-analysis using updated information from individual patients from all available randomised trials was carried out. Data from all patients randomised in all eligible trials were sought directly from those responsible. Updated information on survival, and date of last follow up were obtained, as were details of treatment allocated, date of randomisation, age, sex, histological cell type, stage and performance status. To avoid potential bias, information was requested for all randomised patients including those who had been excluded from the investigators' original analyses. All analyses were done on intention to treat on the endpoint of survival. For trials using cisplatin-based regimens, subgroup analyses by age, sex, histological cell type, tumour stage and performance status were also done.
MAIN RESULTS: Data from 52 trials and 9387 patients were included. The results for modern regimens containing cisplatin favoured chemotherapy in all comparisons and reached conventional levels of significance when used with radical radiotherapy and with supportive care. Trials comparing surgery with surgery plus chemotherapy gave a hazard ratio of 0.87 (13% reduction in the risk of death, equivalent to an absolute benefit of 5% at 5 years). Trials comparing radical radiotherapy with radical radiotherapy plus chemotherapy gave a hazard ratio 0.87 (13% reduction in the risk of death equivalent to an absolute benefit of 4% at 2 years), and trials comparing supportive care with supportive care plus chemotherapy gave a hazard ratio of 0.73 (27% reduction in the risk of death equivalent to a 10% improvement in survival at one year). The essential drugs needed to achieve these effects were not identified. No difference in the size of effect was seen in any subgroup of patients. In all but the radical radiotherapy setting, older trials using long term alkylating agents tended to show a detrimental effect of chemotherapy. This effect reached conventional significance in the adjuvant surgical comparison.
AUTHORS' CONCLUSIONS: At the outset of this meta-analysis there was considerable pessimism about the role of chemotherapy in the treatment of non-small cell lung cancer. These results offer hope of progress and suggest that chemotherapy may have a role in treating this disease.

Biaoxue R, Shuanying Y, Wei L, Wei Z, Zongjuan M. **Maintenance therapy of gefitinib for non-small-cell lung cancer after first-line chemotherapy regardless of epidermal growth factor receptor mutation: A review in Chinese patients**. Current Medical Research and Opinion 2012;28(10):1699-1708.

Abstract: Purpose: Gefitinib is a well known therapy for non-small-cell lung cancer (NSCLC). The purpose of this study was to review clinical reports of gefitinib as maintenance therapy after first-line chemotherapy regardless of epidermal growth factor receptor (EGFR) mutation, and assess its efficacy and safety in Chinese patients.
Materials and methods: Systematic computerized searches of the following databases were conducted from the start of each database up to July 2012; these include Medline, EMBASE, CNKI and www.clinicaltrials.gov. Terms searched include 'non-small-cell lung cancer', 'NSCLC', 'lung cancer', 'lung tumor', 'gefitinib', 'Iressa', 'EGFR' and 'epidermal growth factor receptor tyrosine kinase inhibitors'. A total of 22 studies were reviewed.
Results: In general, the overall response rate (ORR), disease control rate (DCR) and one year survival (OYS) of gefitinib maintenance therapy were 30.89, 67.5 and 50.6 respectively, in addition, the median overall survival (OS) and median progression free survival (PFS) were 13.09 and 7.88 months respectively. Moreover, ORR, DCR, median

survival time (MST) and PFS of female, nonsmoking, lung adenocarcinoma (LAC) patients and patients with rash had higher performance than male, smoking, non-LAC patients and patients without rash (p<0.05). The adverse events (AEs) were mainly skin rashes and diarrhea, most of which were grades 1 or 2 and were well tolerated. Conclusion: Gefitinib produced encouraging efficacy, safety and survival when delivered as maintenance therapy for NSCLC in Chinese patients after first-line chemotherapy regardless of EGFR mutation, especially for the patients who were female, nonsmokers, LAC and with rash. Key limitations of this review include limited subgroup data, small sample sizes, and the lack of EGFR/KRAS data. © 2012 Informa UK Ltd.

Bria E, Milella M, Cuppone F, Novello S, Ceribelli A, Vaccaro V, et al. **Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis**. Annals of Oncology 2011;22(10):2277-2285.

Abstract: BACKGROUND: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) are effective as first-line treatment of advanced non-small-cell lung cancer patients with EGFR mutations (EGFR-M+).
PATIENTS AND METHODS: We conducted a literature-based meta-analysis to quantify the magnitude of benefit with upfront EGFR TKI in EGFR-M+ patients. Meta-regression and sensitivity analyses were also carried out to identify additional predictors of outcome and to assess the influence of trial design.
RESULTS: Five trials (805 patients) were identified (three trials prospectively enrolling EGFR-M+ patients and two retrospective analyses of EGFR-M+ patients). TKI significantly increased progression-free survival (PFS) [hazard ratio (HR) 0.45, 95% confidence interval (CI) 0.36-0.58, P < 0.0001] and overall response rate (ORR) (HR 2.08, 95% CI 1.75-2.46, P < 0.0001)] over chemotherapy, while significantly decreasing neutropenia. No significant difference was observed in overall survival. The rate of exon-19 mutations, female gender, and nonsmoking status were identified as additional predictors of outcome at meta-regression analysis. A significant interaction with trial design was found for both PFS (P = 0.028) and ORR (P = 0.008), suggesting a larger advantage for patients treated within prospective trials.
CONCLUSIONS: In EGFR-M+ patients, first-line TKI increase both PFS and ORR by ~25%, while significantly decreasing toxicity. The role of additional predictive factors and the influence of trial design on the magnitude of the observed benefit warrant further investigation.

Buyse M, Squifflet P, Lange BJ, Alonzo TA, Larson RA, Kolitz JE, et al. **Individual patient data meta-analysis of randomized trials evaluating IL-2 monotherapy as remission maintenance therapy in acute myeloid leukemia**. Blood 2011;117(26):7007-7013.

Abstract: IL-2 is a natural, T cell-derived cytokine that stimulates the cytotoxic functions of T and natural killer cells. IL-2 monotherapy has been evaluated in several randomized clinical trials (RCTs) for remission maintenance in patients with acute myeloid leukemia (AML) in first complete remission (CR1), and none demonstrated a significant benefit of IL-2 monotherapy. The objective of this meta-analysis was to reliably determine IL-2 efficacy by combining all available individual patient data (IPD) from 5 RCTs (N = 905) and summary data from a sixth RCT (N = 550). Hazard ratios (HRs) were estimated using Cox regression models stratified by trial, with HR < 1 indicating treatment benefit. Combined IPD showed no benefit of IL-2 over no treatment in terms of leukemiafree survival (HR = 0.97; P = .74) or overall survival (HR = 1.08; P = .39). Analyses including the sixth RCT yielded qualitatively identical results (leukemia-free survival HR = 0.96, P = .52; overall survival HR = 1.06; P = .46). No significant heterogeneity was found between the trials. Prespecified subset analyses showed no interaction between the lack of IL-2 effect and any factor, including age, sex, baseline performance status, karyotype, AML subtype, and time from achievement of CR1 to initiation of maintenance therapy. We conclude that IL-2 alone is not an effective remission

maintenance therapy for AML patients in CR1. © 2011 by The American Society of Hematology.

Capurso G, Schünemann HJ, Terrenato I, Moretti A, Koch M, Muti P, et al. **Meta-analysis: the use of non-steroidal anti-inflammatory drugs and pancreatic cancer risk for different exposure categories**. Alimentary pharmacology & therapeutics 2007;26(8):1089-1099.

Abstract: BACKGROUND: A better understanding of predictors of risk for pancreatic ductal adenocarcinoma (PDAC) could inform preventive efforts against this lethal cancer. While aspirin (ASA) and non-steroidal anti-inflammatory drugs (NSAIDS) might protect against several gastrointestinal cancers, their role in the development of PDAC remains unclear.
AIM: To conduct a systematic review and meta-analysis on the relation between ASA/NSAIDs exposure and the risk of PDAC.
Methods We searched Pubmed, Embase, Scopus, Cochrane database of systematic reviews and reference lists of identified papers and included observational (cohort or case-control) studies and randomized controlled trials examining exposure to ASA and/or NSAIDs and the incidence or mortality of PDAC. We defined three categories (low, intermediate, high), based on exposure duration and dose.
RESULTS: Eight studies fulfilled our inclusion criteria (four cohort, three case controls, and one randomized controlled trial studies) enrolling 6301 patients between 1971-2004; all but one study took place in the US. The pooled OR were 0.99 (0.83-1.19), 1.11 (0.84-1.47) and 1.09 (0.67-1.75) in the low, intermediate and high exposure groups respectively, with considerable heterogeneity (I(2) ranging 60-86%). Sensitivity analysis by ASA use only, study design or sex did not reveal additional important information.
CONCLUSIONS: This study did not show an association between ASA/NSAIDs and PDAC. The large baseline exposure in controls in North-America may have obscured an association. There is need for additional studies, especially in Europe, to clarify this issue.

Chen P, Sui M, Ye J, Wan Z, Chen F, Luo C. **An integrative analysis of treatment, outcomes and prognostic factors for primary spinal anaplastic ependymomas**. Journal of Clinical Neuroscience 2015;22(6):976-980.

Abstract: The aim of this study was to elucidate the role of treatment modalities in primary spinal anaplastic ependymomas (PSAE) and identify promising prognostic factors. PSAE are rare tumors of the central nervous system with poorly understood clinical characteristics and treatment outcomes. We reviewed the literature in PubMed, Web of Science and Scopus databases to identify patients with PSAE. Multivariate Cox proportional hazards analysis and univariate Kaplan-Meier analysis were performed on the PSAE patients and overall survival (OS) and progression-free survival (PFS) were assessed to evaluate the clinical outcomes. Of the 40 patients with PSAE, the tumors were mostly intramedullary (n = 19; 47.5%) and frequently involved the thoracic cord (n = 25; 62.5%). Eighteen patients suffered recurrence during the follow-up with a median PFS of 24 months. The 1, 2, and 5 year OS rates of the PSAE patients were 91.5%, 82.1%, and 63.1%, respectively. Gross total resection (GTR) was independently associated with prolonged PFS (hazard ratio [HR] 0.11; p = 0.004) and OS (HR 0.11; p = 0.003) in the multivariate analysis. Adjuvant radiotherapy also conferred improved PFS (HR 0.15; p = 0.008) and OS (HR 0.16; p = 0.022). Age, sex, tumor location and chemotherapy did not influence the outcomes in this group. The results of our study suggest that GTR and adjuvant radiotherapy are strong prognostic indicators in patients with PSAE and the role of chemotherapy is yet to be defined.

Chen X, Liu Y, Roe OD, Qian Y, Guo R, Zhu L, et al. **Gefitinib or Erlotinib as Maintenance Therapy in Patients with Advanced Stage Non-Small Cell**

Lung Cancer: A Systematic Review. PLoS ONE 2013;8 (3) (no pagination)(e59314).

Abstract: Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), gefitinib and erlotinib have been tested as maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC). The studies are quite heterogenous regarding study size and populations, and a synopsis of these data could give some more insight in the role of maintenance therapy with TKI.
Methods: In September 2012 we performed a search in the pubmed, EMBASE and Cochrane library databases for randomized phase III trials exploring the role of gefitinib or erlotinib in advanced non-small cell lung cancer. Through a rigorous selection process with specific criteria, five trials (n = 2436 patients) were included for analysis. Standard statistical methods for meta-analysis were applied.
Results: TKIs (gefitinib and erlotinib) significantly increased progression-free survival (PFS) [hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.50-0.76, I² = 78.1%] and overall survival (HR 0.84, 95% CI 0.76-0.93, I² = 0.0%) compared with placebo or observation. The PFS benefit was consistent in all subgroups including stage, sex, ethnicity, performance status, smoking status, histology, EGFR mutation status, and previous response to chemotherapy. Patients with clinical features such as female, never smoker, adenocarcinoma, Asian ethnicity and EGFR mutation positive had more pronounced PFS benefit. Overall survival benefit was observed in patients with clinical features such as female, non-smoker, smoker, adenocarcinoma, and previous stable to induction chemotherapy. Severe adverse events were not frequent. Main limitations of this analysis are that it is not based on individual patient data, and not all studies provided detailed subgroups analysis.
Conclusions: The results show that maintenance therapy with erlotinib or gefitinib produces a significant PFS and OS benefit for unselected patients with advanced NSCLC compared with placebo or observation. Given the less toxicity of TKIs than chemotherapy and simple oral administration, this treatment strategy seems to be of important clinical value. © 2013 Chen et al.

Collins M, Wilhelm M, Conyers R, Herschtal A, Whelan J, Bielack S, et al. **Benefits and adverse events in younger versus older patients receiving neoadjuvant chemotherapy for osteosarcoma: findings from a meta-analysis**. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;31(18):2303-2312.

Abstract: The LIVESTRONG Young Adult Alliance has conducted a meta-analysis of individual patient data from prospective neoadjuvant chemotherapy osteosarcoma studies and registries to examine the relationships of sex, age, and toxicity on survival. Suitable data sets were identified by a survey of published data reported in PubMed. The final pooled data set comprised 4,838 patients from five international cooperative groups. After accounting for important variables known at study entry such as tumor location and histology, females experienced higher overall survival rates than males (P = .005) and children fared better than adolescents and adults (P = .002). Multivariate landmark analysis following surgery indicated that a higher rate of chemotherapy-induced tumor necrosis was associated with longer survival (P < .001), as was female sex (P = .004) and the incidence of grade 3 or 4 mucositis (P = .03). Age group was not statistically significant in this landmark analysis (P = .12). Females reported higher rates of grade 3 or 4 thrombocytopenia relative to males (P < .001). Children reported the highest rates of grade 3 or 4 neutropenia (P < .001) and thrombocytopenia (P < .001). The achievement of good tumor necrosis was higher for females than for males (P = .002) and for children than for adults (P < .001). These results suggest fundamental differences in the way chemotherapy is handled by females compared with males and by children compared with older populations. These differences may influence survival in a disease in which chemotherapy is critical to overall outcomes.

Escherich G, Richards S, Stork LC, Vora AJ. **Meta-analysis of randomised trials comparing thiopurines in childhood acute lymphoblastic leukaemia**. Leukemia 2011;25(6):953-959.

Abstract: Mercaptopurine has been used in continuing treatment of childhood acute lymphoblastic leukaemia since the mid 1950s. Recent advances in the understanding of thiopurine pharmacology indicated that thioguanine (TG) might be more effective than mercaptopurine (MP). The US and UK cooperative groups began randomised thiopurine trials and agreed prospectively to a meta-analysis. All randomised trials of TG versus MP were sought, and data on individual patients were analysed by standard methods. Combining three trials (from US, UK and Germany), the overall event-free survival (EFS) was not significantly improved with TG (odds ratio (OR)=0.89; 95% confidence interval 0.78-1.03). Apparent differences in results between trials may be partly explained by the different types of patients studied. The larger treatment effect reported in males in the US trial was confirmed in the other trials. There was heterogeneity between sex/age subgroups (P=0.001), with significant EFS benefit of TG only observed for males aged<10 years old (OR=0.70; 0.58-0.84), although this did not result in a significant difference in overall survival (OR=0.83; 0.62-1.10). Additional toxicity occurs with TG. Mercaptopurine remains the standard thiopurine of choice, but further study of TG may be warranted to determine whether it could benefit particular subgroups.

Lesley S, Sarah B. **Chemotherapy for high-grade glioma**. Cochrane Database of Systematic Reviews 2002 (3):CD003913.

Abstract: BACKGROUND: Trials on the effect of systemic chemotherapy on survival and recurrence in adults with high-grade glioma have had inconclusive results. We undertook a systematic review and meta-analysis to assess the effects of such treatment on survival and recurrence.

OBJECTIVES: To compare radiotherapy plus chemotherapy with radiotherapy alone in completely resected adults with high-grade glioma. To investigate whether or not predefined patient subgroups benefit more or less from chemotherapy.

SEARCH STRATEGY: MEDLINE and CancerLit searches were supplemented with information from trial registers and by hand searching relevant meeting proceedings and by discussion with relevant trialists and organisations. These searches were carried out in June 1997, June 1999, December 2000 and August 2003.

SELECTION CRITERIA: Trials comparing radiotherapy versus radiotherapy + chemotherapy were eligible for inclusion provided that they randomized adult patients using a method which precluded prior knowledge of treatment assignment.

DATA COLLECTION AND ANALYSIS: A quantitative meta-analysis using updated information from individual patients from all available randomized trials was carried out. Data from all patients randomized in all eligible trials were sought directly from those responsible. Updated information on survival and date of follow-up were obtained, as were details of treatment allocation, date of randomization, age, sex, histological cell type, stage and performance status. To avoid potential bias, information was requested for all randomized patients including those who had been excluded from the investigators' original analyses. All analyses were done on an intention to treat basis on the endpoint of survival. For trials using cisplatin-based regimens, subgroup analyses by age, sex, histological cell type, tumour stage and performance status were also done.

MAIN RESULTS: Data from 12 randomized trials and 3004 patients were included. The results show a significant prolongation of survival associated with chemotherapy, with a hazard ratio of 0.85 (95% CI 0.78-0.91, p=0.00004) or 15% relative decrease in the risk of death. This is equivalent to an absolute increase in one year survival rate of 6% (95% confidence interval 3% to 9%) from 40% to 46% and a two-month increase in median survival time (95% confidence interval one month to three months). There was no evidence that the effect of chemotherapy was different in any group of patients defined by age, sex, histology, performance status or extent of resection.

AUTHORS' CONCLUSIONS: This small but clear improvement in survival from chemotherapy encourages further study of drug treatment of these tumours

Mancuso A, Mazzola A, Cabibbo G, Perricone G, Enea M, Galvano A, et al. **Survival of patients treated with sorafenib for hepatocellular carcinoma recurrence after liver transplantation: A systematic review and meta-analysis**. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2015;47(4):324-330.

Abstract: BACKGROUND: Data on survival and safety of sorafenib for hepatocellular carcinoma recurrence after liver transplant are still equivocal. AIM: We performed a meta-analysis of published studies, with the aim of estimating the 1-year rates of survival, analysing the variability in survival rates and, finally, identifying the factors associated with a longer survival.
METHODS: Data from 8 of the 17 selected studies were pooled, while the other 9 were excluded because survival rates were missing. All included studies were retrospective.
RESULTS: Overall, the 1-year survival ranged from 18% to 90%. Tumour progression was the main cause of death. The second cause was bleeding, reported only in patients undergoing m-Tor inhibitor therapy. The pooled estimate of 1-year survival was 63%. There was a significant heterogeneity among studies (P<0.0001). Among the 34 variables assessed by univariate meta-regression, 5 were associated with an increase in the 1-year survival rate: (1) male gender (P=0.001); (2) Time to progression (P=0.038); and adverse drug events, divided in (3) gastrointestinal (P=0.038), (4) cardiovascular (P=0.029), and (5) dermatological (P=0.014).
CONCLUSIONS: Additional data from multicentre prospective studies are required to clearly determine if sorafenib is a safe and acceptable treatment in hepatocellular carcinoma recurrence after liver transplant. Nevertheless, its association with m-Tor inhibitors should be discouraged.

Sheng J, Yang YP, Yang BJ, Zhao YY, Ma YX, Hong SD, et al. **Efficacy of addition of antiangiogenic agents to taxanes-containing chemotherapy in advanced nonsmall-cell lung cancer: A meta-analysis and systemic review**. Medicine (United States) 2015;94 (31) (no pagination)(e1282).

Abstract: Preclinical researches indicated a potential synergistic effect of taxanes-containing chemotherapy (TCC) and antiangiogenic agents (AAs) on the treatment of advanced nonsmall-cell lung cancer (NSCLC). The advantage of adding AA to TCC in the real world remains confusing. We summarized the current evidences from relevant phase II/III randomized controlled trials (RCTs) by performing this meta-analyses. Electronic databases were searched for eligible literatures. The primary endpoint was overall survival (OS). Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes were calculated using RevMan 5.2. A total of 14 phase II/III RCTs involving 9703 participants were included. Compared to standard TCC, the addition of AA was associated with the significant better OS (HR 0.92, 95% CI 0.87-0.97, P=0.002), prolonged progression-free survival (HR 0.79, 95% CI 0.71-0.87, P < 0.00001), superior response rate (risk ratio [RR] 1.69, 95% CI 1.47-1.95, P<0.0001), and disease control rate (RR 1.19, 95% CI 1.08-1.32, P< 0.00001). Subgroup analyses indicated that patient treated with monoclonal antibodies (HR 0.89, 95% CI 0.82-0.96, P = 0.02) as well as application in second-line (HR 0.91, 95% CI 0.85-0.96, P=0.02) acquired significant OS improvement. Other clinical factors directing significant OS improvement by the combination strategy included nonsquamous cancer (P=0.002), nonsmokers (P=0.0005), and female (P=0.02). Toxicities were greater but generally mild or moderate in the combination group, and were mostly manageable. In summary, the addition of AAs to TCC could improve prognosis of advanced NSCLC. Furthermore, proper selection of patient population and AAs is crucial for clinical trials design and clinical practice in the future.

Stewart LA. **Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials**. Lancet 2002;359(9311):1011-1018.

Abstract: BACKGROUND: Trials on the effect of systemic chemotherapy on survival and recurrence in adults with high-grade glioma have had inconclusive results. We undertook a systematic review and meta-analysis to assess the effects of such treatment on survival and recurrence.
METHODS: We did a systematic review and meta-analysis using updated data on individual patients from all available randomised trials that compared radiotherapy alone with radiotherapy plus chemotherapy. Data for 3004 patients from 12 randomised controlled trials were included (11 published and one unpublished).
FINDINGS: Overall, the results showed significant prolongation of survival associated with chemotherapy, with a hazard ratio of 0.85 (95% CI 0.78-0.91, p<0.0001) or a 15% relative decrease in the risk of death. This effect is equivalent to an absolute increase in 1-year survival of 6% (95% CI 3-9) from 40% to 46% and a 2-month increase in median survival time (1-3). There was no evidence that the effect of chemotherapy differed in any group of patients defined by age, sex, histology, performance status, or extent of resection.
INTERPRETATION: This small but clear improvement in survival from chemotherapy encourages further study of drug treatment of these tumours.

Ye X, Casaclang N, Mahmud SM. **Use of non-steroidal anti-inflammatory drugs and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis**. Hematological oncology 2014.

Abstract: Epidemiological study findings regarding the association between use of non-steroidal anti-inflammatory drugs (NSAIDs) and risk of non-Hodgkin lymphoma (NHL) have been inconsistent. We aimed to systematically review epidemiological studies of the association and calculate pooled relative risks using meta-analytic methods. We searched eight electronic literature databases and three clinical trial registers to identify all studies (including observational studies and randomized clinical trials) of the association published prior to October 2013. Identified studies were independently reviewed by two researchers. We used a random effects model to calculate pooled odds ratio (PORs). Heterogeneity amongst studies was examined using Cochran's Q and I-squared (I(2)) tests; and sources of heterogeneity were explored using subgroup and meta-regression analyses. A total of 17 studies (12 case-control studies and five cohort studies), all adult studies, were included. Use of NSAIDs was not associated with overall risk of NHL [POR = 1.05, and 95% confidence interval (95% CI) 0.90-1.22] or NHL subtypes including B-cell lymphoma, T-cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Aspirin use was associated with reduced risk of CLL/SLL (POR = 0.70, 95% CI 0.54-0.91) but not with the risk of all NHLs (POR = 1.02, 95% CI 0.89-1.17). Use of non-aspirin NSAIDs was associated with increased risk of NHL (POR = 1.41, 95% CI 1.01-1.97) amongst females only. The epidemiologic evidence remains inconclusive. Effects of NSAIDs may differ by drug type, NHL subtype, and sex and more studies taking into consideration these differences are needed. © 2014 The Authors. Hematological Oncology Published by John Wiley & Sons, Ltd.

Psykiske lidelser

Tabell 2: *Antall oversiktsartikler sortert etter medikamentklasse*

Tiltak	Antall referanser: 20
Antidepressiver	10
Andre psykofarmaka	10

Bigos KL, Pollock BG, Stankevich BA, Bies RR. **Sex differences in the pharmacokinetics and pharmacodynamics of antidepressants: an updated review.** Gend Med 2009;6(4):522-543.

Abstract: BACKGROUND: An increasing number of studies have reported differences in the pharmacokinetics and/or pharmacodynamics of antidepressants between women and men.
OBJECTIVES: This article updates previously published literature describing sex differences in the pharmacokinetics and pharmacodynamics of antidepressants, and examines specific issues that face women with psychiatric illness.
METHODS: An English-language literature search was performed with the PubMed database (March 2003-December 2008) using combinations of the search terms sex, gender, and antidepressants. In addition, each antidepressant was identified in the 63rd edition of the Physicians' Desk Reference. RESULTS: The current data suggest that the pharmacokinetics of antidepressants can be substantially different between women and men. Likewise, the response to antidepressants can be quite variable, including sex differences in adverse effects and time to response.
CONCLUSIONS: Despite the many sex differences reported, there is still little published work systematically evaluating potential sex differences in antidepressant pharmacokinetics and pharmacodynamics. More research is needed to guide the treatment of depression and other mental illnesses.

Calati R, Salvina Signorelli M, Balestri M, Marsano A, De Ronchi D, Aguglia E, et al. **Antidepressants in elderly: Metaregression of double-blind, randomized clinical trials**. Journal of Affective Disorders 2013;147(1-3):1-8.

Abstract: Background: Depression is common in the elderly and in the last few years this led to a significant increase in antidepressant prescription rates. However, little is known about antidepressant efficacy profile in relation with socio-demographic and clinical features in this population. The aim of the present study was to define the most suitable socio-demographic and clinical profile for the use of antidepressant treatments in late-life depression.
Methods: MEDLINE, EMBASE and PsycINFO were searched for randomized controlled trials (RCTs) focused on efficacy of antidepressants of all classes in major depressed elderly subjects (>60 years old). Reviews and meta-analyses focusing on this topic have been considered as well. Thirty-four RCTs were included and socio-demographic and clinical features were investigated via meta-regression analysis as moderators of efficacy measures (standardized mean difference based on Hamilton Depressive Rating Scale and Montgomery-Asberg Depression Rating Scale).
Results: A lower rate of response to antidepressants of all classes was found in patients of male gender, of older age, and with a longer mean duration of the current episode. On the contrary, a higher rate of response was found in patients with a higher baseline severity and at their first episode of illness. Subsamples treated with selective serotonin reuptake inhibitors alone yielded similar results.
Limitations: RCTs only have been included.
Conclusions: A number of socio-demographic and clinical features have been found to moderate antidepressant efficacy in elderly population. Those variables could help clinicians for a more individualized treatment. © 2012 Elsevier B.V. All rights reserved.

Frackiewicz EJ, Sramek JJ, Cutler NR. **Gender differences in depression and antidepressant pharmacokinetics and adverse events.** Ann Pharmacother 2000;34(1):80-88.

Abstract: OBJECTIVE: To review data generated by studies examining gender differences in the prevalence of depression, as well as in antidepressant pharmacokinetics, pharmacodynamics, and adverse events.
DATA SOURCES: Published articles and abstracts were identified through MEDLINE (January 1966-April 1999) using the following search terms: antidepressant, response,

gender, pharmacokinetic, pharmacodynamic, female, side effect, and adverse events. All articles that assessed gender differences in antidepressant response, pharmacokinetics, and adverse events, as well as articles that evaluated postulated mechanisms for these differences, were reviewed. Additional articles were identified from bibliographies of retrieved articles.
STUDY SELECTION AND DATA EXTRACTION: All relevant abstracts, studies, and review articles were evaluated.
DATA SYNTHESIS: Gender differences in the prevalence of depression have been reported and may result from the interaction of several factors. Women have been shown to have a higher incidence of depression, which may be due to artifact, social, or biologic reasons. Studies suggest that the pharmacokinetic disposition of popular antidepressants varies between men and women, and women taking antidepressants may exhibit a different adverse event profile. Only one study specifically evaluated gender differences in antidepressant treatment response.
CONCLUSIONS: Further research elucidating gender differences in response to antidepressant treatment and on depression prevalence is needed. Some studies report that the pharmacokinetics of antidepressants may vary between men and women. Therefore, clinicians should be aware that potential differences in antidepressant pharmacokinetics may exist, and a dosage adjustment may be necessary for women to ensure a favorable drug response, compliance, and decreased incidence of adverse events.

Gibiino S, Marsano A, Serretti A. **Specificity profile of venlafaxine and sertraline in major depression: metaregression of double-blind, randomized clinical trials.** The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP) 2014;17(1):1-8.

Abstract: Despite the well-known efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) in the treatment of major depressive disorder, there is a lack of indications for each drug in different groups of patients. The aim of this study is to investigate the possible role of clinical sociodemographic factors as moderators of clinical response to venlafaxine (SNRI) and sertraline (SSRI). Research was performed on Medline and EMBASE for randomized control trials in English focused on sertraline and venlafaxine in the treatment of major depressive disorder and 59 studies were included. Clinical efficacy of each treatment was assessed on the basis of Hamilton Depressive Rating Scale and Montgomery-Asberg Depression Rating Scale. A metaregression analysis was performed to evaluate the role of clinical and sociodemographic factors as moderators of outcome, calculating the effect of each variable with the random-effects method. Gender, ethnicity and duration of depressive episode could have a role in prediction of clinical response to both antidepressants. Venlafaxine seems to have better effects in females and in Caucasian patients. Sertraline seems to be more efficacious in the treatment of females. Both drugs were more efficacious in patients who suffered a shorter episode of illness. Our results could represent an interesting point of view in the perspective of choosing the most suitable therapy based on clinical and social features for each patient. Metaregression is a retrospective analysis, based on the cumulative results of previous studies, so the lack of original data could represent the main limitation in this report and in the interpretation of the results obtained.

Hellem TL, Lundberg KJ, Renshaw PF. **A review of treatment options for co-occurring methamphetamine use disorders and depression**. Journal of addictions nursing 2015;26(1):14-23.

Abstract: Co-occurring methamphetamine use and depression interferes with treatment outcomes. Female methamphetamine users are known to have higher rates of depression than male methamphetamine users, although this is also true for the general population. There are limited treatment options for the management of depression among methamphetamine users. In this integrative review, we summarize data on treatment strategies for co-occurring depression and methamphetamine use disorders.

English-language articles were identified from PsychINFO, CINAHL, PubMed, and Medline as well as from reference lists of key articles. Search terms included "methamphetamine," "depression," and "treatment." Research articles describing psychological (n = 3), pharmacological (n = 6), nutritional supplement (n = 1), and psychological combined with pharmacological (n = 3) approaches for the treatment of methamphetamine use or withdrawal and/or depression are included in this review. Psychological and combination of psychological with pharmacological approaches have not been shown to be effective in treating these co-occurring conditions. Antidepressants have been determined to be ineffective and/or to introduce side effects. Gender differences with response to treatment were examined in only one of the published studies. There is a large gap in knowledge regarding treatment of co-occurring methamphetamine use disorders and depression. Considering that female methamphetamine users experience higher rates of depression than men, a focus on gender-specific treatment approaches is warranted.

Khan A, Brodhead AE, Schwartz KA, Kolts RL, Brown WA. **Sex differences in antidepressant response in recent antidepressant clinical trials.** J Clin Psychopharmacol 2005;25(4):318-324.

Abstract: Some previous reports suggest that women respond differently than men to antidepressant treatment. Much of this literature compares men and women's response to tricyclics to that of newer antidepressants (SSRIs, SNRI), or only examines one particular antidepressant. This study compares men and women's responses to 6 newer antidepressants. A total of 15 randomized, placebo-controlled trials that included 323 depressed patients were examined for sex differences in antidepressant treatment response. Women had a significantly greater response than men to SSRI antidepressants. A similar trend was seen for those assigned to an SNRI antidepressant, although not to the same extent as with SSRI antidepressants. Although these gender differences in treatment response are not large enough to suggest that gender should guide the clinical use of SSRI and SNRI antidepressants, the results do have implications for the design and interpretation of antidepressant clinical trials. These findings also raise the possibility that antidepressants may work somewhat differently in men and women.

Kokras N, Dalla C, Papadopoulou-Daifoti Z. **Sex differences in pharmacokinetics of antidepressants.** Expert Opin Drug Metab Toxicol 2011;7(2):213-226.

Abstract: INTRODUCTION: Sex differences have been identified in antidepressant treatment; however, it remains unclear to what extent pharmacokinetics contributes to these differences. As current antidepressant pharmacotherapy is less than optimal, understanding the role of sex in pharmacokinetics may substantially contribute to a gender-based optimized treatment.

AREAS COVERED: An unrestricted PubMed literature search on antidepressant pharmacokinetics and sex was performed. Sex differences in absorption, distribution, metabolism and elimination of antidepressants, as well as the interaction of sex with age, genetic polymorphisms and gonadal hormones are discussed. We also provide an overview of how each antidepressant presents a particular sex-differentiated pharmacokinetic profile. Most antidepressants present to some extent pharmacokinetic sex differences, which often are further accentuated by gonadal hormones. In most cases, women, particularly elderly women, are expected to have higher exposure to antidepressants when dosed in a similar way as men.

EXPERT OPINION: Although the available pharmacokinetic evidence indicates that women should receive lower doses of antidepressants and men should receive higher doses, current guidelines do not recommend dose adjustment, because these sex differences are considered to be clinically insignificant. Unless we understand the link between pharmacokinetics and pharmacodynamics of antidepressants, it will be difficult to determine whether sex differences are of clinical importance or not. Thus, further systematic and particularly focused research is needed on sex differences in pharmacokinetics.

Kornstein SG, Wohlreich MM, Mallinckrodt CH, Watkin JG, Stewart DE. **Duloxetine efficacy for major depressive disorder in male vs. female patients: data from 7 randomized, double-blind, placebo-controlled trials.** J Clin Psychiatry 2006;67(5):761-770.

Abstract: OBJECTIVE: A number of studies have suggested potential gender differences in the efficacy of antidepressant medications. Pooled data from double-blind, placebo-controlled studies were utilized to compare the efficacy of duloxetine in the treatment of major depressive disorder (MDD) in male and female patients.
METHOD: Efficacy data were pooled from 7 randomized, double-blind, placebo-controlled clinical trials of duloxetine. These studies represent all available data from U.S. acute-phase, placebo-controlled studies of duloxetine for the treatment of MDD. Patients (aged > or = 18 years) meeting DSM-IV criteria for MDD received duloxetine (40-120 mg/day; men, N = 318; women, N = 578) or placebo (men, N = 242; women, N = 484) for up to 9 weeks. Efficacy measures included the 17-item Hamilton Rating Scale for Depression (HAM-D17) total score, HAM-D17 subscales (core, Maier, anxiety, retardation, sleep), the Clinical Global Impressions-Severity of Illness scale (CGI-S) and Patient Global Impression of Improvement scale (PGI-I), the Quality of Life in Depression Scale (QLDS), and Visual Analog Scales (VAS) for pain. The first patient visit was February 1, 1999, and the last patient visit was November 27, 2002.
RESULTS: In both male and female patients, duloxetine produced significantly greater improvement in HAM-D17, CGI-S, and PGI-I when compared with placebo ($p < .05$). Treatment-by-gender interactions did not reach statistical significance, indicating that the magnitude of duloxetine's treatment effects did not differ significantly between male and female patients. However, there was a trend for female patients to show a more robust response than male patients to both duloxetine and placebo. On the basis of VAS assessments of pain severity, duloxetine-treated female patients appeared to exhibit greater improvement than male patients, while women receiving placebo had smaller responses than placebo-treated men. Improvements in quality of life were significantly greater for both men ($p = .006$) and women ($p = .001$) receiving duloxetine than placebo and showed no significant difference by gender.
CONCLUSION: In this analysis of pooled data, the efficacy of duloxetine did not differ significantly in male and female patients.

Stewart DE, Wohlreich MM, Mallinckrodt CH, Watkin JG, Kornstein SG. **Duloxetine in the treatment of major depressive disorder: comparisons of safety and tolerability in male and female patients.** J Affect Disord 2006;94(1-3):183-189.

Abstract: BACKGROUND: While some studies have suggested sex differences in the efficacy of antidepressant medications, there have been few investigations into potential sex differences related to safety and/or tolerability. Pooled data from double-blind, placebo-controlled studies were utilized to assess the safety and tolerability of duloxetine in the treatment of major depressive disorder (MDD) in male and female patients.
METHODS: Safety data were pooled from seven double-blind, placebo-controlled clinical trials of duloxetine. Patients (aged >or=18 years) meeting DSM-IV criteria for MDD received duloxetine (40-120 mg/day, male: N=318, female: N=578) or placebo (male: N=242, female: N=484) for up to 9 weeks. Safety was assessed using discontinuation rates, spontaneously reported treatment-emergent adverse events, changes in vital signs and laboratory analyses.
RESULTS: Discontinuation rates due to adverse events among duloxetine-treated patients were 18.6% for males and 13.5% for females. The most common treatment-emergent adverse events in both male and female patients included nausea, headache, dry mouth, diarrhea and constipation. The only event occurring at significantly different rates in male and female patients was nausea (Breslow Day p-value=0.008), and the significant difference was driven by a placebo nausea rate that was almost three times greater in females compared with males. No significant differential sex effects were found for pulse, blood pressure or weight. No laboratory analyte had an incidence of abnormal high or low values that differed significantly between male and female patients.

LIMITATIONS: This was a post-hoc analysis of pooled data from acute phase clinical trials. Plasma concentrations of duloxetine were not obtained. Adverse event rates were based on spontaneous reports and differential dose-response effects were not evaluated.
CONCLUSIONS: No evidence of clinically meaningful sex differences in the safety and tolerability of duloxetine were uncovered.

Taylor Matthew J, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K. **Strategies for managing sexual dysfunction induced by antidepressant medication.** Cochrane Database of Systematic Reviews 2013 (5).

Abstract: Background: Sexual dysfunction (including altered sexual desire, orgasmic and ejaculatory dysfunction, erectile and other problems) is a relatively common side effect of antidepressant medication. These sexual side effects may compromise a person's lifestyle and result in a lack of compliance with the prescribed antidepressant to the detriment of the person's mental health. A wide range of management strategies are possible to address this problem, including behavioural, psychological and pharmacological approaches.
Objectives: 1. To determine the effectiveness of management strategies for sexual dysfunction caused by antidepressants.2. To determine the adverse effects and acceptability of the different management strategies.
Search methods: We searched the Cochrane Depression, Anxiety and Neurosis Group's Specialized Register (CCDANCTR, to 1 January 2013), which includes relevant randomised controlled trials from the following bibliographic databases: The Cochrane Library (all years), EMBASE (1974 to date), MEDLINE (1950 to date) and PsycINFO (1967 to date). Additional searches were carried out by the author team on the same biomedical databases (using terms for 'sexual dysfunction' only) together with CINAHL (1982 to Jan 2012). The reference lists of reports of all included studies were screened.Selection criteria: We included randomised controlled trials that compared management strategies for antidepressant-induced sexual dysfunction versus placebo or any alternative strategy.Data collection and analysis: Two authors independently extracted data and assessed trial quality. Study authors were contacted for additional information.
Main results: We included 23 trials involving 1886 people in this updated review. Twenty-two of these trials investigated the addition of medication to treat the identified dysfunction, with most agents studied in only single studies. One study investigated switching to an alternative antidepressant.In men, data for the phosphodiesterase inhibitors sildenafil (three studies, 255 participants) and tadalafil (one study, 54 participants) indicated they led to a greater improvement in erectile function than placebo. Combined data from three sildenafil studies found benefit over placebo on International Index of Erectile Function ratings of ability to achieve (MD 1.04, 95% CI 0.65 to 1.44), and maintain erections (MD 1.18, 95% CI 0.78 to 1.59). A single point improvement on these ratings is equivalent to an improvement in frequency from 'sometimes' to 'most times'. Men receiving tadalafil were more likely to report improved erectile function (RR 11.50, 95% CI 3.03 to 43.67). For women it remains uncertain whether sildenafil is more effective than placebo. Unpublished data could reduce this uncertainty. Data from three studies in men and women of bupropion 150 mg twice daily indicate a benefit over placebo on rating scale scores (SMD 1.60, 95% CI 1.40 to 1.81), but response rates in two studies of bupropion 150 mg once daily demonstrated no statistically significant difference in effect (RR 0.62, 95% CI 0.09 to 4.41).Other augmentation strategies failed to demonstrate significant improvements in sexual dysfunction compared with placebo.One trial involving 75 people with sexual dysfunction due to sertraline assessed the effect of changing antidepressant. Switching to nefazodone was significantly less likely to result in the re-emergence of sexual dysfunction than restarting sertraline (RR 0.34, 95% CI 0.19 to 0.60), however, nefazodone is no longer available for clinical use.There is an absence of randomised trials assessing the effects of switching to currently-available antidepressant agents with lower rates of adverse sexual effects, the role of psychological or mechanical interventions, or of techniques such as drug holidays.We identified no data for any of the strategies included in the trials assessed that indicated that they led to a worsening of psychiatric symptoms. However, the relatively small numbers assessed for many of the interventions studied

means that the possibility of such an eff ct cannot confidently be excluded in all cases. Given the small numbers of studies assessing most of the strategies assessed, the presence of any unpublished trials could have substantial effects on estimates of effect. In some cases, only results from particular items or subscales within ratings scales are available. It is likely that this could act to bias estimates of effect obtained, increasing apparent effectiveness.
Authors' conclusions: The evidence currently available is rather limited. For men with antidepressant-induced erectile dysfunction, the addition of sildenafil or tadalafil appears to be an effective strategy. For women with antidepressant-induced sexual dysfunction the addition of bupropion at higher doses appears to be the most promising approach studied so far.

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Aichhorn W, Whitworth AB, Weiss EM, Hinterhuber H, Marksteiner J. **[Differences between men and women in side effects of second-generation antipsychotics]**. Nervenarzt 2007;78(1):45-52.

Abstract: In this review we investigate whether sex differences exist for side effects of second-generation antipsychotics. Results are based on a MEDLINE search for the years 1974 through 2005. Even if pharmacokinetics differ between females and males, significantly higher plasma levels for women have been demonstrated only for olanzapine and clozapine. Hyperprolactinaemia is mainly induced by treatment with risperidone and amisulpride, and there is evidence for more pronounced prolactin levels in females. Most studies reviewed indicate that clozapine and olanzapine are associated with more body weight gain, once more especially in female patients. Furthermore, the few published studies indicate that metabolic syndrome is more frequent in females and there are likely no gender-specific differences between the new antipsychotic medications concerning frequency and degree of acute or chronic movement disturbance. The risk of QT prolongation with torsades de pointes arrhythmia is again higher in females. In conclusion, there is some evidence of sex differences in the side effects of second-generation antipsychotics. For better understanding of the basic mechanisms in sex differences, future studies with a primary focus on this topic are required. More specific data will help to determine how these differences shall affect clinical management.

Bawor M, Dennis BB, Bhalerao A, Plater C, Worster A, Varenbut M, et al. **Sex differences in outcomes of methadone maintenance treatment for opioid use disorder: a systematic review and meta-analysis**. CMAJ open 2015;3(3):E344-351.

Abstract: BACKGROUND: Opioid use disorder is a serious international concern with limited treatment success. Men and women differ in their susceptibility to opioid use disorder and response to methadone treatment and can therefore benefit from sex-specific treatment. We performed a systematic review of the literature on outcomes of methadone maintenance treatment for opioid use disorder in men and women related to drug use, health status and social functioning.
METHODS: We searched PubMed, Embase, PsycINFO and CINAHL for observational or randomized controlled studies involving adults 18 years of age or older undergoing methadone treatment for opioid use disorder. Studies were included if they investigated sex differences in methadone treatment outcomes. Two authors independently reviewed and extracted data. Meta-analyses were performed when possible; risk of bias and quality of evidence were also assessed.
RESULTS: Twenty studies with 9732 participants were included, of which 18 were observational and 2 were randomized controlled trials. Men and women differed significantly in alcohol use (odds ratio [OR] 0.52, 95% confidence interval [CI] 0.31 to 0.86), amphetamine use (OR 1.47, 95% CI 1.12 to 1.94), legal involvement (OR 0.63, 95% CI

0.47 to 0.84) and employment during treatment (OR 0.39, 95% CI 0.21 to 0.73). Opioid use patterns were similar among men and women. Risk of bias was moderate, and quality of evidence was generally low.
INTERPRETATION: Sex differences were evident in polysubstance use, legal involvement and employment status among men and women receiving methadone treatment for opioid use disorders. Although the quality of evidence was low, our review highlights the need for improved implementation of sex-specific treatment strategies.

Davis ML, Smits JA, Hofmann SG. **Update on the efficacy of pharmacotherapy for social anxiety disorder: a meta-analysis**. Expert opinion on pharmacotherapy 2014;15(16):2281-2291.

Abstract: INTRODUCTION: Social anxiety disorder (SAD) is a common mental health problem that tends to be chronic in nature; fortunately, effective pharmacotherapy options exist. The current study provides an updated meta-analytic review of their efficacy and potential guidelines for their application in SAD.
METHODS: A comprehensive search of the current literature yielded 39 randomized, pill placebo-controlled trials of pharmacotherapy for adults diagnosed with SAD. Data on potential moderators of treatment outcome were collected, as well as data necessary to calculate effect sizes using Hedges's g.
RESULTS: The overall effect size of pharmacotherapy for SAD is small to medium (Hedges's g = 0.39). The most effective pharmacotherapy type was phenelzine (Hedges's g = 1.14), followed by paroxetine (Hedges's g = 0.49), venlafaxine ER (Hedges's g = 0.45) and moclobemide (Hedges's g = 0.23).
CONCLUSION: Effect sizes were not moderated by age, sex, length of treatment, diagnostic subtype initial severity, maximum potential dose, or publication year. It is concluded that pharmacotherapy is effective for treating SAD, but there is considerable variation and room for further improvement. Future directions may include pharmacological enhancement of psychological processes, such as d-cycloserine augmentation of exposure procedures.

Graziani M, Nistico R. **Gender differences in pharmacokinetics and pharmacodynamics of methadone substitution therapy**. Frontiers in Pharmacology 2015;6 (MAY) (no pagination)(122).

Abstract: Gender-related differences in the pharmacological effects of drug are an emerging topic. This review examines gender differences in both pharmacokinetic and pharmacodynamic aspects of methadone, a long-acting opioid agonist that is prescribed as a treatment for opioid dependence and the management of chronic pain.
Method: We performed a search in the Medline database from 1990 to 2014 in order to find published literature related to gender differences in pharmacokinetics and pharmacodynamics of methadone.
Results: None of the studies were carried out with the primary or secondary aim to identify any gender differences in the pharmacokinetic profile of methadone. Importantly; high inter-subjects variability in PK parameters was found also intra female population. The reported differences in volume of distribution could be ascribed to the physiological differences between men and women in body weight and composition, taking into account that the dose of methadone was established irrespective of body weight of patients (Peles & Adelson, 2006). On the other hand, the few studies present in literature found no gender difference in some direct pharmacodynamic parameters. Some reports have suggested that female gender is associated with an increased risk for long-QT (LQT)-related cardiac arrhythmias in methadone maintenance subjects.
Conclusion: Even though it may be too simplistic to expect variability only in one parameter to explain inter-individual variation in methadone response, we believe that a better knowledge of gender-related differences might have significant implications for better outcomes in opioid dependence substitution therapy in women.

Haack S, Seeringer A, Thurmann PA, Becker T, Kirchheiner J. **Sex-specific differences in side effects of psychotropic drugs: genes or gender?** Pharmacogenomics 2009;10(9):1511-1526.

Abstract: Sex differences observed in the adverse effects associated with psychotropic drugs have not been reported consistently in the literature. In this review, we discuss the current published data on sex differences observed in the occurrence, symptomatology and reporting of the adverse effects associated with psychotropic drug effects, and discuss their clinical relevance. We reviewed the published data up to April 2009 on sex differences in the side effects of antipsychotics, antidepressant and mood stabilizers, by systematically searching PubMed using combinations of search terms and retrieving relevant references specifically reporting on these issues. The majority of the data was retrieved from clinical studies where the main outcome parameters did not relate specifically to sex differences. In most instances, sex was associated with other factors influencing side effects such as age, disease and body weight. Sex-related differences were reported in the side effects associated with antipsychotic drug-induced weight gain and metabolic syndrome, symptoms of sexual dysfunction caused by antidepressants and antipsychotic drugs and cardiac arrhythmic side effects associated with antipsychotic drugs. Women might differ from men not only in incidence but also in the presentation of clinical symptoms associated with adverse psychotropic drug effects. Clinicians should be made aware of the differences reported in the literature regarding the symptomatology, severity and recognition of the adverse psychotropic drug effects found in men and women.

Moteshafi H, Zhornitsky S, Brunelle S, Stip E. **Comparing tolerability of olanzapine in schizophrenia and affective disorders: a meta-analysis**. Drug Safety 2012;35(10):819-836.

Abstract: BACKGROUND: Olanzapine is prescribed for a number of psychiatric disorders, including schizophrenia, bipolar mania, and unipolar and bipolar depression. Olanzapine treatment is associated with tolerability issues such as metabolic adverse effects (e.g. weight gain, increase in blood glucose, triglycerides and total cholesterol levels), extrapyramidal symptoms [EPS] (e.g. parkinsonism, akathisia, tardive dyskinesia) and sedative adverse effects. Metabolic issues lead to some long-term consequences, which include cardiovascular diseases (CVD) and type 2 diabetes mellitus, and these complications cause high rates of mortality and morbidity among patients with severe mental illnesses. The expanded indications of olanzapine in psychiatry suggest a need to investigate whether there is a difference in the incidence and severity of adverse effects related to category diagnosis. Are the adverse effects expressed differently according to phenotype? Unfortunately, there are no reported studies that investigated these differences in adverse effects associated with olanzapine treatment in psychiatric patients with different phenotypes.
OBJECTIVE: The aim of the present meta-analysis is to separately examine olanzapine-induced cardiometabolic adverse effects and EPS in patients with schizophrenia and affective disorders.
DATA SOURCES: A search of computerized literature databases PsycINFO (1967-2010), PubMed (MEDLINE), EMBASE (1980-2010) and the clinicaltrials.gov website for randomized clinical trials was conducted. A manual search of reference lists of published review articles was carried out to gather further data.
STUDY SELECTION: Randomized controlled trials were included in our study if (i) they assessed olanzapine adverse effects (metabolic or extrapyramidal) in adult patients with schizophrenia or affective disorders; and (ii) they administered oral olanzapine as monotherapy during study.
DATA EXTRACTION: Two reviewers independently screened abstracts for choosing articles and one reviewer extracted relevant data on the basis of predetermined exclusion and inclusion criteria. It should be mentioned that for the affective disorders group we could only find articles related to bipolar disorder.
DATA SYNTHESIS: Thirty-three studies (4831 patients) that address olanzapine monotherapy treatment of adults with schizophrenia or bipolar disorder were included in the analysis. The primary outcomes were metabolic adverse effects (changes in weight, blood glucose, low-density lipoprotein, total cholesterol and triglyceride levels). The

secondary outcomes of our study were assessing the incidence of some EPS (parkinsonism, akathisia and use of antiparkinson medication). The tolerability outcomes were calculated separately for the schizophrenia and bipolar disorder groups and were combined in a meta-analysis. Tolerability outcomes show that olanzapine contributes to weight gain and elevates blood triglycerides, glucose and total cholesterol levels in both schizophrenia and bipolar disorder patients. However, olanzapine treatment produced significantly more weight gain in schizophrenia patients than in bipolar disorder patients. In addition, increases in blood glucose, total cholesterol and triglyceride levels were higher in the schizophrenia group compared with the bipolar disorder group, even though these differences were not statistically significant. Based on our results, the incidence of parkinsonism was significantly higher in the schizophrenia group than in the bipolar disorder group. Subgroup analysis and logistic regression were used to assess the influence of treatment duration, dose, industry sponsorship, age and sex ratio on tolerability outcome.
CONCLUSIONS: Our results suggest that schizophrenia patients may be more vulnerable to olanzapine-induced weight gain. The findings may be explained by considering the fact that in addition to genetic disposition for metabolic syndrome in schizophrenia patients, they have an especially high incidence of lifestyle risk factors for CVD, such as poor diet, lack of exercise, stress and smoking. It might be that an antipsychotic induces severity of adverse effect according to the phenotype.

Viguera AC, Tondo L, Baldessarini RJ. **Sex differences in response to lithium treatment**. The American journal of psychiatry 2000;157(9):1509-1511.

Abstract: OBJECTIVE: Although sex differences occur with some psychotropic drug treatments, they are not well defined for mood-stabilizing agents, including lithium. The authors' goal was to investigate whether there are differences between the sexes in response to lithium.
METHOD: Studies identified in a literature search were analyzed for reports of sex differences in clinical response to lithium in major affective syndromes.
RESULTS: Data from 17 studies published in 1967-1998, involving 1,548 adults treated with lithium for a mean of 38.6 months (SD=30.5), yielded similar weighted response rates to lithium in 1,043 women (65.6% [N=684]) and 505 men (61.0% [N=308]).
CONCLUSIONS: The results indicate little difference between the sexes in clinical response to lithium treatment of bipolar and related affective disorders.

Wehmeier PM, Schacht A, Escobar R, Hervas A, Dickson R. **Health-related quality of life in ADHD: a pooled analysis of gender differences in five atomoxetine trials**. Atten Defic Hyperact Disord 2012;4(1):25-35.

Abstract: Attention-deficit/hyperactivity disorder (ADHD) is associated with considerable impairment in health-related quality of life (HR-QoL). Atomoxetine has been found to improve HR-QoL in both children and adolescents. However, there is scarcity of data on gender differences in treatment responses to ADHD medications. This pooled analysis of five atomoxetine trials aimed to evaluate treatment differences with respect to HR-QoL and ADHD symptoms across genders. Data from 5 clinical atomoxetine trials (4 from Europe and 1 from Canada) with similar inclusion and exclusion criteria and similar durations (8- to 12-week follow-up) were included in the pooled analysis. All studies included the Child Health and Illness Profile-Child Edition (CHIP-CE) Parent Report Form. In addition, correlations between HR-QoL and ADHD core symptoms were compared between girls and boys. Data from 136 girls and 658 boys (mean age: 9.6 and 9.7 years, respectively) were pooled. Boys and girls were similarly impaired at baseline with minor differences in some of the subdomains. Treatment effect of atomoxetine was significant in both groups for the Risk Avoidance domain and its subdomains. No gender effect with both clinical and statistical significance was found for treatment outcome. Correlations between ADHD Rating Scale and CHIP-CE scores were similar in both genders and were generally low at baseline and moderate at endpoint and for the change from baseline to endpoint. Atomoxetine was effective in improving some aspects of HR-QoL in both genders without any significant differences across genders. Correlations between core symptoms of ADHD and HR-QoL were low to moderate in both boys and girls.

Whitney Z, Procyshyn RM, Fredrikson DH, Barr AM. **Treatment of clozapine-associated weight gain: A systematic review**. European Journal of Clinical Pharmacology 2015;71(4):389-401.

Abstract: Purpose: Clozapine is an antipsychotic drug with superior efficacy in treatment-resistant schizophrenia. Clozapine is associated with a low likelihood of extrapyramidal symptoms and other neurological side-effects but a high propensity to induce weight gain and general metabolic dysregulation. Various pharmacological and behavioral treatment approaches for reducing clozapine-associated weight gain exist in the literature; however, there are currently no clear clinical guidelines as to which method is preferred. The aim of the current review is to systematically summarize studies that have studied both pharmacological and non-pharmacological interventions to attenuate or reverse clozapine-associated weight gain.
Methods: A systematic review of EMBASE and MEDLINE databases of all articles published prior to January 2014 was conducted. Seventeen studies were identified as meeting inclusion criteria and included in the review.
Results: Aripiprazole, fluvoxamine, metformin, and topiramate appear to be beneficial; however, available data are limited to between one and three randomized controlled trials per intervention. Orlistat shows beneficial effects, but in males only. Behavioral and nutritional interventions also show modest effects on decreasing clozapine-associated weight gain, although only a small number of such studies exist.
Conclusions: While a number of pharmacological interventions can produce modest weight loss, each may be associated with negative side effects, which should be considered before beginning treatment. Given the pressing need to improve cardiometabolic health in most clozapine-treated patients, substantially more research is needed to develop sound clinical practice guidelines for the treatment of clozapine-associated weight gain.

Young SL, Taylor M, Lawrie SM. **"first do no harm." A systematic review of the prevalence and management of antipsychotic adverse effects**. Journal of Psychopharmacology 2015;29(4):353-362.

Abstract: Aims: We aim to identify the prevalence and management strategies of nine clinically important categories of antipsychotic adverse effects, namely: extrapyramidal symptoms; sedation; weight gain; type II diabetes; hyperprolactinaemia; metabolic syndrome, dyslipidaemia; sexual dysfunction; and cardiovascular effects.
Background: Antipsychotic drugs are widely prescribed for schizophrenia and other mental disorders. The adverse effects of antipsychotics are common, with a potential negative impact on adherence and engagement. Despite this, the scientific study of the prevalence or management of adverse antipsychotic effects is a neglected area.
Method: A systematic review was undertaken using pre-defined search criteria and three databases, with hand searching of citations and references. Inclusion was agreed on by two independent researchers after review of abstracts or full text. Quality analysis of included studies was conducted using pre-agreed criteria.
Results: In total, 53 studies met inclusion criteria, revealing the following: (1) antipsychotic polypharmacy was associated with increased frequency of adverse effects, and (2) a longer duration of treatment is associated with greater severity (e.g. higher BMI); (3) clozapine was more strongly associated with metabolic disturbance than other antipsychotics in three studies and olanzapine was associated with the most weight gain in three studies; (4) hyperprolactinaemia was more common in women than men, but 50% men noted sexual dysfunction versus 2550% in women; (5) despite clinical guideline recommendations there is a low rate of baseline testing for lipids and glucose; and (6) seven studies described adverse effect management strategies, but only two examined their efficacy one found a significant reduction in weight with non-pharmacological group therapy and the other found a significant reduction in dyslipidaemia with statins.
Conclusions: Antipsychotic adverse effects are diverse and frequently experienced, but are not often systematically assessed. There is a need for further scientific study concerning the management of these side effects.

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Averbuch M, Katzper M. **A search for sex differences in response to analgesia**. Arch Intern Med 2000;160(22):3424-3428.

Abstract: BACKGROUND: It is generally accepted that males and females respond differently to painful conditions. With few exceptions, according to the published literature, females demonstrate a lower pain threshold and a lower tolerance of painful stimuli. There is some support in the literature that females experience greater analgesic efficacy than do males after the administration of narcotic analgesics. We compared the analgesic response of females and males to ibuprofen in a post-third-molar extraction dental pain model.
METHODS: We performed a meta-analysis of 314 subjects included in the ibuprofen treatment arm of 7 double-blind, post-third-molar extraction dental pain (moderate to severe) studies, which were submitted to the agency electronically. The inclusion and exclusion criteria were practically identical in all studies. Pain relief and pain intensity measurements used the same metrics in all studies and were recorded just before and at least at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 6. 0 hours after drug administration.
RESULTS: The study included 195 female subjects and 119 male subjects (mean age, 21 years). Other than requiring dental extractions, the subjects were all healthy. Postoperative baseline pain was greater in females than in males to a statistically significant degree (P =.006). Both pain intensity and pain relief scores demonstrated the well-established analgesic effect of ibuprofen in the pooled data set as well as in all the individual studies. Moreover, the mean pain intensity and pain relief scores over time for the female and male treatment groups were not noticeably different at any time point after drug administration, with no imputation for missing values. Analysis of the data using the "baseline observation carried-forward" technique for remedicated subjects (the technique recommended by the Food and Drug Administration for efficacy analysis of acute analgesic medications) produced the same results, which were confirmed by analysis of variance and t tests at each time point of the study.
CONCLUSIONS: Our results demonstrated no sex effect on the analgesic response to ibuprofen. These results were obtained under the post-third-molar extraction setting, in which the least possible confounding factors are present. To fully establish the generality of this phenomenon, studies should be carried out in other pain models and using analgesic medications with different mechanisms of action. Arch Intern Med. 2000;160:3424-3428.

Chen M, Ma L, Drusano GL, Bertino JS, Jr., Nafziger AN. **Sex differences in CYP3A activity using intravenous and oral midazolam.** Clin Pharmacol Ther 2006;80(5):531-538.

Abstract: BACKGROUND: Studies examining sex differences in CYP3A activity have produced conflicting results. Our objective is to investigate whether sex differences exist in CYP3A activity as assessed by intravenous (IV) or oral midazolam pharmacokinetic analysis in healthy volunteers. METHODS: Data from 13 previous studies were used. A single dose of IV midazolam (0.025 mg/kg) was administered to 66 white adults (37 women and 29 men; mean age, 36.3+/-7.7 years). A single dose of oral midazolam, 0.075 mg/kg (5 studies), 0.15 mg/kg (1 study), or 5 mg (1 study), was administered to 72 adults (71 white and 1 Asian; 37 women and 35 men; mean age, 38.3+/-8.9 years). Pharmacokinetic parameters were determined via population methods by use of a nonparametric adaptive grid program and a 2-compartment IV and 1-compartment oral absorption model. The maximum a posteriori probability Bayesian method was used to estimate each subject's pharmacokinetic parameters. Monte Carlo simulation was performed to determine the probability distribution of the area under the concentration-time curves (AUCs).
RESULTS: Women exhibited 11% higher mean weight-corrected total body midazolam clearance and 28% higher oral clearance compared with men (P<or=.01). The median

AUC of IV midazolam was 0.05 mg.h/L (range, 0.02-0.14 mg.h/L) in women and 0.06 mg.h/L (range, 0.02-0.14 mg.h/L) in men. The median AUC of oral midazolam was 0.11 mg.h/L (range, 0.02-0.60 mg.h/L) in women and 0.12 mg.h/L (range, 0.04-0.45 mg.h/L) in men.
CONCLUSIONS: Although women showed significantly greater hepatic and intestinal CYP3A activity, only a minor sex difference in AUC was noted. Therefore the observed disparity may be of negligible clinical importance.

Hu ZY, Zhao YS. **Sex-dependent differences in cytochrome P450 3A activity as assessed by midazolam disposition in humans: a meta-analysis.** Drug metabolism and disposition: the biological fate of chemicals 2010;38(5):817-823.

Abstract: Controversy exists concerning the sex-dependent differences in cytochrome P450 3A activity in humans. Meta-analysis of selected studies may address this question. Meta-analysis was performed on published or unpublished data in terms of sex-dependent differences in midazolam (MDZ) disposition in humans. The following pharmacokinetic parameters were included for the analysis: MDZ oral and systemic clearance, area under the concentration-time curve (AUC) of oral and intravenous MDZ, MDZ oral bioavailability (F), and MDZ gastrointestinal extraction (E(G)). Ten studies including 409 healthy volunteers were identified. Women exhibited 16% higher weight-corrected MDZ oral clearance ($P < 0.001$) and 20% higher systemic clearance ($P = 0.002$) than men. No significant difference in the AUC after oral dosing of MDZ was noted between sexes. Women showed lower AUC of intravenous MDZ than men ($P = 0.02$). No sex-dependent differences were observed in F and E(G). In conclusion, women showed significantly greater hepatic CYP3A activity than men, whereas no sex-dependent difference in intestinal CYP3A activity was observed.

Niesters M, Dahan A, Kest B, Zacny J, Stijnen T, Aarts L, et al. **Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies**. Pain 2010;151(1):61-68.

Abstract: Although a contribution of sex in opioid efficacy has garnered much attention, the confirmation and direction of any such difference remain elusive. We performed a systematic review of the available literature on sex differences in mu and mixed mu/kappa opioid effect on acute and experimental pain. Fifty unique studies (including three unpublished studies) were included in the analyses. Across the 25 clinical studies on mu-opioids there was no significant sex-analgesia association. Restricting the analysis to patient-controlled analgesia (PCA) studies (irrespective of the opioid) yielded greater analgesia in women (n=15, effect size 0.22, 95% c.i. 0.02-0.42, P=0.028). Further restricting the analysis to PCA morphine studies yielded an even greater effect in women (n=11, effect size=0.36, 95% c.i. 0.17-0.56, P=0.003). Meta-regression indicated that the longer the duration of PCA, the difference in effect between the sexes further increased. Across experimental pain studies on mu-opioids women had greater antinociception from opioids (n=11, effect size=0.35; 95% c.i. 0.01-0.69, P=0.047), which was predominantly due to 6 morphine studies. Female patients had greater mu/kappa opioid analgesia (n=7, effect size 0.84; 95% c.i. 0.25-1.43, P=0.005), but no sex-analgesia association was present in experimental studies (n=7). Sex differences exist in morphine-induced analgesia in both experimental pain studies and clinical PCA studies, with greater morphine efficacy in women. The data on non-morphine mu and mixed mu/kappa-opioids are less convincing and require further study.

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Cepeda-Benito A, Reynoso JT, Erath S. **Meta-analysis of the efficacy of nicotine replacement therapy for smoking cessation: differences between men and women**. J Consult Clin Psychol 2004;72(4):712-722.
Abstract: Gender differences in the efficacy of nicotine replacement therapies (NRTs) were examined in a meta-analytical review of 90 effect sizes obtained from a sample of 21 double-blind, placebo-controlled randomized studies. Although NRT was more effective for men than placebo at 3-month, 6-month, and 12-month follow-ups, the benefits of NRT for women were clearly evident only at the 3- and 6-month follow-ups. Giving NRT in conjunction with high-intensity nonpharmacological support was more important for women than men. That is, NRT and low support were efficacious for women at only short-term follow-up, and men benefited from NRT at all the follow-ups regardless of the intensity of the adjunct support. The results suggest that long-term maintenance of NRT treatment gains decrease more rapidly for women than men.

Huang Y, Li W, Yang L, Jiang Y, Wu Y. **Long-term efficacy and safety of varenicline for smoking cessation: A Systematic review and meta-analysis of randomized controlled trials.** Journal of Public Health (Germany) 2012;20(4):355-365.
Abstract: Aim: To evaluate the long-term efficacy and potential risk of psychiatric side effects of varenicline for smoking cessation compared with placebo or nicotine replacement therapy.
Subject and methods: Systematic search of electronic databases (MEDLINE, EMBASE, Cochrane Central Register, SCI) up to March 2011. Two reviewers independently determined the eligibility of randomized controlled trials comparing varenicline with placebo, or nicotine replacement therapy with follow-up of at least 12 months. Information was independently extracted by 2 reviewers.
Results: Ten trials involving 6,375 smokers were included in the meta-analysis. The pooled risk ratios (RR) for continuous abstinence was 2.83 (95% CI: 2.20-3.63) at 52 weeks for varenicline (1 mg, twice per day) versus placebo. Varenicline seemed to be more effective in smokers with chronic obstructive pulmonary disease (RR, 3.33) than smokers with cardiovascular diseases (RR, 2.64) or health smokers (RR, 2.52), non-Asian smokers than Asian smokers (2.98 vs. 1.94), elder smokers than younger smokers (2.87 vs. 2.52), female smokers than male smokers (2.98 vs. 1.94). The five predominant reported adverse events for varenicline compared to placebo were vomiting, nausea, abnormal dreams, constipation, and dysgeusia. There was no sufficient evidence that varenicline was associated with an increased risk of psychiatric side effects (RR, 1.45, 95% CI: 0.90-2.32).
Conclusion: Varenicline therapy compared with placebo is associated with a favorable effect on smoking cessation at the end of 52 weeks. However, the psychiatric adverse events related with varenicline should be further studied with larger qualified study. People with preexisting mental illnesses should be prudently treated with varenicline.
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McKee SA, Smith PH, Kaufman M, Mazure CM, Weinberger AH. **Sex Differences in Varenicline Efficacy for Smoking Cessation: A Meta-Analysis**. Nicotine Tob Res 2016;18(5):1002-1011.
Abstract: INTRODUCTION: Women have lower rates of quitting than men with both bupropion and nicotine replacement. It is unknown whether varenicline demonstrates differential efficacy for men and women. The purpose of this study was to conduct the first comprehensive meta-analysis of clinical trial data examining sex differences in the efficacy of varenicline for smoking cessation.
METHODS: Searching MEDLINE, EMBASE, and PsychINFO, 17 of 43 clinical trials of varenicline for smoking cessation published through December 31, 2014 were low-bias randomized double-blind placebo-controlled trials. Data (n = 6710 smokers, 34% female, n = 16 studies, 96% of available data) was analyzed with Metafor program in R. Outcome endpoints were 7-day point-prevalence (PP) and continuous-abstinence (CA)

at week 12 (end of treatment), week 24 (6-month follow-up), and week 52 (12-month follow-up).
RESULTS: Using placebo, women were less likely than men to quit (PP-12, CA-24; P < .05 for sex). Using varenicline, similar rates of abstinence for men and women were demonstrated for all six outcomes (eg, PP-12 abstinence rates were 53% in both women and men). Varenicline versus placebo outcomes demonstrated that varenicline was more effective for women for short and intermediate outcomes (PP-12, CA-12, CA-24; P < .05 sex x medication interaction). For end-of-treatment PP, varenicline was 46% more effective for women. For continuous abstinence, varenicline was 34% (CA-12) and 31% (CA-24) more effective for women.
CONCLUSIONS: Unlike other smoking cessation medications, varenicline demonstrated greater efficacy among women smokers for short and immediate-term outcomes and equal efficacy for 1-year outcomes. Varenicline may be particularly useful for reducing the sex disparity typically seen in rates of smoking cessation.
IMPLICATIONS: Varenicline is currently the most effective FDA-approved smoking cessation medication and this is the first demonstration that women compared with men have a preferred therapeutic response for a smoking cessation medication when considering short-term outcomes. Importantly, this is also the first demonstration that women have similar rates of quitting to men when considering longer-term, 1-year outcomes.

Munafò M, Bradburn M, Bowes L, David S. **Are there sex differences in transdermal nicotine replacement therapy patch efficacy?** A meta-analysis. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2004;6(5):769-776.

Abstract: Smoking-related death and disability rates for women have risen sharply recently. Despite lower smoking cessation success rates for women using behavioral therapies, data are limited on whether specific pharmacological therapies are equally efficacious in men and women. Using meta-analytic techniques, we examined whether significant differences in therapeutic efficacy of nicotine replacement therapy (NRT) for smoking cessation exist by sex. Out of the 31 randomized clinical trials of NRT that met inclusion criteria, 11 contributed to the analysis. The odds ratios for NRT vs. placebo were derived from each trial separately by sex for males and females, and these ratios were combined to give a pooled estimate of the effect of sex in response to NRT. NRT was effective at all time points in men (< 6 months: OR = 2.05, 95% CI= 1.61-2.60; 6 months: OR = 1.98, 95% CI = 1.51-2.60; 12 months: OR = 1.86, 95% CI = 1.39-2.50) and women (< 6 months: OR = 2.09, 95% CI = 1.65-2.65; 6 months, OR = 1.52, 95% CI = 1.17-1.98; 12 months: OR = 1.63, 95% CI = 1.22-2.18). At all time points, no significant difference was observed between sexes (< 6 months: OR = .97, 95% CI = .69-1.36; 6 months: OR = 1.33, 95% CI = .91-1.95; 12 months: OR = 1.21, 95% CI = .79-1.84). The results of this meta-analysis do not support the hypothesis that NRT has higher therapeutic efficacy for men than women.

Perkins KA, Scott J. **Sex differences in long-term smoking cessation rates due to nicotine patch**. Nicotine Tob Res 2008;10(7):1245-1250.

Abstract: Compared to men, women may be at greater risk for smoking-related diseases and have greater difficulty quitting smoking. Sex differences in medication response could guide treatment for smoking cessation to improve women's quit rates. We conducted a meta-analysis of the 14 placebo-controlled nicotine patch trials (N = 6,250) for which long-term (6 months) clinical outcome results could be determined separately by sex. This analysis updated a meta-analysis of 11 of these trials that found no significant sex differences due to nicotine patch. The increase in quitting due to the nicotine vs. placebo patch was only about half as large in women as in men. Pooled absolute quit rates at 6 months for nicotine and placebo patch, respectively, were 20.1% and 10.8% in men, and 14.7% and 10.1% in women. The odds ratio for quitting due to nicotine vs. placebo patch was lower in women (OR = 1.61) than in men (OR = 2.20), with an interaction odds ratio of 1.40 (95% CI = 1.02-1.93, p = .04). This sex difference did not vary significantly by whether or not formal counseling was provided. Poorer

outcomes in women vs. men treated with nicotine patch suggests that increasing the quit rates of women smokers may require supplementing patch treatment or use of other medications.

Scharf D, Shiffman S. **Are there gender differences in smoking cessation, with and without bupropion?** Pooled- and meta-analyses of clinical trials of Bupropion SR. Addiction 2004;99(11):1462-1469.

Abstract: AIMS: In this study, we examine gender differences in smoking cessation with and without treatment with Bupropion SR. We test whether women and men have comparable success rates quitting smoking regardless of treatment, whether Bupropion SR is effective for women, and whether Bupropion SR efficacy differs for men and women.
DESIGN: A literature search was conducted to identify relevant trials. Data were analyzed with individual-level (pooled) and study-level (meta-analytical) statistics.
PARTICIPANTS: Data from 4421 participants in 12 randomized smoking cessation trials of Bupropion SR 300 mg versus placebo were analyzed.
FINDINGS: Results from the meta-analysis revealed that Bupropion SR was an effective aid to smoking cessation [odds ratio (OR) = 2.49, 95% confidence interval (CI) = 2.06-3.00]. Moreover, Bupropion SR proved to be an effective cessation aid for women (OR = 2.47, 95% CI = 1.92-3.17). No treatment-gender interaction was observed; women and men benefited equally from treatment with Bupropion SR (Q = 0.01, NS). Overall, women were less successful at quitting than men, regardless of treatment (OR = 0.79, 95% CI = 0.65-0.95). These results were replicated with pooled, individual-level analyses.
CONCLUSIONS: Bupropion SR is an effective smoking cessation aid for women. In these trials, women have less success quitting smoking than men, whether treated with Bupropion SR or placebo. There is a need to understand more about why women are less able to quit.

Thomas KH, Martin RM, Knipe DW, Higgins JP, Gunnell D. **Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis**. BMJ (Clinical research ed) 2015;350:h1109.

Abstract: OBJECTIVE: To determine the risk of neuropsychiatric adverse events associated with use of varenicline compared with placebo in randomised controlled trials.
DESIGN: Systematic review and meta-analysis comparing study effects using two summary estimates in fixed effects models, risk differences, and Peto odds ratios.
DATA SOURCES: Medline, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov.
ELIGIBILITY CRITERIA FOR SELECTING STUDIES: Randomised controlled trials with a placebo comparison group that reported on neuropsychiatric adverse events (depression, suicidal ideation, suicide attempt, suicide, insomnia, sleep disorders, abnormal dreams, somnolence, fatigue, anxiety) and death. Studies that did not involve human participants, did not use the maximum recommended dose of varenicline (1 mg twice daily), and were cross over trials were excluded.
RESULTS: In the 39 randomised controlled trials (10 761 participants), there was no evidence of an increased risk of suicide or attempted suicide (odds ratio 1.67, 95% confidence interval 0.33 to 8.57), suicidal ideation (0.58, 0.28 to 1.20), depression (0.96, 0.75 to 1.22), irritability (0.98, 0.81 to 1.17), aggression (0.91, 0.52 to 1.59), or death (1.05, 0.47 to 2.38) in the varenicline users compared with placebo users. Varenicline was associated with an increased risk of sleep disorders (1.63, 1.29 to 2.07), insomnia (1.56, 1.36 to 1.78), abnormal dreams (2.38, 2.05 to 2.77), and fatigue (1.28, 1.06 to 1.55) but a reduced risk of anxiety (0.75, 0.61 to 0.93). Similar findings were observed when risk differences were reported. There was no evidence for a variation in depression and suicidal ideation by age group, sex, ethnicity, smoking status, presence or absence of psychiatric illness, and type of study sponsor (that is, pharmaceutical industry or other).
CONCLUSIONS: This meta-analysis found no evidence of an increased risk of suicide or attempted suicide, suicidal ideation, depression, or death with varenicline. These

findings provide some reassurance for users and prescribers regarding the neuropsychiatric safety of varenicline. There was evidence that varenicline was associated with a higher risk of sleep problems such as insomnia and abnormal dreams. These side effects, however, : are already well recognised. SYSTEMATIC REVIEW REGISTRATION: PROSPERO 2014:CRD42014009224.

Vogel RI, Hertsgaard LA, Dermody SS, Luo X, Moua L, Allen S, et al. **Sex differences in response to reduced nicotine content cigarettes**. Addictive Behaviors 2014;39(7):1197-1204.

Abstract: Background: When switching from usual brand cigarettes, very low nicotine content (VLNC) cigarettes lead to a reduction in the number of cigarettes smoked, toxicant exposure, withdrawal symptoms and dependence. One area that has been relatively unexplored is what factors might moderate the effects of VLNC cigarettes. This exploratory analysis focuses on sex differences in responses to VLNC cigarettes and nicotine replacement therapy.
Methods: An exploratory secondary analysis of a randomized trial of 235 participants (58% female, mean age 47 years) comparing a) 0.05-0.09 mgnicotine yield cigarettes; b) 21mgnicotine patch and 3) 0.05-0.09 nicotine yield cigarettes with 21mg nicotine patch was conducted. We focused on sex differences in product use, and impact of products on withdrawal response from usual brand cigarettes and abstinence by randomized group.
Results: The combination of VLNC cigarettes and nicotine patch was more effective in reducing use of VLNC cigarettes and withdrawal symptoms among males than females, whereas females were equally responsive to VLNC cigarettes with and without the nicotine patch. Females were more likely to quit smoking than males when assigned to either of the conditions that incorporated the VLNC cigarettes; however, males were more likely to quit smoking in the nicotine patch alone condition than females.
Conclusion: Sex of the smoker may be an important determinant for effects of VLNC cigarettes and nicotine patch. Future large randomized trials to confirm these results are needed. (PsycINFO Database Record (c) 2014 APA, all rights reserved) (journal abstract).

Weinberger AH, Smith PH, Kaufman M, McKee SA. **Consideration of sex in clinical trials of transdermal nicotine patch: a systematic review.** Experimental and clinical psychopharmacology 2014;22(5):373-383.

Abstract: Transdermal nicotine patch (TNP) is 1 of the most commonly used smoking cessation treatments; however, the efficacy of TNP by sex is not yet clear. The purpose of the current review was to synthesize how sex has been considered in published clinical trials of TNP for smoking cessation. The specific aims of the study were to examine the inclusion of sex in analyses of cessation outcomes, TNP-related variables (compliance, side effects), and quit-related variables (withdrawal, cravings); to review the consideration of sex-related variables (menstrual cycle phase, pregnancy); and to identify needs for future research. Potential articles published through December 31, 2013 were identified through a MEDLINE search of the terms "clinical trial," "nicotine patch," and "smoking cessation." Forty-two studies used all 3 terms and met the inclusion criteria. Approximately half of the studies reported that they considered sex in smoking cessation outcomes, with 15 studies finding no difference by sex and 7 studies finding better outcomes for men versus women. Only 5 studies reported data on outcomes by sex in their publications. No studies reported analysis of TNP compliance or withdrawal by sex. In the 1 study that examined side effects by sex, more women than men reported discontinuing TNP because of skin irritation. No study examined the association of cessation outcomes with menstrual cycle phase. There is a need to include sex in research on TNP, as well as other pharmacological and behavioral smoking treatments, to clarify the picture of treatment efficacy for women compared with men.

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Alhawassi TM, Krass I, Bajorek BV, Pont LG. **A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting.** Clinical interventions in aging 2014;9:2079-2086.

Abstract: Adverse drug reactions (ADRs) are an important health issue. While prevalence and risk factors associated with ADRs in the general adult population have been well documented, much less is known about ADRs in the elderly population. The aim of this study was to review the published literature to estimate the prevalence of ADRs in the elderly in the acute care setting and identify factors associated with an increased risk of an ADR in the elderly. A systematic review of studies published between 2003 and 2013 was conducted in the Cochrane Database of Systematic Reviews, EMBASE, Google Scholar and MEDLINE. Key search terms included: "adverse drug reactions", "adverse effects", "elderly patients and hospital admission", "drug therapy", "drug adverse effects", "drug related", "aged", "older patients", "geriatric", "hospitalization", and "emergency admissions". For inclusion in the review, studies had to focus on ADRs in the elderly and had to include an explicit definition of what was considered an ADR and/or an explicit assessment of causality, and a clear description of the method used for ADR identification, and had to describe factors associated with an increased risk of an ADR. Fourteen hospital-based observational studies exploring ADRs in the elderly in the acute care setting were eligible for inclusion in this review. The mean prevalence of ADRs in the elderly in the studies included in this review was 11.0% (95% confidence interval [CI]: 5.1%-16.8%). The median prevalence of ADRs leading to hospitalization was 10.0% (95% CI: 7.2%-12.8%), while the prevalence of ADRs occurring during hospitalization was 11.5% (95% CI: 0%-27.7%). There was wide variation in the overall ADR prevalence, from 5.8% to 46.3%. Female sex, increased comorbid complexity, and increased number of medications were all significantly associated with an increased risk of an ADR. Retrospective studies and those relying on identification by the usual treating team reported lower prevalence rates. From this review, we can conclude that ADRs constitute a significant health issue for the elderly in the acute care setting. While there was wide variation in the prevalence of ADRs in the elderly, based on the findings of this study, at least one in ten elderly patients will experience an ADR leading to or during their hospital stay. Older female patients and those with multiple comorbidities and medications appear to be at the highest risk of an ADR in the acute care setting.

Bacon RA, Mizoguchi H, Schwartz JR. **Assessing therapeutic effectiveness of scalp treatments for dandruff and seborrheic dermatitis, part 2: the impact of gender and ethnicity on efficacy**. Journal of Dermatological Treatment 2014;25(3):237-240.

Abstract: BACKGROUND: Dandruff and seborrheic dermatitis (D/SD) are common and troublesome scalp conditions that affect individuals independent of gender or ethnicity.AIM: To evaluate whether population gender or ethnic origins impact the magnitude of anti-dandruff therapeutic benefit obtained from use of a potentiated zinc pyrithione shampoo treatment.

METHODS: A retrospective evaluation of anti-dandruff clinical data covering a single-product technology was conducted to assess whether statistically meaningful differences were observed for gender or ethnic sub-populations. An analysis of covariance was performed on the pooled subject-level data.

RESULTS: Meta-analysis of clinical data involving 1114 subjects from seven trials demonstrated the lack of statistically significant impact of gender on flaking or selected biomarker measures. Similarly, a smaller population chosen to assess ethnicity demonstrated the lack of differences between Asian and Caucasian clinical sub-population responses (flaking severity).

CONCLUSION: Through the use of both expert symptom grading and objective biomarker assessments, therapeutic efficacy of a potentiated zinc pyrithione shampoo was found to be independent of gender and ethnicity, being consistent with the lack of functional differences in skin from these populations.

Boev R, Song D, Bedenbaugh A, Haeusler JM. **Improving SAR symptoms with levocetirizine: evaluating active and placebo effects in pollen challenge vs. natural exposure studies**. Current Medical Research & Opinion 2011;27(1):107-114.

Abstract: OBJECTIVE: Despite a plethora of published data on levocetirizine, no meta-analyses exist on the effect of study design, and covariates like age, gender, and baseline symptom severity on treatment response. The objective of this study was the efficacy of levocetirizine 5 mg tablets and matching placebo at reducing allergy symptoms in adult subjects with seasonal allergic rhinitis under various pollen exposure study conditions and by age, gender and baseline symptom severity.
METHODS: This was a meta-analysis of original reports from randomized, double-blind, placebo-controlled studies. Clinical studies without detailed reports, open-label, non-randomized and non-controlled studies, or paediatric studies, were excluded. Study subjects were divided into an environmental exposure (EE) group or a natural exposure (NE) group.
RESULTS: Data from 3640 subjects were analysed (n=2174 for levocetirizine, n=1466 for placebo). The overall results confirmed the efficacy of levocetirizine 5 mg, with an approximately 40% symptom score improvement from baseline, in both the EE and NE groups. While levocetirizine showed no gender- or age-related differences in efficacy, female subjects responded better to placebo in the EE, but not in the NE group; younger subjects (<30 years of age) responded less favourably to placebo compared with older subjects (> 50 years of age). Levocetirizine was consistently superior to placebo regardless of baseline symptom score levels. The highest significance levels between the active and placebo groups were observed in subjects sensitized to animal dander and grass.
CONCLUSIONS: Differences between an oral antihistamine and placebo in clinical studies of allergic rhinitis might be due to a different response to placebo rather than to the active drug. Levocetirizine seems to have consistent efficacy regardless of age, gender, and baseline scores.

Castilho JL, Melekhin VV, Sterling TR. **Sex differences in HIV outcomes in the highly active antiretroviral therapy era: a systematic review**. AIDS Res Hum Retroviruses 2014;30(5):446-456.

Abstract: To assess sex disparities in AIDS clinical and laboratory outcomes in the highly active antiretroviral therapy (HAART) era we conducted a systematic review of the published literature on mortality, disease progression, and laboratory outcomes among persons living with HIV and starting HAART. We performed systematic PubMed and targeted bibliographic searches of observational studies published between January, 1998, and November, 2013, that included persons starting HAART and reported analyses of mortality, progression to AIDS, or virologic or immunologic treatment outcomes by sex. Risk ratios (relative risks, odd ratios, and hazard ratios) and 95% confidence intervals were obtained. Sixty-five articles were included in this review. Thirty-nine studies were from North America and Europe and 26 were from Latin America, Asia, and Africa. Forty-four studies (68%) showed no statistically significant difference in risk of mortality, progression to AIDS, or virologic or immunologic treatment outcomes by sex. Decreased risk of death among females compared to males was observed in 24 of the 25 articles that included mortality analyses [pooled risk ratio 0.72 (95% confidence interval=0.69-0.75)], and decreased risk of death or AIDS was observed in 9 of the 13 articles that examined the composite outcome [pooled risk ratio=0.91 (0.84-0.98)]. There was no significant effect of sex on the risk of progression to AIDS [pooled risk ratio=1.15 (0.99-1.31)]. In this systematic review, females starting HAART appeared to have improved survival compared to males. However, this benefit

was not associated with decreased progression to either AIDS or to differences in virologic or immunologic treatment outcomes.

Cheng J. **Doxycycline sclerotherapy in children with head and neck lymphatic malformations**. Journal of Pediatric Surgery 2015;50(12):2143-2146.

Abstract: Objective This is a systematic review of the literature describing doxycycline sclerotherapy (DS) to treat pediatric head and neck lymphatic malformations and examine patient factors associated with treatment success.
Data sources PubMed, EMBASE, and Ovid. Review methods A query of PubMed, EMBASE, and Ovid search engines (1995-2014) for studies examining outcomes for doxycycline sclerotherapy (DS) as primary treatment strategy for children with head and neck lymphatic malformations was undertaken. Successful outcome was defined as clinical resolution of symptoms or greater than 50% reduction in radiographic involvement.
Results Five studies met the inclusion criteria for review. All were retrospective case series reports with high risk of bias. The dose of doxycycline used in all but one of the studies was 10 mg/mL, and the highest concentration administered was 20 mg/mL. Thirty-eight children met the inclusion criteria for analysis. Thirty-two (84.2%) children were successfully treated with DS, with 23 (60.5%) utilizing only one treatment session. Average follow-up was 9.7 months. Age, gender, de Serres stage 1, and type of lymphatic malformation were not related to successful treatment outcome ($p = 0.23$, 1, 1, and 0.13, respectively).
Conclusions DS is very effective for treatment of macrocystic and mixed head and neck lymphatic malformations in children. Overall success with DS treatment in children with lymphatic malformation of the head and neck was 84.2%. DS has distinct advantages over other sclerotherapy agents including that it is inexpensive and widely available, and has minimal side effects. No associated patient characteristics were found to predict improved success.

Forte ML, Butler M, Andrade KE, Vincent A, Schousboe JT, Kane RL. **Treatments for Fibromyalgia in Adult Subgroups**.2015. (AHRQ Comparative Effectiveness Reviews).

Abstract: OBJECTIVE: We conducted a systematic literature review of clinical trials to assess the comparative effectiveness of treatments for fibromyalgia in subgroups of highly affected or clinically comoplex adults. We focused on patient subgroups rather than overall treatment effects to complement a large systematic review being conducted on fibromyalgia treatments at McMaster University.
DATA SOURCES: We searched Medline(®), Embase(®), PsycINFO(®), AMED, and the Cochrane Central Register of Controlled Trials (CENTRAL) plus reference lists of included studies and recent systematic reviews.
METHODS: Two investigators screened abstracts of identified references for eligibility (enrolled adults with fibromyalgia, examined treatment effects, had a control group, and assessed outcomes at least 3 months after treatment initiation). Full-text articles were reviewed to identify outcomes reporting for at least one adult subgroup: women, older or obese adults, individuals with coexisting mental health conditions, high severity or longer fibromyalgia duration, multiple medical comorbidities, or other chronic pain conditions. Primary outcomes included pain, symptom improvement, function, fatigue, sleep quality, participation, and health-related quality of life. We extracted data, assessed risk of bias of individual studies, and evaluated strength of evidence for each comparison and outcome.
RESULTS: We identified 22 randomized controlled trials (RCTs), 8 pooled analyses of patient-level RCT data, and 4 observational studies that met inclusion criteria; 59 percent were drug trials. Adults with fibromyalgia and major depressive disorder (MDD) were studied most often; drug studies also reported outcomes by age, sex, race, and anxiety. Most drug trials examined duloxetine effects on pain and global improvement; trial duration was typically 3 months. Low-strength evidence for duloxetine suggests that subgroups of adults with fibromyalgia and MDD do not experience differential short-term treatment effects. Other subgroup evidence is largely insufficient. For nearly all comparisons, treatment-by-subgroup interactions were not significant. Most

interaction results were reported in text; only two RCTs and five pooled RCT analyses displayed data on subgroup outcomes. Losses to followup were considerable; dropout reporting was not subgroup specific. Adverse effects were reported for the MDD subgroup in one duloxetine pooled analysis; these were similar to overall adverse effects. Studies were not powered to detect subgroup effects.
CONCLUSION: Despite the prevalent belief that fibromyalgia treatments may behave differently in subgroups, evidence to date is largely insufficient for fibromyalgia subgroup effects of interventions other than duloxetine in adults with concomitant MDD. Future studies should be designed to support subgroup analysis to improve clinical applicability.

Gender-specific differences of drug effects with regard to age groups (Project record). Health Technology Assessment Database 2015 (2).

Griffioen M, Halsey N. **Gender differences in immediate hypersensitivity reactions to vaccines: a review of the literature**. Public Health Nurs 2014;31(3):206-214.

Abstract: OBJECTIVE: To examine published studies of immediate hypersensitivity reactions (IHS) following vaccination and to determine whether women are at an increased risk of developing IHS after vaccination.
DESIGN AND SAMPLE: PubMed was reviewed for vaccine articles reporting IHS by gender through June 2012. Data were abstracted on type of study, vaccine, hypersensitivity reaction, and statistic reported. MEASURES: Articles were included if they described experimental, quasi-experimental, correlational or descriptive studies and IHS was reported by gender.
RESULTS: Of 847 articles found in PubMed, 11 met the inclusion criteria. In eight studies, more women than men reported IHS, in two studies more men than women reported IHS and in one study the count was even.
CONCLUSION: Limited data from these studies suggest that women may have higher rates of IHS reactions following vaccination than men. Limitations to the available data include the lack of denominator data and that the definition of IHS was not consistent across the studies. Large-scale population-based studies are indicated to determine if there are differences in rates by gender and biologic basis for these differences.

Hansen RA, Gartlehner G, Lohr KN, Kaufer DI. **Functional outcomes of drug treatment in Alzheimer's disease: a systematic review and meta-analysis**. Drugs & Aging 2007;24(2):155-167.

Abstract: BACKGROUND: Patient functioning is an important outcome in Alzheimer's disease, but treatment-related improvements in patient function are difficult to quantify because a number of different scales are used in its measurement.
OBJECTIVE: To evaluate systematically the evidence relating to patient functioning as an outcome measure in the drug treatment of Alzheimer's disease. Data were obtained by searching MEDLINE((R)), EMBASE, The Cochrane Library and the International Pharmaceutical Abstracts from 1980 through to December 2005 for studies assessing functional outcomes with donepezil, galantamine, rivastigmine and memantine in Alzheimer's disease. Reference lists were searched manually and pharmaceutical manufacturers were invited to submit dossiers. Trained reviewers abstracted data and assessed the internal validity (quality) of trials using predefined criteria. Standardised effect sizes (i.e. Cohen's standardised mean difference [d]) for various functional outcome scales and pooled mean incidence and 95% CIs for adverse events were calculated and summarised qualitatively and quantitatively. Meta regression was used to explore potential heterogeneity.
RESULTS: Overall, the standardised effect size for functional outcome measures was small (d = 0.1-0.4) among included studies. However, effect sizes consistently favoured drug treatment over placebo. For all drugs, pooled standardised effect sizes were consistent in both short (<24 weeks; d = 0.25; 95% CI 0.13, 0.37) and long trials (>/=24

weeks; d = 0.29; 95% CI 0.22, 0.36). The pooled effect size was not significantly affected by parameters such as disease severity, age, gender and drug dose. Adverse events were generally limited to gastrointestinal problems, weight loss and dizziness, all of which were reported in <20% of patients on average.
CONCLUSIONS: Standardised estimates of effect size across diverse functional outcome measures for drug treatment in patients with Alzheimer's disease were small and the data reflect only a modest trend favouring active treatment over placebo. However, given the current lack of other effective treatments for Alzheimer's disease, this trend supports the clinical benefits of these treatments with regard to this important health outcome.

Halsey NA, Griffioen M, Dreskin SC, Dekker CL, Wood R, Sharma D, et al. **Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: reports to VAERS**. Vaccine 2013;31(51):6107-6112.

Abstract: BACKGROUND: Hypersensitivity disorders following vaccinations are a cause for concern.
OBJECTIVE: To determine the type and rate by age, gender, and vaccine received for reported hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines.
DESIGN: A systematic review of reports to the Vaccine Adverse Event Reporting System (VAERS) following monovalent 2009 pandemic influenza A (H1N1) vaccines.
SETTING/PATIENTS: US Civilian reports following vaccine received from October 1, 2009 through May 31, 2010.
MEASUREMENTS: Age, gender, vaccines received, diagnoses, clinical signs, and treatment were reviewed by nurses and physicians with expertise in vaccine adverse events. A panel of experts, including seven allergists reviewed complex illnesses and those with conflicting evidence for classification of the event.RESULTS: Of 1984 reports, 1286 were consistent with immediate hypersensitivity disorders and 698 were attributed to anxiety reactions, syncope, or other illnesses. The female-to-male ratio was >4:1 for persons 20-to-59 years of age, but approximately equal for children under 10. One hundred eleven reports met Brighton Collaboration criteria for anaphylaxis; only one-half received epinephrine for initial therapy. The overall rate of reported hypersensitivity reactions was 10.7 per million vaccine doses distributed, with a 2-fold higher rate for live vaccine.
LIMITATIONS: Underreporting, especially of mild events, would result in an underestimate of the true rate of immediate hypersensitivity reactions. Selective reporting of events in adult females could have resulted in higher rates than reported for males.
CONCLUSIONS: Adult females may be at higher risk of hypersensitivity reactions after influenza vaccination than men. Although the risk of hypersensitivity reactions following 2009 pandemic influenza A (H1N1) vaccines was low, all clinics administering vaccines should be familiar with treatment guidelines for these adverse events, including the use of intramuscular epinephrine early in the course of serious hypersensitivity reactions.

Juul KV, Klein BM, Norgaard JP. **Long-term durability of the response to desmopressin in female and male nocturia patients**. Neurourol Urodyn 2013;32(4):363-370.

Abstract: AIMS: To explore the durability of efficacy and gender differences during chronic administration of desmopressin in nocturia.
METHODS: This pooled analysis of three short-term efficacy studies, with extensions, of desmopressin administered as orally disintegrating tablet (ODT) or solid tablet in nocturia treatment, comprised 351 patients completing 40-56 weeks' treatment. Efficacy endpoints of change in number of nocturnal voids and duration of initial undisturbed sleep period from baseline were analyzed to determine response durability and gender differences.
RESULTS: The mean decrease in number of nocturnal voids during short-term treatment was maintained and further reduced during the long term. At 52 weeks, the mean

decrease in number of nocturnal voids from baseline reached 1.4-2.1 voids for desmopressin ODT 25-100 microg. Following 40-week tablet treatment, the decrease in number of nocturnal voids was 0.8-1.5 for desmopressin 100-400 microg. The mean decrease in nocturnal voids (25-50 microg ODT) was greater for females than males. For females, the improvement in initial period of undisturbed sleep was 2.5-3 hr for desmopressin ODT 25-100 microg, compared with 1.3-2.6 hr for males. No gender difference in efficacy was seen in the tablet studies.
CONCLUSIONS: The decrease in nocturnal voids and improvement in sleep with short-term desmopressin treatment were maintained throughout long-term treatment. A durable gender difference in efficacy in favor of females was observed with desmopressin ODT 25 microg. Further, large-scale long-term trials are needed to confirm the durability of efficacy with gender-specific doses of desmopressin.

Kamath GR, Shah DP, Hwang LY. **Immune response to hepatitis B vaccination in drug using populations: a systematic review and meta-regression analysis**. Vaccine 2014;32(20):2265-2274.

Abstract: Injecting and non-injecting drug users are at increased risk of contracting HBV infection, and show lower antibody response to hepatitis B vaccination compared to the general population. This systematic review and meta-regression analysis aimed to estimate seroprotection rates and identify host or vaccine factors associated with varying immune response following hepatitis B vaccination in drug using populations. Original research articles were searched using online databases (Medline, PubMed, and Embase) and from reference lists of eligible articles. HBV vaccine intervention studies reporting seroprotection rates in drug users, published in English during or after 1989 were eligible. Of 978 citations reviewed, 11 studies were eligible and included for final analysis. The reported seroprotection rates ranged from 54.5% to 97.1%. The studies were significantly heterogeneous (Q=180.850, p=0.000). Measurement of anti-HBs antibody at 2 months after the third vaccine dose (RR=2.62, 95%CI=1.16-5.94, p=0.026) was significantly associated with higher seroprotection rates compared to measurement at 1 month and 6 month following third vaccine dose. Age, gender, current drug use, vaccine dose and schedule, anti-HBc, anti-HCV and anti-HIV antibody seropositivity, and proportion of IDU study population did not show a significant association with seroprotection rates. Recommendations for future research include the definition of a standardized time point for the measurement of anti-HBs antibody levels, to enhance comparability of the immune response between different studies. Studies should strive to accurately report all potentially relevant factors affecting immune response to vaccine. Long-term follow up studies are needed to assess the seroprotection status in drug using populations receiving hepatitis B vaccine by standard or accelerated schedules.

Kargar M, Mansouri A, Hadjibabaie M, Javadi M, Radfar M, Gholami K. **Anti-tuberculosis drugs adverse reactions: a review of the Iranian literature**. Expert opinion on drug safety 2014;13(7):875-891.

Abstract: INTRODUCTION: Tuberculosis (TB) treatment, in particular therapy for multidrug-resistant TB (MDR-TB), is associated with toxicities and adverse drug reactions (ADRs).
AREAS COVERED: This paper reviews Iranian literature reporting ADRs which occurred during tuberculosis treatment. English language papers were sourced from PubMed, ScienceDirect, Wiley, Ovid and Proquest, with Google Scholar searched for Persian language articles. Reported ADRs, proportion of patients with ADRs, risk factors and determinants, as well as the characteristics of the studies were reviewed. 21 articles were included; about 60% of them were in English and three included patients with MDR-TB. The ratio of ADR per capita was 1.9 (in 6 studies) and 33.63% of patients developed an ADR (in 7 studies). Hepatitis (2.5 - 45.3%) was reported in nearly all of the studies. The mean time from initiation of medication to development of hepatitis ranged from 4.67 to 25.25 days (in 6 studies). Most cases of mortality were due to hepatotoxicity. Except for comorbidities and female gender, other risk factors such as HIV and length of hospitalization were only reported in one article.

EXPERT OPINION: The pattern of ADRs in Iranian articles was found to be similar to many other studies in the present review. We suggest that future studies resolve the confounding factors in this area that are mentioned in this review.

Nicastri E, Leone S, Angeletti C, Palmisano L, Sarmati L, Chiesi A, et al. **Sex issues in HIV-1-infected persons during highly active antiretroviral therapy: a systematic review**. J Antimicrob Chemother 2007;60(4):724-732.

Abstract: BACKGROUND: Since the introduction of highly active antiretroviral therapy (HAART), morbidity and mortality rates have sharply decreased among HIV-infected patients. Studies of possible differences between men and women in the course of HIV infection give conflicting results. The objective of this study was to assess sex differences during HAART.
METHODS: A literature search by using the MEDLINE database between March 2002 and February 2007 was performed to identify all published studies on the sex-specific differences on the impact of HAART. All articles with measures of effect (preferably adjusted odds ratio, relative risk or hazard ratio with 95% CI) of sex on viroimmunological and clinical parameters during HAART were included. Five different topics of interest in our research were selected: time of initiation of HAART, adherence, viroimmunological response, clinical response and adverse reactions during HAART.
RESULTS: US data report an initiation of HAART at an earlier disease stage in men compared with women. After initiation of HAART, most authors do not report any viroimmunological difference, although a few clinical studies showed a significantly better virological response in women compared with men. Nevertheless, women were more likely to be less adherent to antiretrovirals and to have non-structured treatment interruptions than men. This is likely to be related to the higher number of adverse reactions they experience during HAART. Finally, discordant opinions with regard to clinical benefits during HAART exist, but recent clinical and observational trials suggest a better clinical outcome for women.
CONCLUSIONS: We found little evidence of sex differences during antiretroviral treatment. Nevertheless, most of these studies were underpowered to detect sex differences and had limited follow-up at 6 or 12 months. Design of new gender-sensitive clinical trials with both prolonged follow-up and sample size representative of the current HIV prevalence among women are strongly needed to detect the likely sex differences of antiretroviral agents during HIV infection.

Ordooei Javan A, Shokouhi S, Sahraei Z. **A review on colistin nephrotoxicity**. European Journal of Clinical Pharmacology 2015;71(7):801-810.

Abstract: Purpose: Colistin is an antibiotic that was introduced many years ago and was withdrawn because of its nephrotoxicity. Nowadays, reemergence of this antibiotic for multi-drug resistant Gram-negative infections, and a new high dosing regimen recommendation increases concern about its nephrotoxicity. This review attempts to give a view on colistin nephrotoxicity, its prevalence especially in high doses, the mechanism of injury, risk factors, and prevention of this kidney injury. Method: The data collection was done in PubMed, Scopus and Cochrane databases. The keywords for search terms were "colistin", "nephrotoxicity", "toxicity", "renal failure", "high dose", and "risk factor". Randomized clinical trials and prospective or retrospective observational animal and human studies were included. In all, 60 articles have been reviewed. Result and conclusion: Colistin is a nephrotoxic antibiotic; a worldwide increase in nosocomial infections has led to an increase in its usage. Nephrotoxicity is the concerning adverse effect of this drug. The mechanism of nephrotoxicity is via an increase in tubular epithelial cell membrane permeability, which results in cation, anion and water influx leading to cell swelling and cell lysis. There are also some oxidative and inflammatory pathways that seem to be involved in colistin nephrotoxicity. Risk factors of colistin nephrotoxicity can be categorized as dose and duration of colistin therapy, co-administration of other nephrotoxic drugs, and patient-related factors such as age, sex, hypoalbuminemia, hyperbilirubinemia, underlying disease and severity of patient illness.

Udina M, Castellvi P, Moreno-Espana J, Navines R, Valdes M, Forns X, et al. **Interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis.** Journal of Clinical Psychiatry 2012;73(8):1128-1138.

Abstract: Objective: To carry out a systematic review of the risk factors for, and incidence of, major depressive episode (MDE) related to antiviral therapy for chronic hepatitis C.

Data Sources: The MEDLINE, PsycINFO, and Cochrane databases were searched to locate articles published from the earliest available online year until June 2011 using the keywords hepatitis C, interferon-alpha, peginterferon, pegylated interferon, depression, and mood and Boolean operators. Articles written in English, Spanish, and French were included.

Study Selection: Prospective studies reporting incidence of interferon-alpha-induced MDE were included. At baseline, patients did not present a DSM-IV/ICD depressive episode, and evaluation was performed by a trained clinician. Twenty-six observational studies met the inclusion criteria.

Data Extraction: Extracted data included authors, year of publication, design, characteristics of the population, viral coinfection, adjunctive psychopharmacology, instruments to assess depression, dose and type of interferon-alpha, adjunctive ribavirin treatment, and follow-up time. Outcome of incidence of MDE (primary outcome measure) was abstracted, as were potential predictive variables. Data Synthesis: A full review was performed. Meta-analysis of the cumulative incidence of induced MDE as a function of time was carried out. Odds ratios (ORs) and mean differences were used to estimate the strength of association of variables.

Results: Overall cumulative incidence of depression was 0.25 (95% CI, 0.16 to 0.35) and 0.28 (95% CI, 0.17 to 0.42) at 24 and 48 weeks of treatment, respectively. According to our analysis, high baseline levels of interleukin 6 (mean difference = 1.81; 95% CI, 1.09 to 2.52), female gender (OR = 1.40; 95% CI, 1.02 to 1.91), history of MDE (OR = 3.96; 95% CI, 2.52 to 6.21), history of psychiatric disorder (OR = 3.18; 95% CI, 1.60 to 6.32), subthreshold depressive symptoms (mean difference = 0.96; 95% CI, 0.31 to 1.61), and low educational level (mean difference = -0.99; 95% CI, -1.59 to -0.39) were predictive variables of MDE during antiviral treatment.

Conclusions: One in 4 chronic hepatitis C patients who start interferon and ribavirin treatment will develop an induced major depressive episode. Clinicians should attempt a full evaluation of patients before starting antiviral treatment in order to identify those at risk of developing interferon-induced depression.

Verster JC, Roth T. **Gender differences in highway driving performance after administration of sleep medication: a review of the literature**. Traffic Injury Prevention 2012;13(3):286-292.

Abstract: OBJECTIVES: It is generally assumed that there are minimal gender differences in the safety and efficacy of central nervous system drugs, as is evidenced by men and women receiving the same drug dosage. There is, however, evidence that drugs may have a differential effect on performance in men and women, given reported differences in pharmacokinetics as well as the presence or absence and severity of adverse effects. It is especially important to verify whether gender differences in performance exist in case of activities that have potentially dangerous outcomes such as driving a car. This review summarizes the current scientific evidence on gender differences in driving performance after treatment with hypnotic drugs.

METHODS: A literature search was conducted to obtain all studies that conducted on-road driving tests to examine the effects hypnotic drugs on driving. Cross-references were checked and technical reports and raw data were obtained, if possible.RESULTS: Fourteen studies were evaluated. Many studies did not allow analyses of gender effects because only women were included. Others did not report data on gender analyses. Technical reports and additional data analyses revealed significant gender differences in driving performance the morning following bedtime administration of flurazepam (30 mg) and after middle-of-the-night administration of zolpidem (10 mg). No significant gender differences were found for ramelteon (8 mg), lormetazepam (1 and 2 mg), zaleplon (10 and 20 mg), and zopiclone (7.5 mg).

CONCLUSIONS: Although the available data are limited, the results show that significant gender differences have been found for some drugs but not others. Therefore, in the future more research is needed to reveal potential gender differences and to determine what mediates them.

Yu EW, Bauer SR, Bain PA, Bauer DC. **Proton pump inhibitors and risk of fractures: A meta-analysis of 11 international studies**. American Journal of Medicine 2011;124(6):519-526.

Abstract: Background: Concerns have been raised about the risk of fractures with acid-suppressive medications, such as proton pump inhibitors and histamine <inf>2</inf>-receptor antagonists.
Methods: This meta-analysis evaluated the association between proton pump inhibitor or histamine<inf>2</inf>-receptor antagonist use and fractures. We performed a systematic search of published literature (1970 to October 10, 2010) in MEDLINE, EMBASE, and other sources. Ten publications reporting 11 studies were considered eligible for analysis.
Results: All studies were observational case-control or cohort studies and primarily evaluated older adults. The summary effect estimate for risk of hip fracture increased modestly among individuals taking proton pump inhibitors (relative risk [RR] 1.30, 95% confidence interval [CI], 1.19-1.43). There also was an increase in spine (RR 1.56, 95% CI, 1.31-1.85) and any-site fractures (RR 1.16, 95% CI, 1.04-1.30) among proton pump inhibitor users. These findings were similar in both men and women and after stratification by duration of use. In contrast, histamine<inf>2</inf>-receptor antagonist use was not significantly associated with increased risk of hip fracture (RR 1.12, 95% CI, 0.97-1.30).
Conclusion: In this meta-analysis of observational studies, proton pump inhibitors modestly increased the risk of hip, spine, and any-site fractures, whereas histamine<inf>2</inf>-receptor antagonists were not associated with fracture risk. The possibility of residual confounding cannot be excluded. Further skeletal evaluation should be considered for patients who are taking proton pump inhibitors and also at risk for osteoporotic fracture.

Vedlegg

Søkestrategier

Database: Cochrane Library (CDSR, DARE, HTA)
Dato for søk: 06.06.16

#1	MeSH descriptor: [Drug Therapy] explode all trees	126818
#2	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees	2761
#3	Any MeSH descriptor with qualifier(s): [Drug effects - DE]	106612
#4	Any MeSH descriptor with qualifier(s): [Drug therapy - DT]	183059
#5	Any MeSH descriptor with qualifier(s): [Adverse effects - AE]	113791
#6	(drug* or pharma* or medicin*):ti,ab,kw	311285
#7	#1 or #2 or #3 or #4 or #5 or #6	465576
#8	MeSH descriptor: [Sex Factors] explode all trees	5238
#9	(sex or sexes or gender* or "women and men"):ti,ab,kw	40463
#10	#8 or #9	40463
#11	#7 and #10 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only)	143
#12	(drug* or pharma* or medicin*)	532479
#13	#1 or #2 or #3 or #4 or #5 or #12	564755
#14	(sex or sexes or gender* or "women and men")	48812
#15	#8 or #14	48812
#16	#13 and #15 Publication Year from 2011 to 2016, in Cochrane Reviews (Protocols only), Other Reviews and Technology Assessments	1154
#17	#11 or #16	1297

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Dato for søk: 06.06.16

1 exp Drug Therapy/ (1155761)

2 exp "Drug-Related Side Effects and Adverse Reactions"/ (98233)

3 (ae or de or dt).fs. (4943571)

4 ((drug* or pharmac* or medicin*) adj5 (effect* or reaction* or event* or toxic*)).ti,ab. (251764)

5 1 or 2 or 3 or 4 (5437676)

6 exp Sex Factors/ (229221)

7 ((sex or sexes or gender*) adj5 (factor* or difference* or distinction* or dissimilar* or divergen* or variation*)).ti,ab. (108553)

8 ((sex or gender) adj specific).ti. (4150)

9 6 or 7 or 8 (306502)

10 meta-analysis.pt. (67090)

11 meta-analy*.ti,ab. (95383)

12 systematic review.kw. (4480)

13 ((systematic* or literature) adj3 (overview or review* or search*)).ti,ab. (320763)

14 10 or 11 or 12 or 13 (388644)

15 5 and 9 and 14 (1177)

16 limit 15 to yr="2011 -Current" (465)

Database: Embase <1974 to 2016 June 03>
Dato for søk: 06.06.16

1 exp drug therapy/ (2105451)

2 exp adverse drug reaction/ (414605)

3 (ae or de or dt).fs. (3705058)

4 ((drug* or pharmac* or medicin*) adj5 (effect* or reaction* or event* or toxic*)).ti,ab. (340457)

5 1 or 2 or 3 or 4 (5064810)

6 exp sex difference/ (316051)

7 ((sex or sexes or gender*) adj5 (factor* or difference* or distinction* or dissimilar* or divergen* or variation*)).ti,ab. (141606)

8 ((gender or sex) adj specific).ti. (4935)

9 6 or 7 or 8 (394445)

10 "systematic review"/ (107268)

11 meta analysis/ (109242)

12 ((systematic* or literature) adj3 (overview or review* or search*)).ti,ab. (375784)

13 meta-analy*.ti,ab. (117945)

14 10 or 11 or 12 or 13 (490162)

15 5 and 9 and 14 (2181)

16 limit 15 to yr="2011 -Current" (978)

Database: PsycINFO 1806 ot June Week 1 2016

Dato for søk: 07.06.16

1 exp Drug Therapy/ (126153)

2 ((drug* or pharmac* or medicin*) adj5 (effect* or reaction* or event* or toxic*)).ti,ab. (35284)

3 exp "Side Effects (Drug)"/ (49021)

4 1 or 2 or 3 (176122)

5 exp human sex differences/ (99922)

6 ((sex or sexes or gender*) adj5 (factor* or difference* or distinction* or dissimilar* or divergen* or variation*)).ti,ab. (71844)

7 ((sex or gender) adj specific).ti. (1063)

8 5 or 6 or 7 (133777)

9 4 and 8 (2603)

10 limit 9 to ("reviews (maximizes sensitivity)" and yr="2011 -Current") (541)

Database: Epistemonikos

Dato for søk: 05.06.16

Title, abstract: ((gender* OR sex OR sexes) AND (drug* OR pharma* OR medicin*))

: 4 broad synthesis, 9 structured summaries, 417 systematic reviews

Database: PROSPERO

Dato for søk: 07.06.16

gender-specific : 20

sex-specific : 15

Database: POP-databasen

Dato for søk: 05.06.16

gender : 2
sex : 1
sexes : 0

Database: SBU pågående prosjekter
Dato for søk: 05.06.16
Bladde gjennom.

Database: PubMed Clinical Queries
Dato for søk: 05.06.16

«gender specific» : 229
«sex specific» : 274
«sex differences» : 353
«gender differences» : 443

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