Teaching Papers - Harm

Martinez, C., S. Rietbrock, et al. (2005). "**Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study**." Bmj **330**(7488): 389.

Type of Question: Harm **Intermediate Nested case-control**.

Teaching Notes: Well-described methodology Important topic with much controversy, widely publicized (Do SSRIs cause more suicidal behavior?); Large sample size; Paper includes clear discussion of many of the weaknesses in the methods and discussion sections; Possible Discussion Points: -Use of case-control design for rare outcome-Is this an optimal database for the study question? ·Are outcomes likely to be completely captured? ·Is there predictable bias in a specified direction? ·Did they select groups appropriately for analysis (e.g., why is venlafaxine included as "other" rather than SSRI?)? ·How likely is a primary care database to include accurate diagnoses of major depressive disorder and other psychiatric disorders?- Is it appropriate to include only those patients with depressive and related disorders while excluding those prescribed SSRIs for other or unidentified indications?- In the multivariable model was it appropriate to include the number of covariates? (multiple comparisons) (See related article in table: Treatment of Adolescents with Depression (TADS) RCT, Therapy/Harm)

Abstract: OBJECTIVE: To compare the risk of non-fatal self harm and suicide in patients taking selective serotonin reuptake inhibitors (SSRIs) with that of patients taking tricyclic antidepressants, as well as between different SSRIs and different tricyclic antidepressants. DESIGN: Nested case-control study. SETTING: Primary care in the United Kingdom. PARTICIPANTS: 146,095 individuals with a first prescription of an antidepressant for depression. MAIN OUTCOME MEASURES: Suicide and non-fatal self harm. RESULTS: 1968 cases of non-fatal self harm and 69 suicides occurred. The overall adjusted odds ratio of non-fatal self harm was 0.99 (95% confidence interval 0.86 to 1.14) and that of suicide 0.57 (0.26 to 1.25) in people prescribed SSRIs compared with those prescribed tricyclic antidepressants. We found little evidence that associations differed over time since starting or stopping treatment. We found some evidence that risks of non-fatal self harm in people prescribed SSRIs compared with those prescribed tricyclic antidepressants differed by age group (interaction P = 0.02). The adjusted odds ratio of non-fatal self harm for people prescribed SSRIs compared with users of tricylic antidepressants for those aged 18 or younger was 1.59 (1.01 to 2.50), but no association was apparent in other age groups. No suicides occurred in those aged 18 or younger currently or recently prescribed tricyclic antidepressants or SSRIs. CONCLUSION: We found no evidence that the risk of suicide or non-fatal self harm in adults prescribed SSRIs was greater than in those prescribed tricyclic antidepressants. We found some weak evidence of an increased risk of non-fatal self harm for current SSRI use among those aged 18 or younger. However, preferential prescribing of SSRIs to patients at higher risk of suicidal behaviour cannot be ruled out.

Wooltorton, E. (2003). "**Salmeterol (Serevent) asthma trial halted early**." Cmaj **168**(6): 738.

Type of Question: Harm **Advanced Case-control**.

Teaching Notes: The FDA Talk Paper August 14, 2003 and the Health and Drug Alert that was issued by the Canadian Medical Association in JAMC both allude to data from the SMART trial (Salmeterol Multi-Center Asthma Research Trial) that was stopped in interim analysis in 2003. Interim analysis in 2002 showed a non-significant trend toward more asthma related life threatening events in all patients and a significant increase in the subgroup of black patients. The SMART trial prompted the drug warning for salmeterol. However, the SMART trial remains unpublished. Thus, the Williams study (case-control) is the best evidence actually published. Good discussion points: Used in conjunction with FDA Talk Paper Aug 14, 2003 regarding the SMART trial or other (GSK warning insert, Micromedex adverse reactions, etc.) makes for an interesting discussion regarding harm and finding the evidence- Where is the publication of SMART (Salmeterol Multi-Center Asthma Research Trial)? Why might the drug company sponsors not have published it? Other discussion points:Surrogate endpointsUse of both "odds ratio' and 'risk ratio' language. Why does this matter for a case-control study?Is extracting drug data from the chart an accurate method of determining who was and was not actually taking salmeterol? Why might the Case-Control data possibly differ from the SMART data (at least the data we do know)? See also: Williams 2003 and FDA Talk Paper - Labeling changes for drug products that contain salmeterol (http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01248.html viewed 12/28/05)

Abstract: No abstract

Wysowski, D. K., M. Pitts, et al. (2001). "**An analysis of reports of depression and suicide in patients treated with isotretinoin**." J Am Acad Dermatol **45**(4): 515-519.

Type of Question: Harm **Beginner / Intermediate Case Series of FDA reports**.

Teaching Notes: This paper is specifically good for discussion regarding how to make decisions about potential harms of therapy when there are no controlled trials available. Good discussion points: Can use this as a jumping point to discuss the 'hierarchy of evidence' and to drive home that, in the end, you need to make clinical decisions with whatever evidence is available.

Abstract: BACKGROUND: The Food and Drug Administration (FDA) has received reports of depression and suicide in patients treated with isotretinoin. OBJECTIVE: Our purpose was to provide the number and describe the cases of depression and suicide reported to the FDA in US patients treated with isotretinoin and to consider the nature of a possible association between isotretinoin and depression. METHODS: An analysis was made of reports of depression, suicidal ideation, suicide attempt, and suicide in US isotretinoin users voluntarily submitted to the manufacturer and the FDA from 1982 to May 2000 and entered in the FDA's Adverse Event Reporting System database. RESULTS: From marketing of isotretinoin in 1982 to May 2000, the FDA received reports of 37 US patients treated with isotretinoin who committed suicide; 110 who were hospitalized for depression, suicidal ideation, or suicide attempt; and 284 with nonhospitalized depression, for a total of 431 patients. Factors suggesting a possible association between isotretinoin and depression include a temporal association between use of the drug and depression, positive dechallenges (often with psychiatric treatment), positive rechallenges, and possible biologic plausibility. Compared with all drugs in the FDA's Adverse Event Reporting System database to June 2000, isotretinoin ranked within the top 10 for number of reports of depression and suicide attempt. CONCLUSION: The FDA has received reports of depression, suicidal ideation, suicide attempt, and suicide in patients treated with isotretinoin. Additional studies are needed to determine whether isotretinoin causes depression and to identify susceptible persons. In the meantime, physicians are advised to inform patients prescribed isotretinoin (and parents, if appropriate) of the possibility of development or worsening of depression. They should advise patients (and parents) to immediately report mood swings and symptoms suggestive of depression such as sadness, crying, loss of appetite, unusual fatigue, withdrawal, and inability to concentrate so that patients can be promptly evaluated for appropriate treatment, including consideration of drug discontinuation and referral for psychiatric care.

Murphy, T. V., P. M. Gargiullo, et al. (2001). "**Intussusception among infants given an oral rotavirus vaccine**." N Engl J Med **344**(8): 564-572.

Type of Question: Harm **Intermediate Case-control**.

Teaching Notes: A well done case-controlled study in pediatrics with clear methodology and results. Good discussion points: Provides a basis for discussion of case-controlled methods and post-marketing surveillance data for investigating harm from preventative (i.e. vaccine) or therapeutic interventions.

Abstract: BACKGROUND: Intussusception is a form of intestinal obstruction in which a segment of the bowel prolapses into a more distal segment. Our investigation began on May 27, 1999, after nine cases of infants who had intussusception after receiving the tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV) were reported to the Vaccine Adverse Event Reporting System. METHODS: In 19 states, we assessed the potential association between RRV-TV and intussusception among infants at least 1 but less than 12 months old. Infants hospitalized between November 1, 1998, and June 30, 1999, were identified by systematic reviews of medical and radiologic records. Each infant with intussusception was matched according to age with four healthy control infants who had been born at the same hospital as the infant with intussusception. Information on vaccinations was verified by the provider. RESULTS: Data were analyzed for 429 infants with intussusception and 1763 matched controls in a case-control analysis as well as for 432 infants with intussusception in a case-series analysis. Seventy-four of the 429 infants with intussusception (17.2 percent) and 226 of the 1763 controls (12.8 percent) had received RRV-TV (P=0.02). An increased risk of intussusception 3 to 14 days after the first dose of RRV-TV was found in the case-control analysis (adjusted odds ratio, 21.7; 95 percent confidence interval, 9.6 to 48.9). In the case-series analysis, the incidence-rate ratio was 29.4 (95 percent confidence interval,

16.1 to 53.6) for days 3 through 14 after a first dose. There was also an increase in the risk of intussusception after the second dose of the vaccine, but it was smaller than the increase in risk after the first dose. Assuming full implementation of a national program of vaccination with RRV-TV, we estimated that 1 case of intussusception attributable to the vaccine would occur for every 4670 to 9474 infants vaccinated. CONCLUSIONS: The strong association between vaccination with RRV-TV and intussusception among otherwise healthy infants supports the existence of a causal relation. Rotavirus vaccines with an improved safety profile are urgently needed.

Kernan, W. N., C. M. Viscoli, et al. (2000). "**Phenylpropanolamine and the risk of hemorrhagic stroke**." N Engl J Med **343**(25): 1826-1832.

Type of Question: Harm **Intemediate Case-control**.

Teaching Notes: This is a good example of a case Control study in the setting of a very rare outcome; The paper is a fun one because it was controversial and led to the removal of phenylpropanolamine from the market. Broadly applicable due to OTC. Good discussion points: Fun for discussing issues of applicability as there are different findings in different groups of folks (e.g. men vs. women). Might you use the same data to tell different patients different things? Other fun way to use this paper might be to consider how one would use this data to make a policy decision (e.g. in a formulary setting)

Abstract: BACKGROUND: Phenylpropanolamine is commonly found in appetite suppressants and cough or cold remedies. Case reports have linked the use of products containing phenylpropanolamine to hemorrhagic stroke, often after the first use of these products. To study the association, we designed a case-control study. METHODS: Men and women 18 to 49 years of age were recruited from 43 U.S. hospitals. Eligibility criteria included the occurrence of a subarachnoid or intracerebral hemorrhage within 30 days before enrollment and the absence of a previously diagnosed brain lesion. Random-digit dialing identified two matched control subjects per patient. RESULTS: There were 702 patients and 1376 control subjects. For women, the adjusted odds ratio was 16.58 (95 percent confidence interval, 1.51 to 182.21; P=0.02) for the association between the use of appetite suppressants containing phenylpropanolamine and the risk of a hemorrhagic stroke and 3.13 (95 percent confidence interval, 0.86 to 11.46; P=0.08) for the association with the first use of a product containing phenylpropanolamine. All first uses of phenylpropanolamine involved cough or cold remedies. For men and women combined, the adjusted odds ratio was 1.49 (95 percent confidence interval, 0.84 to 2.64; P=0.17) for the association between the use of a product containing phenylpropanolamine and the risk of a hemorrhagic stroke, 1.23 (95 percent confidence interval, 0.68 to 2.24; P=0.49) for the association with the use of cough or cold remedies that contained phenylpropanolamine, and 15.92 (95 percent confidence interval, 1.38 to 184.13; P=0.03) for the association with the use of appetite suppressants that contained phenylpropanolamine. An analysis in men showed no increased risk of a hemorrhagic stroke in association with the use of cough or cold remedies containing phenylpropanolamine. No men reported the use of appetite suppressants. CONCLUSIONS: The results suggest that phenylpropanolamine in appetite suppressants, and possibly in cough and cold remedies, is an independent risk factor for hemorrhagic stroke in women.

Silverstein, F. E., G. Faich, et al. (2000). "**Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study**." Jama **284**(10): 1247-1255.

Type of Question: Harm **Intermediate / Advanced RCT**.

Teaching Notes: This is a sample packet. See the entire teaching package that is in this section. This paper is an example of evaluation of Harm using RCT methodology. It is an opportunity to discuss that there are multiple methodologies that can be used for each kind of question. Beware, however, that questions of harm are frequently not answered by RCT (if the outcomes are too rare or if there are ethical issues of randomization when known harms are involved.) Good discussion points: See sample package for using this paper to bring up some issues of ethics in medical reporting and drug company sponsorship of clinical trials.

Abstract: CONTEXT: Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a spectrum of toxic effects, notably gastrointestinal (GI) effects, because of inhibition of

cyclooxygenase (COX)-1. Whether COX-2-specific inhibitors are associated with fewer clinical GI toxic effects is unknown. OBJECTIVE: To determine whether celecoxib, a COX-2-specific inhibitor, is associated with a lower incidence of significant upper GI toxic effects and other adverse effects compared with conventional NSAIDs. DESIGN: The Celecoxib Long-term Arthritis Safety Study (CLASS), a double-blind, randomized controlled trial conducted from September 1998 to March 2000. SETTING: Three hundred eighty-six clinical sites in the United States and Canada. PARTICIPANTS: A total of 8059 patients (>/=18 years old) with osteoarthritis (OA) or rheumatoid arthritis (RA) were enrolled in the study, and 7968 received at least 1 dose of study drug. A total of 4573 patients (57%) received treatment for 6 months. INTERVENTIONS: Patients were randomly assigned to receive celecoxib, 400 mg twice per day (2 and 4 times the maximum RA and OA dosages, respectively; n = 3987); ibuprofen, 800 mg 3 times per day (n = 1985); or diclofenac, 75 mg twice per day (n = 1996). Aspirin use for cardiovascular prophylaxis (</=325 mg/d) was permitted. MAIN OUTCOME MEASURES: Incidence of prospectively defined symptomatic upper GI ulcers and ulcer complications (bleeding, perforation, and obstruction) and other adverse effects during the 6-month treatment period. RESULTS: For all patients, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.76% vs 1.45% (P =.09) and 2. 08% vs 3.54% (P =.02), respectively. For patients not taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 0.44% vs 1.27% (P =.04) and 1.40% vs 2.91% (P =.02). For patients taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib vs NSAIDs were 2.01% vs 2.12% (P =.92) and 4.70% vs 6.00% (P =.49). Fewer celecoxib-treated patients than NSAID-treated patients experienced chronic GI blood loss, GI intolerance, hepatotoxicity, or renal toxicity. No difference was noted in the incidence of cardiovascular events between celecoxib and NSAIDs, irrespective of aspirin use. CONCLUSIONS: In this study, celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages. The decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly. JAMA. 2000;284:1247-1255

Williams, C., L. Crossland, et al. (1998). "**Case-control study of salmeterol and near-fatal attacks of asthma**." Thorax **53**(1): 7-13.

Type of Question: Harm **Advanced Case-control**.

Teaching Notes: The FDA Talk Paper August 14, 2003 and the Health and Drug Alert that was issued by the Canadian Medical Association in JAMC both allude to data from the SMART trial (Salmeterol Multi-Center Asthma Research Trial) that was stopped in interim analysis in 2003. Interim analysis in 2002 showed a non-significant trend toward more asthma related life threatening events in all patients and a significant increase in the subgroup of black patients. The SMART trial prompted the drug warning for salmeterol. However, the SMART trial remains unpublished. Thus, the Williams study (case-control) is the best evidence actually published. Good discussion points: Used in conjunction with FDA Talk Paper Aug 14, 2003 regarding the SMART trial or other (GSK warning insert, Micromedex adverse reactions, etc.) makes for an interesting discussion regarding harm and finding the evidence- Where is the publication of SMART (Salmeterol Multi-Center Asthma Research Trial)? Why might the drug company sponsors not have published it? Other discussion points:Surrogate endpointsUse of both "odds ratio' and 'risk ratio' language. Why does this matter for a case-control study?Is extracting drug data from the chart an accurate method of determining who was and was not actually taking salmeterol? Why might the Case-Control data possibly differ from the SMART data (at least the data we do know)? See also: Wooltorton 2003 and FDA Talk Paper - Labeling changes for drug products that contain salmeterol (http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01248.html viewed 12/28/05)

Abstract: BACKGROUND: A case-control study was undertaken to investigate the hypothesis that the use of the long acting beta agonist salmeterol increases the risk of a near-fatal attack of asthma. METHODS: The cases comprised admissions to the intensive care unit (ICU) for asthma in 14 major hospitals within the Wessex region in 1992. For each of the cases four age-matched controls were selected from asthma admissions to the same hospital during the same period. Information on prescribed drug therapy for the 48 cases and 185 controls was collected from the hospital admission records. RESULTS: The patients admitted to the ICU had greater chronic asthma severity and had generally been

prescribed more asthma drugs than the control admissions to hospital. The relative risk of a near-fatal attack of asthma in patients prescribed inhaled salmeterol was 2.32 (95% CI 1.05 to 5.16), p = 0.04. However, the salmeterol relative risk decreased to 1.42 (95% CI 0.49 to 4.10), p = 0.52 when the analysis was restricted to the more chronically severe patients (those in the subgroup of patients with a hospital admission for asthma in the previous 12 months). These findings suggest that the increased unadjusted relative risk with salmeterol is predominantly due to confounding by severity--that is, the increased relative risk is due to patients with more severe asthma (at greatest risk of a near-fatal asthma attack) being preferentially prescribed salmeterol. This interpretation is supported by the finding in this study that, within the control group (selected from the population of asthmatics requiring hospital admission), salmeterol was preferentially prescribed to the most severe patients (a threefold greater prescription of salmeterol to control patients if they had been admitted to hospital in the 12 months prior to the index admission). There was no increased risk of a near-fatal attack of asthma in patients prescribed a beta agonist by metered dose inhaler (OR 0.75 (95% CI 0.31 to 1.78), p = 0.51). In contrast, the relative risks for beta agonists delivered by nebulisation (OR 3.86 (95% CI 1.99 to 7.50), p < 0.001) and oral theophylline (OR 2.45 (95% CI 1.26 to 4.78), p < 0.01) were increased and did not markedly decrease when the analysis was restricted to the more severe asthmatic subjects. CONCLUSIONS: Although these findings are not conclusive, particularly because of the small numbers involved in some subgroup analyses, they suggest that the use of salmeterol by patients with chronic severe asthma is not associated with a significantly increased risk of a near-fatal attack of asthma. If a near-fatal asthma attack is considered to be an intermediate step in a process by which a severe attack of asthma may become fatal, these results would suggest that salmeterol is unlikely to be associated with an increased risk of death, at least by this mechanism.

Cumming, R. G., P. Mitchell, et al. (1997). "**Use of inhaled corticosteroids and the risk of cataracts**." N Engl J Med **337**(1): 8-14.

Type of Question: Harm **Beginner / Intermediate Cross sectional**.

Teaching Notes: This is a population based cross sectional study. Very good example of a population based sampling frame. Good discussion points: Good for discussion of prevalence, ratios and confidence intervals. Can use to discuss questions of etiology and dose response - relationships

Abstract: BACKGROUND: The use of systemic corticosteroids is a risk factor for the development of posterior subcapsular cataracts, but the association between inhaled corticosteroids and cataracts is uncertain. METHODS: We conducted a population-based, cross-sectional study of vision and common eye diseases in an urban area of the Blue Mountains, near Sydney, Australia. We recruited 3654 people 49 to 97 years of age; the participation rate was 82 percent. We collected information by questionnaire on potential risk factors for cataracts, including the current or prior use of inhaled corticosteroids (beclomethasone or budesonide). Photographs of the subjects' lenses were graded, without information on the subjects, to determine the presence and severity of cortical, nuclear, and posterior subcapsular cataracts. RESULTS: Three hundred seventy subjects reported using inhaled corticosteroids, 164 currently and 206 previously. Among these subjects, after adjustment for age and sex, there was a higher prevalence of nuclear cataracts (relative prevalence, 1.5; 95 percent confidence interval, 1.2 to 1.9) and posterior subcapsular cataracts (relative prevalence, 1.9; 95 percent confidence interval, 1.3 to 2.8) than among the subjects with no inhaled-corticosteroid use, but the prevalence of cortical cataracts was not significantly higher (relative prevalence, 1.1; 95 percent confidence interval, 0.9 to 1.3). Higher cumulative lifetime doses of beclomethasone were associated with higher risks of posterior subcapsular cataracts (P for trend <0.001); the highest prevalence (27 percent) was found in subjects whose lifetime dose was over 2000 mg (relative prevalence, 5.5). Adjusting for the use of systemic corticosteroids and other potential confounders had little effect on the magnitude of the associations. The associations with posterior subcapsular cataracts, but not those with nuclear cataracts, were less marked when the analyses were restricted to subjects who had never used systemic corticosteroids. CONCLUSIONS: The use of inhaled corticosteroids is associated with the development of posterior subcapsular and nuclear cataracts.

Marcantonio, E. R., G. Juarez, et al. (1994). "**The relationship of postoperative delirium with psychoactive medications**." Jama **272**(19): 1518-1522.

Type of Question: Harm **Beginner / Intermediate Nested case-control**.

Teaching Notes: Outstanding, prospective methodology for a case-control study (one of the best we've been able to find) Great attention to matching of cases and controls Good discussion points: Awesome paper for discussion of methods of a case control study because it is so well done and avoids some of the usual pitfalls.

Abstract: OBJECTIVE--To examine the role of medications with known psychoactive properties in the development of postoperative delirium. DESIGN--Nested case-control study within a prospective cohort study. SETTING--General surgery, orthopedic surgery, and gynecology services at Brigham and Women's Hospital, Boston, Mass. PATIENTS--Cases (n = 91) were patients enrolled in a prospective cohort study who developed delirium during postoperative days 2 through 5. One or two controls (n = 154) were matched to each case by the calculated preoperative risk for delirium using a predictive model developed and validated in the prospective cohort study. MAIN OUTCOME MEASURES--Medication exposures were ascertained from the medical record by a reviewer blinded to the study hypothesis. Exposures to narcotics, benzodiazepines, and anticholinergics were recorded for the 24-hour period before delirium developed in the 91 cases and for the same 24-hour postoperative period for the 154 matched controls. RESULTS--Delirium was significantly associated with postoperative exposure to meperidine (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.3 to 5.5) and to benzodiazepines (OR, 3.0; 95% CI, 1.3 to 6.8). Meperidine had similar associations with delirium whether administered via epidural or patient-controlled routes, although only the epidural route reached significance (OR, 2.4; 95% CI, 1.3 to 4.4; OR, 2.1; 95% CI, 0.4 to 10.7, respectively). For benzodiazepines, long-acting agents had a trend toward stronger association with delirium than did short-acting agents (OR, 5.4; 95% CI, 1.0 to 29.2; vs 2.6; 1.1 to 6.5), and high-dose exposures had a trend toward slightly stronger association than low-dose exposures (OR, 3.3; 95% CI, 1.0 to 11.0; vs 2.6; 0.8 to 9.1). Neither narcotics (OR, 1.4; 95% CI, 0.5 to 4.3) nor anticholinergic drugs (OR, 1.5; 95% CI, 0.6 to 3.4) were significantly associated with delirium as a class, although statistical power was limited because of the high use of narcotics and the low use of anticholinergics in the study population. CONCLUSIONS--Clinicians caring for patients at risk for delirium should carefully evaluate the need for meperidine and benzodiazepines in the postoperative period and consider alternative therapies whenever possible.

Wang, P. S., S. Schneeweiss, et al. (2005). "**Risk of death in elderly users of conventional vs. atypical antipsychotic medications**." N Engl J Med **353**(22): 2335-2341.

Type of Question: Harm **Intermediate / Advanced Cohort, retrospective**.

Teaching Notes: Important clinical question relevant to generalists and geriatricians regarding commonplace treatment practices (administration of antipsychotics to demented elderly patients) now thought to cause harm. Administrative databases capture most of the elderly population and include complete mortality data based on medicare and social security. Clearly defined exposure groups and methodologyAppropriate modeling after initial analysis includes utilization of propensity scores, instrumental-variable analysis and modeling strategies to control for possible biases in what doctors prescribed in the first place, with sensitivity analysis also conducted. Good discussion points: How does one confirm cause and effect in a retrospective cohort study? Validity criteria for "harm" articles(more advanced): use of propensity score and adjustment for variables that may have contributed to bias in prescribing patterns. Given the information in this article in context of limited information for effectiveness of any intervention for agitation in dementia…what would participants choose to do in order to treat behavioral symptoms in dementia?

Abstract: BACKGROUND: Recently, the Food and Drug Administration (FDA) issued an advisory stating that atypical antipsychotic medications increase mortality among elderly patients. However, the advisory did not apply to conventional antipsychotic medications; the risk of death with these older agents is not known. METHODS: We conducted a retrospective cohort study involving 22,890 patients 65 years of age or older who had drug insurance benefits in Pennsylvania and who began receiving a conventional or atypical antipsychotic medication between 1994 and 2003. Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after the initiation of therapy with an antipsychotic medication. We controlled for potential confounding variables with the use of traditional multivariate Cox models, propensity-score adjustments, and an instrumental-variable analysis. RESULTS: Conventional antipsychotic medications were associated with a significantly higher adjusted risk of death

than were atypical antipsychotic medications at all intervals studied (< or =180 days: relative risk, 1.37; 95 percent confidence interval, 1.27 to 1.49; <40 days: relative risk, 1.56; 95 percent confidence interval, 1.37 to 1.78; 40 to 79 days: relative risk, 1.37; 95 percent confidence interval, 1.19 to 1.59; and 80 to 180 days: relative risk, 1.27; 95 percent confidence interval, 1.14 to 1.41) and in all subgroups defined according to the presence or absence of dementia or nursing home residency. The greatest increases in risk occurred soon after therapy was initiated and with higher dosages of conventional antipsychotic medications. Increased risks associated with conventional as compared with atypical antipsychotic medications persisted in confirmatory analyses performed with the use of propensity-score adjustment and instrumental-variable estimation. CONCLUSIONS: If confirmed, these results suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should not be used to replace atypical agents discontinued in response to the FDA warning.

Juni, P., L. Nartey, et al. (2004). "**Risk of cardiovascular events and rofecoxib: cumulative meta-analysis**." Lancet **364**(9450): 2021-2029.

Type of Question: Harm **Intermediate Meta-analysis**.

Teaching Notes: Topical question of broad clinical interest which learners find interesting. Robust cumulative meta-analysis showing the chronology of relevant RCTs on the topic demonstrating harm of this commonly prescribed medication.

Abstract: BACKGROUND: The cyclo-oxygenase 2 inhibitor rofecoxib was recently withdrawn because of cardiovascular adverse effects. An increased risk of myocardial infarction had been observed in 2000 in the Vioxx Gastrointestinal Outcomes Research study (VIGOR), but was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of rofecoxib. We used standard and cumulative random-effects meta-analyses of randomised controlled trials and observational studies to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2004. METHODS: We searched bibliographic databases and relevant files of the US Food and Drug Administration. We included all randomised controlled trials in patients with chronic musculoskeletal disorders that compared rofecoxib with other non-steroidal anti-inflammatory drugs (NSAIDs) or placebo, and cohort and case-control studies of cardiovascular risk and naproxen. Myocardial infarction was the primary endpoint. FINDINGS: We identified 18 randomised controlled trials and 11 observational studies. By the end of 2000 (52 myocardial infarctions, 20742 patients) the relative risk from randomised controlled trials was 2.30 (95% CI 1.22-4.33, p=0.010), and 1 year later (64 events, 21432 patients) it was 2.24 (1.24-4.02, p=0.007). There was little evidence that the relative risk differed depending on the control group (placebo, non-naproxen NSAID, or naproxen; p=0.41) or trial duration (p=0.82). In observational studies, the cardioprotective effect of naproxen was small (combined estimate 0.86 [95% CI 0.75-0.99]) and could not have explained the findings of the VIGOR trial. INTERPRETATION: Our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified.

Castellsague, X., F. X. Bosch, et al. (2002). "**Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners**." N Engl J Med **346**(15): 1105-1112.

Type of Question: Harm **Intermediate / Advanced Case Control (pooled)**.

Teaching Notes: Pros: Allows for discussion of case definition and identification and appropriate controls. Adjustment for known risk factors. Cons:Logistic regression used to generate ORs (more difficult to discuss compared to 2x2 table). Few people have much experience critically appraising SR of Case controlled studies and new learners may be overwhelmed

Abstract: BACKGROUND: It is uncertain whether male circumcision reduces the risks of penile human papillomavirus (HPV) infection in the man and of cervical cancer in his female partner. METHODS: We pooled data on 1913 couples enrolled in one of seven case-control studies of cervical carcinoma in situ and cervical cancer in five countries. Circumcision status was self-reported, and the accuracy of the data was confirmed by physical examination at three study sites. The presence or absence of penile HPV DNA was assessed by a polymerase-chain-reaction assay in 1520 men and yielded a valid result in the case of 1139 men (74.9 percent). RESULTS: Penile HPV was detected in 166

of the 847 uncircumcised men (19.6 percent) and in 16 of the 292 circumcised men (5.5 percent). After adjustment for age at first intercourse, lifetime number of sexual partners, and other potential confounders, circumcised men were less likely than uncircumcised men to have HPV infection (odds ratio, 0.37; 95 percent confidence interval, 0.16 to 0.85). Monogamous women whose male partners had six or more sexual partners and were circumcised had a lower risk of cervical cancer than women whose partners were uncircumcised (adjusted odds ratio, 0.42; 95 percent confidence interval, 0.23 to 0.79). Results were similar in the subgroup of men in whom circumcision was confirmed by medical examination. CONCLUSIONS: Male circumcision is associated with a reduced risk of penile HPV infection and, in the case of men with a history of multiple sexual partners, a reduced risk of cervical cancer in their current female partners.

Moses-Kolko, E. L., D. Bogen, et al. (2005). "**Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications**." Jama **293**(19): 2372-2383.

Type of Question: Harm **Moderate ot Advanced Systematic Review**.

Teaching Notes: Good article if you want to expose learners to systematic review addressing harm instead of therapy

Abstract: CONTEXT: A neonatal behavioral syndrome linked to in utero serotonin reuptake inhibitor (SRI) exposure during the last trimester of pregnancy has been identified. The US Food and Drug Administration (FDA) and drug manufacturers have recently agreed to a class labeling change for SRIs, which include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), to include information about potential adverse events in neonates exposed in utero. Integration of data about the neonatal behavioral syndrome into the management of pregnancy in women who take SRIs is a current challenge for physicians. OBJECTIVES: To review evidence regarding the SRI-related neonatal syndrome and to help clinicians guide their patients in a risk-benefit decision-making process. DATA SOURCES: We searched MEDLINE (1966-February 2005) and PsycINFO (1974-February 2005). All articles related to neonatal signs after in utero SRI exposure were acquired, as well as unpublished data on this topic from the FDA advisory committee meeting of June 2004. References cited in case reports and studies were reviewed. Foreign-language literature was included and translated to English. STUDY SELECTION AND DATA EXTRACTION: Studies were included if they had clearly identified maternal SRI exposure for a minimum of the final trimester of pregnancy through delivery and assessed neonatal outcomes. We identified 13 case reports describing a total of 18 cases. Nine cohort studies met criteria. When not included in the published article, relative risks and 95% confidence intervals (CIs) were computed from raw data and summary risk ratios and 95% CIs were determined with Mantel-Haenszel estimates. DATA SYNTHESIS: Compared with early gestational SRI exposure or no exposure, late SRI exposure carries an overall risk ratio of 3.0 (95% CI, 2.0-4.4) for a neonatal behavioral syndrome. The most SRI-related neonatal case reports involved fluoxetine and paroxetine exposures. Neonates primarily display central nervous system, motor, respiratory, and gastrointestinal signs that are usually mild and disappear by 2 weeks of age. Medical management has consisted primarily of supportive care in special care nurseries. A severe syndrome that consists of seizures, dehydration, excessive weight loss, hyperpyrexia, or intubation is rare in term infants (1/313 quantifiable cases). There have been no reported neonatal deaths attributable to neonatal SRI exposure. CONCLUSIONS: Available evidence indicates that in utero exposure to SRIs during the last trimester through delivery may result in a self-limited neonatal behavioral syndrome that can be managed with supportive care. The risks and benefits of discontinuing an SRI during pregnancy need to be carefully weighed for each individual patient. Development and validation of assessment methods and clinical management strategies are critical to advancing this research.

Yang, Y. X., J. D. Lewis, et al. (2006). "**Long-term proton pump inhibitor therapy and risk of hip fracture**." Jama **296**(24): 2947-2953.

Type of Question: Harm **Advanced Nested Case Control**.

Teaching Notes: Nested case control study looking at association between PPI treatment and hip fracture. Good methodology for explaining a nested case control design.

Abstract: CONTEXT: Proton pump inhibitors (PPIs) may interfere with calcium absorption through induction of hypochlorhydria but they also may reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps. OBJECTIVE: To determine the association between PPI therapy and risk of hip fracture. DESIGN, SETTING, AND PATIENTS: A nested case-control study was conducted using the General Practice Research Database (1987-2003), which contains information on patients in the United Kingdom. The study cohort consisted of users of PPI therapy and nonusers of acid suppression drugs who were older than 50 years. Cases included all patients with an incident hip fracture. Controls were selected using incidence density sampling, matched for sex, index date, year of birth, and both calendar period and duration of up-to-standard follow-up before the index date. For comparison purposes, a similar nested case-control analysis for histamine 2 receptor antagonists was performed. MAIN OUTCOME MEASURE: The risk of hip fractures associated with PPI use. RESULTS: There were 13,556 hip fracture cases and 135,386 controls. The adjusted odds ratio (AOR) for hip fracture associated with more than 1 year of PPI therapy was 1.44 (95% confidence interval [CI], 1.30-1.59). The risk of hip fracture was significantly increased among patients prescribed long-term high-dose PPIs (AOR, 2.65; 95% CI, 1.80-3.90; P<.001). The strength of the association increased with increasing duration of PPI therapy (AOR for 1 year, 1.22 [95% CI, 1.15-1.30]; 2 years, 1.41 [95% CI, 1.28-1.56]; 3 years, 1.54 [95% CI, 1.37-1.73]; and 4 years, 1.59 [95% CI, 1.39-1.80]; P<.001 for all comparisons). CONCLUSION: Long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture.

Miceli, A., R. Capoun, et al. (2009). "**Effects of angiotensin-converting enzyme inhibitor therapy on clinical outcome in patients undergoing coronary artery bypass grafting**." J Am Coll Cardiol **54**(19): 1778-1784.

Type of Question: Harm **Advanced retrospective cohort**.

Teaching Notes: Good to teach propensity score and importance of randomization

Abstract: OBJECTIVES: This study evaluates the effect of pre-operative angiotensin-converting enzyme inhibitor (ACEI) therapy on early clinical outcomes after coronary artery bypass grafting (CABG). BACKGROUND: Therapy with ACEIs has been shown to reduce the rate of mortality and prevent cardiovascular events in patients with coronary artery disease. However, their pre-operative use in patients undergoing CABG is still controversial. METHODS: A retrospective, observational, cohort study was undertaken of prospectively collected data on 10,023 consecutive patients undergoing isolated CABG between April 1996 and May 2008. Of these, 3,052 patients receiving pre-operative ACEI were matched to a control group by propensity score analysis. RESULTS: Overall rate of mortality was 1%. Pre-operative ACEI therapy was associated with a doubling in the risk of death (1.3% vs. 0.7%; odds ratio [OR]: 2.00, 95% confidence interval [CI]: 1.17 to 3.42; p = 0.013). There was also a significant difference between the ACEI and control group in the risk of post-operative renal dysfunction (PRD) (7.1% vs. 5.4%; OR: 1.36, 95% CI: 1.1 to 1.67; p = 0.006), atrial fibrillation (AF) (25% vs. 20%; OR: 1.34, 95% CI: 1.18 to 1.51; p < 0.0001), and increased use of inotropic support (45.9% vs. 41.1%; OR: 1.22, 95% CI: 1.1 to 1.36; p < 0.0001). In a multivariate analysis, pre-operative ACEI treatment was an independent predictor of mortality (p = 0.04), PRD (p = 0.0002), use of inotropic drugs (p < 0.0001), and AF (p < 0.0001). CONCLUSIONS: Pre-operative therapy with ACEI is associated with an increased risk of mortality, use of inotropic support, PRD, and new onset of post-operative AF.

Schilcher, J., K. Michaelsson, et al. (2011). "**Bisphosphonate use and atypical fractures of the femoral shaft**." N Engl J Med **364**(18): 1728-1737.

Type of Question: Harm **Beginner case-control/cohort**.

Teaching Notes: great to compare/contrast a cohort with RR reported and case control with OR reported in the same paper, and great to point out that even strong associations may not change practice if events are very rare. great for creating 2x2 tables of both the cohort numbers and the case control numbers to compare and contrast; great example of huge relative association having little bearing on absolute risks, since risk is tiny. Easy to find the relevant numbers for calculating RR and OR.

Abstract: BACKGROUND: Studies show conflicting results regarding the possible excess risk of atypical fractures of the femoral shaft associated with bisphosphonate use. METHODS: In Sweden, 12,777 women 55 years of age or older sustained a fracture of the femur in 2008. We reviewed radiographs of 1234 of the 1271 women who had a subtrochanteric or shaft fracture and identified 59

patients with atypical fractures. Data on medications and coexisting conditions were obtained from national registries. The relative and absolute risk of atypical fractures associated with bisphosphonate use was estimated by means of a nationwide cohort analysis. The 59 case patients were also compared with 263 control patients who had ordinary subtrochanteric or shaft fractures. RESULTS: The age-adjusted relative risk of atypical fracture was 47.3 (95% confidence interval [CI], 25.6 to 87.3) in the cohort analysis. The increase in absolute risk was 5 cases per 10,000 patient-years (95% CI, 4 to 7). A total of 78% of the case patients and 10% of the controls had received bisphosphonates, corresponding to a multivariable-adjusted odds ratio of 33.3 (95% CI, 14.3 to 77.8). The risk was independent of coexisting conditions and of concurrent use of other drugs with known effects on bone. The duration of use influenced the risk (odds ratio per 100 daily doses, 1.3; 95% CI, 1.1 to 1.6). After drug withdrawal, the risk diminished by 70% per year since the last use (odds ratio, 0.28; 95% CI, 0.21 to 0.38). CONCLUSIONS: These population-based nationwide analyses may be reassuring for patients who receive bisphosphonates. Although there was a high prevalence of current bisphosphonate use among patients with atypical fractures, the absolute risk was small. (Funded by the Swedish Research Council.).

Schjerning Olsen, A. M., E. L. Fosbol, et al. (2011). "**Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study**." Circulation **123**(20): 2226-2235.

Type of Question: Harm **Cohort Study**.

Teaching Notes: cohort to review HARM - Denmark, great cohort, but some issues with validity/sample sizes/confounding by indication, as well as small absolute risk of harm.

Abstract: BACKGROUND: Despite the fact that nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated among patients with established cardiovascular disease, many receive NSAID treatment for a short period of time. However, little is known about the association between NSAID treatment duration and risk of cardiovascular disease. We therefore studied the duration of NSAID treatment and cardiovascular risk in a nationwide cohort of patients with prior myocardial infarction (MI). METHODS AND RESULTS: Patients >/=30 years of age who were admitted with first-time MI during 1997 to 2006 and their subsequent NSAID use were identified by individual-level linkage of nationwide registries of hospitalization and drug dispensing from pharmacies in Denmark. Risk of death and recurrent MI according to duration of NSAID treatment was analyzed by multivariable time-stratified Cox proportional-hazard models and by incidence rates per 1000 person-years. Of the 83 677 patients included, 42.3% received NSAIDs during follow-up. There were 35 257 deaths/recurrent MIs. Overall, NSAID treatment was significantly associated with an increased risk of death/recurrent MI (hazard ratio, 1.45; 95% confidence interval, 1.29 to 1.62) at the beginning of the treatment, and the risk persisted throughout the treatment course (hazard ratio, 1.55; 95% confidence interval, 1.46 to 1.64 after 90 days). Analyses of individual NSAIDs showed that the traditional NSAID diclofenac was associated with the highest risk (hazard ratio, 3.26; 95% confidence interval, 2.57 to 3.86 for death/MI at day 1 to 7 of treatment). CONCLUSIONS: Even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent MI in patients with prior MI. Neither short- nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited from a cardiovascular safety point of view.

Freedman, N. D., Y. Park, et al. (2012). "**Association of coffee drinking with total and cause-specific mortality**." N Engl J Med **366**(20): 1891-1904.

Type of Question: Harm **Beginner Cohort Study**.

Teaching Notes: cohort study on coffee consumption and mortality; good for teaching association/causation, adjusting for confounders (smoking is a major confounder) and also "dose reponse" of coffee and its impact on mortality, and it's a fun topic that should reassure the coffee drinkers in the room!

Abstract: BACKGROUND: Coffee is one of the most widely consumed beverages, but the association between coffee consumption and the risk of death remains unclear. METHODS: We examined the association of coffee drinking with subsequent total and cause-specific mortality among 229,119 men and 173,141 women in the National Institutes of Health-AARP Diet and Health Study who were 50 to 71 years of age at baseline. Participants with cancer, heart disease, and stroke were

excluded. Coffee consumption was assessed once at baseline. RESULTS: During 5,148,760 person-years of follow-up between 1995 and 2008, a total of 33,731 men and 18,784 women died. In age-adjusted models, the risk of death was increased among coffee drinkers. However, coffee drinkers were also more likely to smoke, and, after adjustment for tobacco-smoking status and other potential confounders, there was a significant inverse association between coffee consumption and mortality. Adjusted hazard ratios for death among men who drank coffee as compared with those who did not were as follows: 0.99 (95% confidence interval [CI], 0.95 to 1.04) for drinking less than 1 cup per day, 0.94 (95% CI, 0.90 to 0.99) for 1 cup, 0.90 (95% CI, 0.86 to 0.93) for 2 or 3 cups, 0.88 (95% CI, 0.84 to 0.93) for 4 or 5 cups, and 0.90 (95% CI, 0.85 to 0.96) for 6 or more cups of coffee per day (P<0.001 for trend); the respective hazard ratios among women were 1.01 (95% CI, 0.96 to 1.07), 0.95 (95% CI, 0.90 to 1.01), 0.87 (95% CI, 0.83 to 0.92), 0.84 (95% CI, 0.79 to 0.90), and 0.85 (95% CI, 0.78 to 0.93) (P<0.001 for trend). Inverse associations were observed for deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections, but not for deaths due to cancer. Results were similar in subgroups, including persons who had never smoked and persons who reported very good to excellent health at baseline. CONCLUSIONS: In this large prospective study, coffee consumption was inversely associated with total and cause-specific mortality. Whether this was a causal or associational finding cannot be determined from our data. (Funded by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics.).

Frei, P., A. H. Poulsen, et al. (2011). "**Use of mobile phones and risk of brain tumours: update of Danish cohort study**." BMJ **343**: d6387.

Type of Question: Harm **Beginner Cohort Study**.

Teaching Notes: cohort study from Denmark (land of amazing population based data) showing a lack of association between cell phone use and brain tumors

Abstract: OBJECTIVE: To investigate the risk of tumours in the central nervous system among Danish mobile phone subscribers. DESIGN: Nationwide cohort study. SETTING: Denmark. PARTICIPANTS: All Danes aged >/= 30 and born in Denmark after 1925, subdivided into subscribers and non-subscribers of mobile phones before 1995. MAIN OUTCOME MEASURES: Risk of tumours of the central nervous system, identified from the complete Danish Cancer Register. Sex specific incidence rate ratios estimated with log linear Poisson regression models adjusted for age, calendar period, education, and disposable income. RESULTS: 358,403 subscription holders accrued 3.8 million person years. In the follow-up period 1990-2007, there were 10,729 cases of tumours of the central nervous system. The risk of such tumours was close to unity for both men and women. When restricted to individuals with the longest mobile phone use--that is, >/= 13 years of subscription--the incidence rate ratio was 1.03 (95% confidence interval 0.83 to 1.27) in men and 0.91 (0.41 to 2.04) in women. Among those with subscriptions of >/= 10 years, ratios were 1.04 (0.85 to 1.26) in men and 1.04 (0.56 to 1.95) in women for glioma and 0.90 (0.57 to 1.42) in men and 0.93 (0.46 to 1.87) in women for meningioma. There was no indication of dose-response relation either by years since first subscription for a mobile phone or by anatomical location of the tumour--that is, in regions of the brain closest to where the handset is usually held to the head. CONCLUSIONS: In this update of a large nationwide cohort study of mobile phone use, there were no increased risks of tumours of the central nervous system, providing little evidence for a causal association.