ATTACHMENT I – RESULTS AND CONCLUSIONS

For each of the CERs reviewed, this Attachment provides the findings of our searches of the literature and FDA MedWatch Database and expert assessments, along with our overall recommendation regarding updating and the conclusion(s) on which each recommendation is based.

CER 1. Comparative Effectiveness of Management for Gastroesophageal Reflux Disease

For this assessment, a limited literature search was conducted for the years 2005-2008. This search included the five generalist journals listed in the Methods and five specialty journals (as recommended by the subject matter experts): Gastroenterology; American Journal of Gastroenterology; Clinical Gastroenterology and Hepatology; Gut; and Alimentary Pharmacology and Therapeutics. The search identified 296 titles, of which 124 were obtained in full text for further review. The remaining titles were rejected because they were editorials, letters, non-systematic reviews, or did not include topics of relevance. Of those selected for further review, 35 were abstracted into an evidence table (Attachment I). The remaining articles were rejected because they had already been included in the earlier report or did not include a comparison of interest.

We consulted the project lead, four members of the TEP, and 6 additional experts for their assessments. Of these 11 individuals, 6 responded.

Table 2.1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.1 CER 1. Comparative Effectiveness of Management for Gastroesophageal Reflux Disease (GERD): Are the conclusions still valid?

Conclusions From CER Executive Summary	RAND Literature Search	FDA /Health Canada	Expert Opinion EPC Investigator, 5 Other Experts	Conclusion from SCEPC
Key Question 1: What is the evidence of the comparative effectiveness of medical, surgical, and endoscopic treatments for improving objective and subjective outcomes in patients with chronic GERD?				
Medical therapy with PPIs and surgery (fundoplication) appeared to be similarly effective for improving symptoms and decreasing esophageal acid exposure. 10 percent to 65 percent of surgical patients still require medications. The limited data available did not support a significant benefit of fundoplication compared with medical therapy for preventing Barrett's esophagus or esophageal adenocarcinoma.	A multicenter randomized controlled trial (RCT) found laparoscopic antireflux surgery (LARS) vs. esomeprazole were similarly effective and well-tolerated over 3 years (Lundell, 2008).	FDA 6/30/2008 approved ACIPHEX (RABEPRAZOLE SODIUM) in short-term treatment of symptomatic GERD in adolescent patients 12 years of age and above.	All experts agreed this conclusion is still valid. One expert notes that very little is new (see Spechler, 2001).	Conclusion is still valid and this portion of the CER does not need updating.
Of the three nonrandomized studies that compared an endoscopic procedure with laparoscopic fundoplication in patients with GERD documented by pH or endoscopy, the longest follow-up was 8 months, and all three studies had significant bias that may invalidate the results. Two studies reported that more patients treated with laparoscopic fundoplication were satisfied with their results compared with those who had EndoCinchTM. One of these studies and a study of Stretta® also found less need for PPIs in patients who had fundoplication.	A nonrandomized prospective study of 51 patients with persistent GERD comparing transesophageal endoscopic plication (TEP) with laparoscopic Nissen fundoplication (LNF) found that both techniques improved symptom score, acid regurgitation, quality of life, and reduced requirement for PPIs. Control of heartburn and acid reflux was better for LNF. TEP, like LNF, had comparable safety and efficacy (Mahmood, 2006). A RCT comparing	Not applicable.	Experts agreed this conclusion is no longer applicable as these endoscopic techniques are no longer in use. One expert noted that the overall appeal for these interventions has dropped off significantly, so there has been very little in the way of important new studies on endotherapies for GERD. One expert said the conclusion was no longer relevant since endoscopic therapy for GERD is not actively being used. Stretta is off the market.	Original conclusion should probably be deleted as the endoscopic procedure is no longer in use.

Legend: AE: adverse event (or effect); GE: gastroenteritis; GERD: gastroesophageal reflux disease; H2As: histamine 2 receptor antagonists; LARS: laparoscopic antireflux surgery; LNF: laparoscopic Nissen fundoplication; NERD: non-erosive reflux disease; PPI: proton pump inhibitor; RCT: randomized controlled trial; TEP: trans-esophageal endoscopic plication

Conclusions From CER Executive Summary	RAND Literature Search	FDA /Health Canada	Expert Opinion EPC Investigator, 5 Other Experts	Conclusion from SCEPC
	endoluminal gastroplasty (EndoCinch) with polymer injection (Enteryx) over 6 months demonstrated equal effectiveness in reducing PPI dosages and improving symptoms of patients. (Domagk, 2006)			
There was no head-to-head comparison of medical treatments with endoscopic treatments.	No new evidence.	Not applicable.	Two experts agreed the conclusion is no longer applicable as these endoscopic techniques are no longer in use. One expert noted there is nothing new.	Original conclusion should probably be deleted as the endoscopic procedure is no longer in use.
PPIs were superior to H2RAs (histamine 2 receptor inhibitors) in resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks. There was no difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for relief of symptoms at 8 weeks. No significant difference was found in the comparisons of esomeprazole 40 mg with lansoprazole 30 mg or pantoprazole 40 mg for relief of symptoms at 4 weeks. Similarly, there was no difference in the comparison of esomeprazole 20 mg with omeprazole 20 mg in relief of symptoms at 4 weeks.	A meta-analysis of 10 studies compared rates of endoscopic healing, symptom relief, and adverse events of esomeprazole versus alternative PPIs in treatment of erosive esophagitis. Esomeprazole demonstrated a statistically significant improvement, but only modest clinical benefit in improved healing of erosive esophagitis at 8-weeks. There is no evidence of what is believed to be “clinically meaningful improvement in symptom relief” between PPIs (Gralnek, 2006). A systematic review of RCTs in patients with reflux esophagitis demonstrates esomeprazole consistently has higher healing rates when compared with standard dose PPIs at 4 and 8 weeks (Edwards, 2006).	FDA 4/27/2007 revised the Precautions section of PRILOSEC (OMEPRAZOLE) “Concomitant administration of omeprazole and voriconazole (a combined inhibitor of CYP2C19 and CYP3A4) resulted in more than doubling of the omeprazole exposure. Dose adjustment of omeprazole is not normally required. However, in patients with Zollinger-Ellison's syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered.” FDA 6/30/2008 approved ACIPHEX (RABEPRAZOLE SODIUM) in short-term treatment of symptomatic GERD in adolescent patients 12 years of age and above.	One expert noted a meta-analysis revealed a benefit for esomeprazole for healing rates and symptom response rates (Gralnek, 2006). Other experts stated the conclusion was still valid.	Conclusion is probably out of date and this portion of the CER may need updating based on a wealth of new data.

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Conclusions From CER Executive Summary	RAND Literature Search	FDA /Health Canada	Expert Opinion EPC Investigator, 5 Other Experts	Conclusion from SCEPC
	A new RCT of patients with erosive esophagitis comparing PPI maintenance therapy demonstrates esomeprazole 20 mg qday is more effective than lansoprazole 15 mg qday in maintaining endoscopic/symptomatic mission in patients with healed erosive esophagitis (Devault, 2006). A new of GERD patients demonstrates famotidine 20 mg BID and omeprazole 20 mg qday were both effective in improving GERD symptoms, particularly non-erosive GERD disease over a period of 8 weeks (Wada, 2006). A new RCT of patients with healed erosive esophagitis demonstrates esomeprazole 20 mg is superior to pantoprazole 20 mg for maintenance therapy following healed erosive esophagitis and relief of GERD symptoms at 6 months (Lubenz, 2005). A new RCT of patients with NERD found that, in patients who are H pylori negative, omeprazole is more effective than famotidine for control of GERD symptoms, but in H. pylori positive symptoms, similar efficacy was observed (Fujiwara, 2005).			

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Conclusions From CER Executive Summary	RAND Literature Search	FDA /Health Canada	Expert Opinion EPC Investigator, 5 Other Experts	Conclusion from SCEPC
For maintenance medical treatment of 6 months to 1 year, PPIs taken at a standard dose were more effective than those taken at a lower dose.	No new evidence.	FDA 4/21/2008 revised warning section of PREVACID (Lansoprazole) for inclusion of Clostridium difficile associated diarrhea. "Physicians use combination therapy with PREVACID plus amoxicillin and clarithromycin for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or five-year history of duodenal ulcer) to eradicate H. pylori."	Experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Laparoscopic fundoplication was as effective as open fundoplication for relieving heartburn and regurgitation, improving quality of life, and decreasing use of antisecretory medications. Almost 90 percent of patients who were followed for 5 or more years in both surgical arms reported improvement in symptoms.	No new evidence.	Not applicable.	Experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Compared to sham, StrettaTM was more effective in improving symptoms of reflux and improving quality of life at 6 months and was associated with a decrease in the need for antisecretory medications. Improvement of esophageal pH exposure compared with sham could not be demonstrated for StrettaTM.	Compared to sham, endoscopic gastroplication using Endocinch device reduced acid-inhibitory drug use, improved GERD symptoms, and improved quality of life (Schwartz, 2007).	Not applicable.	Experts agreed the conclusion is no longer applicable as these endoscopic techniques are no longer in use. One expert said this was also true in the Endocinch sham trial although this study was not as rigorous as the Stretta study (Schwartz, 2007). One expert noted that Stretta is off the market because of adverse events.	Original conclusion should probably be deleted as the endoscopic procedure is no longer in use.
Key Question 2: Is there evidence that effectiveness of medical, surgical, and				

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Conclusions From CER Executive Summary	RAND Literature Search	FDA /Health Canada	Expert Opinion EPC Investigator, 5 Other Experts	Conclusion from SCEPC
endoscopic treatments varies for specific patient subgroups?				
Patients on maintenance antireflux medications may have higher rates of esophagitis if they have any of the following factors: increased severity of esophagitis at baseline (pretreatment), younger age, and moderate to severe regurgitation.	No new evidence.	No new information.	Experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
There is no substantial evidence to support a difference in surgical outcome based on age, preoperative presence or severity of esophagitis, lower esophageal sphincter incompetence, or esophageal body hypomotility. Patients treated surgically who have a history of psychiatric disorders may have worse symptom and satisfaction outcomes than those without a significant psychiatric history.	No new evidence.	No new information.	Experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Key Question 3: What are the short- and long-term adverse effects associated with specific medical, surgical, and endoscopic therapies for GERD?				
Higher adverse event rates were described for PPIs than for H2RAs or placebo. The most commonly cited events for PPIs and H2RAs were headache, diarrhea, and abdominal pain.	No new evidence.	FDA 4/21/2008 revised warning section of PREVACID (Lansoprazole) for inclusion of Clostridium difficile associated diarrhea. "Physicians use combination therapy with PREVACID plus amoxicillin and clarithromycin for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or five-year history of duodenal ulcer) to eradicate H. pylori" FDA 4/27/2007 revised the Precautions section of PRILOSEC (OMEPRAZOLE) "Concomitant administration of	Experts agreed the conclusion is still valid. One expert notes it is important to capture the new data regarding other complications of PPIs (albeit rare complications), like Clostridium difficile colitis, pneumonia, osteoporosis, interstitial cystitis, and small intestinal bacterial overgrowth. It might also be important to emphasize that the side effect profile varies by PPI type. For example, headache is more common with Esomeprazole, diarrhea with lansoprazole.	Conclusion is possibly out of date and this portion of the CER may need updating based on expert opinion about newly recognized adverse events.

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Conclusions From CER Executive Summary	RAND Literature Search	FDA /Health Canada	Expert Opinion EPC Investigator, 5 Other Experts	Conclusion from SCEPC
		omeprazole and voriconazole (a combined inhibitor of CYP2C19 and CYP3A4) resulted in more than doubling of the omeprazole exposure. Dose adjustment of omeprazole is not normally required. However, in patients with Zollinger-Ellison syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered."		
The most commonly reported complications occurring intraoperatively or within 30 days after open fundoplication were the need for splenectomy, dysphagia, inability to belch, and inability to vomit. The most commonly reported complications for laparoscopic procedures were gastric or esophageal injury or perforation, splenic injury or splenectomy, pneumothorax, bleeding, pneumonia, fever, wound infections, bloating, and dysphagia. Major complications were generally reported at very low rates.	No new evidence.	No new information.	Experts agree still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Frequently reported complications for endoscopic treatments (intraoperatively or within 30 days after the procedure) included chest or retrosternal pain, gastrointestinal injury, bleeding, and short-term dysphagia. The frequency and types of complications varied with the different procedures. Serious complications, including fatalities, have also been described.	No new evidence.	No new information.	One expert noted that Enteryx is now off the market because of severe AEs. The specific AE profiles depend very much on which endotherapy is being used. One expert said that esophageal perforations have been reported. Stretta is off the market	Original conclusion should probably be deleted as the endoscopic procedure is no longer in use.

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Additional information:

One expert suggested:
One might considering summarizing the literature comparing the effectiveness of continuous with on-demand proton pump inhibitor therapy for patients with GERD

Therefore, RAND researched this topic: Timing of treatment-"On-demand" vs. "intermittent" vs. "continuous" therapy:
a) A systematic review of 17 studies found on-demand PPI is effective in long-term management of patients with NERD or mild and uninvestigated forms of GERD, but not in patients with severe erosive esophagitis. These studies include on-demand PPI vs. placebo and continuous PPI. (Pace, 2007)
b) A systematic review of the efficacy of intermittent and on-demand therapy with H2As and PPIs in patients with erosive esophagitis or symptomatic heartburn found, regarding intermittent therapy, neither PPIs nor H2As were effective in maintaining control of esophagitis patients. In regards to on-demand therapy, PPIs may work in a proportion of non-erosive GERD patients (Zachy, 2005).
c) A RCT of patients with erosive reflux esophagitis found that once daily esomeprazole 20 mg was better than "on-demand" for maintaining healed erosive esophagitis at 6 months (Sjostedt, 2005).
d) A RCT of patients with NERD or low grade esophagitis demonstrates a slightly higher rate of symptom relief at 6 months with the continuous rabeprazole group versus the on-demand group. For overall quality of life, there was not difference between the groups. Daily consumption was lower for the on-demand treatment group (Bour, 2005).
e) A RCT of GERD patients demonstrates that at 6 months, on-demand treatment with lansoprazole in symptomatic patients after short-term, continuous treatment is more effective than placebo in improving symptoms (Bigard, 2005).

Laryngeal/pharyngeal symptoms attributed to GERD. Caveat: the cause and effect relationship of GERD and laryngo-phayngeal reflux remains unclear:
a) Meta-analysis of 5 studies using high-dose PPIs for treatment of laryngeal or pharyngeal symptoms was no more effective than placebo in provident symptomatic improvement or resolution of laryngo-pharyngeal symptoms (Gatta, 2007).
b) A RCT of 39 patients with laryngopharyngeal reflux treated with pantoprazole vs. placebo found no difference in symptom improvement between the two groups (Wo, 2006).
c) Systematic review and meta-analysis of RCTs of patients with chronic cough associated with GERD demonstrated use of PPI for treatment has some effect in some adults, but is less universal than suggested in consensus guidelines on chronic cough (Chang, 2006).

Acupuncture vs. doubling PPI dose:
A RCT of 30 patients with refractory heartburn compared doubling PPI dose vs. acupuncture twice weekly found adding acupuncture was more effective than doubling PPI dose in controlling GERD symptoms (Dickman, 2007).

Double dose or change PPI:
A RCT of patients with persistent heartburn symptoms found switching patients to different PPI was as effective as increasing PPI dosage to twice daily for controlling heartburn symptoms (Fass, 2006).

Long-term prevention of erosive or ulcerative GERD relapse:
A RCT of patients with healed erosive/ulcerative GERD found 5-year maintenance therapy with rabeprazole was effective in preventing relapse of erosive/ulcerative GERD. 20 mg was better than 10 mg. Both was better than placebo (Caos, 2005).

New endoscopic techniques:
Radiofrequency energy delivery allows reduction or discontinuation of PPI therapy in patients with PPI-dependent symptoms (Coron, 2008).

AZD0865, potassium-competitive acid blocker:
a) A RCT comparing a potassium-competitive acid blocker (AZD0865) did not provide clinical benefit over esomeprazole in patients with nonerosive reflux disease (Dent, 2008).

b) A RCT compared three doses of potassium-competitive acid blocker (AZD0865) (25, 50, 75 mg) with esomeprazole 40 mg. At 4 weeks, healing rates of esophagitis was similar to

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Conclusions From CER Executive Summary	RAND Literature Search	FDA /Health Canada	Expert Opinion EPC Investigator, 5 Other Experts	Conclusion from SCEPC

esomeprazole. No significant difference was found in heartburn control. AZD0865 at 75 mg was demonstrated reversible increases in liver transaminases (Kahrilas, 2007).

Nocturnal symptoms:
a) A RCT in GERD patients with nocturnal heartburn concludes single-dose rabeprazole 20mg increases intragastric pH more than pantoprazole 40mg qday (Warrington, 2007).
b) A randomized controlled trial in GERD patients with nocturnal symptoms, comparing immediate-release omeprazole 40 mg oral suspension, delayed release lansoprazole 30 mg capsules, and delayed-release esomeprazole 30 mg capsules. Omeprazole was superior to lansoprazole and comparable to esomeprazole (Katz, 2007).
c) A RCT in erosive esophagitis patients on daily PPI with experience night-time heart burn finds OTC ranitidine 75 mg reduced symptoms vs. placebo on day 3, but not on day 14 (Vakil, 2006).
d) A RCT of patients with nocturnal GERD demonstrates immediate-release omeprazole reduced nocturnal gastric acidity better than delayed-release pantoprazole (Castell, 2005).

Early response to therapy predicts complete resolution:
Pooled analysis from three multicenter, double-blind trials of patients receiving PPI found that heartburn resolution during 1st week of PPI therapy is the best predictor of treatment success at week 4 (Talley, 2006).

Rebound acid hypersecretion:
A systematic review of 8 studies demonstrates no strong evidence for clinically relevant increased acid production after cessation of PPI therapy. Only 1 study included patients with reflux esophagitis, and the remaining 7 studies enrolled healthy volunteers (Gatta, 2007).

Risk of bacterial gastroenteritis:
A case control study of patients with acute bacterial gastroenteritis (GE) compared with a control group without acute bacterial GE found current PPI use was associated with increased risk of bacterial GE. H2A use was not associated with increased risk. Caveat is that this is a heterogeneous patient population, including some with GERD (Rodriguez, 2007).

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CER 2. Effectiveness of Noninvasive Tests for Breast Abnormalities

For this assessment, a limited literature search was conducted for the years 2005-2008. This search included the five generalist journals listed in the Methods and seven specialty journals (those most frequently cited in the original CER): CA: A Cancer Journal for Clinicians, Radiological Clinics of North America, Journal of Nuclear Medicine, European Journal of Nuclear Medicine, Radiology, Journal of Magnetic Resonance Imaging, and Journal of Ultrasound Medicine. The search identified 1,465 titles, of which 54 were obtained in full text for further review. The remaining titles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance. Of the 54 selected for further review, 20 were abstracted. The remaining articles were rejected because they had already been included in the earlier report or did not include a comparison of interest.

We consulted the project lead, two members of the TEP and one other expert for their assessments. Of these four individuals, one responded.

Table 2.2 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.2 CER 2. Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities: Are the conclusions still valid?

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions Only one expert provided input	Conclusion from SC EPC
Key Question 1: What are the sensitivity and specificity of the tests for diagnosis of breast cancer in women presenting with an abnormal mammogram or a palpable breast abnormality?				
To place the tests' accuracy information into perspective, an average woman in the U.S. who has an abnormal mammogram requiring a biopsy for evaluation has approximately a 20-percent risk of cancer. For women at this average level of risk of cancer after an abnormal mammogram, based upon the tests' negative likelihood ratios: * For every 1,000 women who had a negative PET scan, about 924 women would have avoided an unnecessary biopsy, but 76 women would have missed cancers. * For every 1,000 women who had a negative scintimammogram, about 907 women would have avoided an unnecessary biopsy, but 93 women would have missed cancers. (These numbers are for nonpalpable lesions only; numbers could not be calculated for all lesions.) * For every 1,000 women who had a negative MRI, about 962 women would have avoided an unnecessary biopsy, but 38 women would have missed cancers. * For every 1,000 women who had a negative US, about 950 women For every 1,000 women who had a negative US, about 950 women would have avoided an unnecessary biopsy, but 50 women would have missed cancers.	A meta-analysis of 44 studies of magnetic resonance imaging (MRI) in patients suspected of having breast cancer estimated the sensitivity at 0.90% and the specificity at 72% (Peters, 2008).	No new information.	One expert agreed that the conclusion is still valid.	It is difficult to estimate whether this conclusion is still valid or not, since it consists of calculations made based on operating characteristics of the test with "average" level of cancer risk. Using data from the Peters, 2008 meta-analysis, the "missed cancers" number would be 20, not 38. Therefore, this conclusion is possibly out of date, although probably modestly so.
Although all of the technologies evaluated could reduce the need for biopsy in women with an abnormal mammogram who do not have cancer, each would miss some cancers.	No literature will change this conclusion, since there is no test with 100% sensitivity.	No new information.	One expert agreed that the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Key Question 2: For women with relevant demographic risk factors (e.g., age, family history) and clinical risk factors (e.g., Breast Imaging Reporting and Data System [BIRADS] status or morphologic characteristics of the lesion), what are the positive and negative predictive values of the above diagnostic tests (Magnetic Resonance Imaging, Positron Emission Tomography, Scintimammography, or Ultrasound)?				

Legend: BIRADS: Breast Imaging Reporting and Data System; MRI: magnetic resonance imaging; PET: positron emission tomography; US: ultrasound

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions Only one expert provided input	Conclusion from SC EPC
In general, the higher a woman's risk of cancer is before undergoing a noninvasive test, the higher is the risk that she has cancer even if the test is negative. If a less than 2-percent risk of having breast cancer with a negative diagnostic test is considered an acceptable level of risk for a diagnostic test to reliably preclude biopsy, none of these tests was sufficiently accurate to replace biopsy for women at average risk of breast cancer.	A systematic review of MRI to screen women at high risk for breast cancer included 11 studies and the summary negative likelihood ratio was 0.70 (Warner, 2008). The American Cancer Society released new guidelines for the use of MRI as an adjunct to mammography that recommended its use in women at increased risk (Saslow, 2008). A study of 969 women with breast cancer assessed the utility of MRI of the contralateral breast, which had no abnormalities on clinical examination or mammography. MRI detected breast cancer in 30 women (3.1%). The sensitivity was 91%, the specificity was 88%, and the negative predictive value of MRI was 99% (Lehman, 2007). A group of 2,809 women at elevated risk of breast cancer and with heterogeneously dense breast tissue were randomized to receive screening with mammography and ultrasound (US) or with mammography alone. The additional yield of added US was 4.2 cancers per 1000 women screened. The diagnostic accuracy of mammography alone was 0.78 and this increased to 0.91 with the addition of ultrasound (Berg, 2008).	No new information.	One expert noted that there might be some new evidence on MRI, particularly for certain subgroups of women.	Conclusion is probably out of date and this portion of the CER may need updating based on new data on MRI and US.
Key Question 3: Are there other factors that affect the accuracy or acceptability of the tests considered in Questions 1 and 2?				
Based on results for only nonpalpable lesions (usually detected by mammography), data were insufficient to estimate the accuracy of PET scanning, MRI, or US. Scintimammography was not sufficiently accurate to avoid biopsy in women at average risk as judged by the acceptability standard of less than a 2-percent risk of breast cancer with a negative diagnostic test. Based on results for only palpable lesions, data were insufficient to estimate the accuracy of PET scanning, MRI, ultrasound, and scintimammography.	New meta-analysis reports sensitivities and specificities for MRI, Lehman, 2008, although the ability to separate results based on non-palpable versus palpable lesions is unknown	No new information.	One expert said that there wasn't really a conclusion and does not think sufficient evidence is available to reach one.	Conclusion is possibly out of date and this portion of the CER may need updating based on the new meta-analysis. It would need to be reviewed to assess whether data can be stratified.

Legend: BIRADS: Breast Imaging Reporting and Data System; MRI: magnetic resonance imaging; PET: positron emission tomography; US: ultrasound

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions Only one expert provided input	Conclusion from SC EPC
Are there new data that could inform the key questions that might not be addressed in the conclusions? New technologies such as proton MR spectroscopy (Tozaki, 2008) and ultrasound elastography (Zhi, 2007) continue to appear; whether data are sufficient to justify adding these to the CER is not known.				

Legend: BIRADS: Breast Imaging Reporting and Data System; MRI: magnetic resonance imaging; PET: positron emission tomography; US: ultrasound

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CER 3. Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment

For this assessment, a limited literature search was conducted for the years 2004-2008. This search included the five generalist journals listed in the Methods and five specialty journals (as recommended by the subject matter experts): Cancer, Journal of Clinical Oncology, Annals of Oncology, Oncology, and British Journal of Cancer.

The search identified 94 titles, of which 24 were obtained in full text for further review. The remaining 70 titles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance. Of the 24 selected for further review, 16 were abstracted into an evidence table (Attachment II). The remaining articles were rejected because they had already been included in the earlier report or did not include a comparison of interest. An additional four articles were subsequently reviewed and added at the suggestion of the experts.

We consulted the project lead, 5 members of the TEP, and three additional experts for their assessments. Of these 9 individuals, four responded.

Table 2.3 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.3 CER 3. Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Are the conclusions still valid?

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts:	Conclusion from SCEPC
Key Question 1: What are the comparative efficacy and safety of epoetin (alfa or beta) and darbepoetin?				
The evidence does not show any clinically significant difference between epoetin and darbepoetin in hemoglobin response, transfusion reduction, and thromboembolic events (TEE). For each of the above outcomes, more evidence is available on epoetin than darbepoetin.	For hematologic response, no new studies compared epoetin to darbepoetin. 3 randomized controlled trial (RCT)s of epoetin A, 1 trial of epoetin B, and 2 trials of darbepoetin showed increases or smaller decreases in hemoglobin (Hb) compared with placebo controls; (Wright, 2007; Wilkinson, 2006; Razzouk, 2006; Aapro, 2008b; Pirker, 2006; Norager, 2006) 1 RCT of epoetin A vs. amifostine showed smaller reduction in Hb with epoetin A (Han, 2008). For rates of transfusion, 1 RCT compared epoetin to darbepoetin showed darbepoetin reduced transfusion incidence to a non-significantly greater degree than epoetin (Glaspy, 2006). 2 RCTs of epoetin A showed significant reduction in need for transfusion (including one study in children)(Wilkinson, 2006; Razzouk, 2006); 1 RCT of Darbepoetin showed non-significant decrease in need for transfusion (Smith, 2008) and 1 showed a significant decrease (Pirker, 2008). For TEE, 2 meta-analyses and 1 open-label multi-center RCT of epoetin B showed increased incidence of TEE vs. placebo, although event rates varied widely among treated and untreated patients (Aapro, 2008a; Aapro, 2006; Aapro, 2008b). No study showed an effect on TEE-related mortality or serious TEEs.	At the ODAC meeting in March 2008, FDA presented data on 5 new studies (4 darbepoetin and 1 epoetin) that showed evidence of tumor progression or worse survival in some patient populations. FDA Medwatch 1/08/07 revised Box Label for epoetin to read "WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION. To minimize these risks, as well as the risk of serious cardio- and thrombovascular events, • Use the lowest dose needed to avoid red blood cell transfusions. • Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy. • Discontinue following the completion of a chemotherapy course. Perisurgery: PROCRIT/EPOGEN® increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis."	Three experts judged this conclusion is still valid. The fourth said it is probably still valid; however: "although no new evidence that I am aware of regarding clinical differences in safety and efficacy of the two drugs, a number of new studies have raised concerns regarding the safety and efficacy of the class that have led to new FDA labeling and changes in reimbursement policy. At the ODAC meeting in March 2008, FDA presented data on 5 new studies (4 darbepoetin and 1 epoetin) that showed evidence of tumor progression or worse survival in some patient populations."	Conclusion is possibly out of date and this portion of the CER may need updating, based on new data presented to the FDA and difference in expert opinion.
The evidence is not sufficient for conclusions on effects of either epoetin or darbepoetin on quality of life (QoL), tumor response and progression, survival, or adverse outcomes other than TEE. Trials did not completely or	Epoetin A significantly improved QoL as measured by median CLAS scores (energy level, ability to do daily activities, overall QoL) (Wilkinson, 2006); Epoetin A did not significantly improve mean PedsQL-GCS generic score and cancer specific score in children, but change in Hb correlated with PedsQL-GCS total score in the epoetin-treated	No new information.	No opinions provided by experts	Conclusion is still valid and this portion of the CER does not need updating.

Legend: DSMB: Data safety monitoring board; ESA: Erythropoiesis stimulating agent; Hb: Hemoglobin; ODAC: Oncology Drug Advisory Committee; QoL: Quality of life; RCT: Randomized controlled trial; TEE: Thromboembolic event; VTE: Venous thromboembolism

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts:	Conclusion from SCEPC
consistently report quality of life (QoL) results, so 12 potentially relevant studies were unusable for this analysis, and quantitative analysis could not be performed for the 15 remaining studies. Overall, QoL measures tended to favor treatment with epoetin or darbepoetin…	group (Razzouk, 2006); Darbepoetin significantly improved work capacity compared to placebo but did not affect fatigue, postural sway, or QoL (Norager, 2006).			
The limited evidence available does not suggest that erythropoietic stimulants improve solid tumor response to a concurrent course of cancer therapy. Whether erythropoietic stimulants accelerate progression of some cancers, as reported by one study is uncertain.	Two meta-analyses of epoetin B showed similar effects on tumor response and disease progression. One showed a slight beneficial effect on disease progression (Aapro, 2006); the second showed a trend toward a beneficial effect on tumor progression (Aapro, 2008a). A new review states that both epoetin and darbepoetin have been linked to decreased survival (Glaspy, 2009).	(See reference to FDA Medwatch Revised Box Label above)	Three experts judged that the conclusion remains valid, but with the following comments: "The first part remains true: Erythropoiesis stimulating agents (ESAs) do not improve solid tumor responses (this is now supported by more and better-quality evidence); however, there are now several additional studies suggesting ESAs may accelerate progression of some cancers." One expert cited a new review: "May be associated with adverse outcomes (Glaspy, 2009) " "Increased tumor progression" " (Henke, 2003; Leyland-Jones, 2005; Bennett, 2008) [Henke 2003 and Leyland-Jones 2005 were included in the	Conclusion is out of date and this portion of the CER needs updating based on new data and agreement of expert opinion.

Legend: DSMB: Data safety monitoring board; ESA: Erythropoiesis stimulating agent; Hb: Hemoglobin; ODAC: Oncology Drug Advisory Committee; QoL: Quality of life; RCT: Randomized controlled trial; TEE: Thromboembolic event; VTE: Venous thromboembolism

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts:	Conclusion from SCEPC
			original report] One expert judged that the conclusion is no longer valid: "New Evidence: Although uncertainty still remains on overall effect of ESAs on tumor progression, 5 new studies (4 darbepoetin and 1 epoetin) showed evidence of tumor progression or worse survival in some patient populations. Balance of evidence does not demonstrate any improvement in solid tumor response."	
Of 40 RCTs reporting on survival, only seven were actually designed to assess effects on survival. No studies designed to test survival used epoetin or darbepoetin as currently recommended; rather, all seven trials sought to maintain Hb levels >12 g/dL. Two of the seven trials, one on metastatic breast cancer (n=939) and one on head and neck cancer (n=351), showed poorer overall survival for patients treated with epoetin; this prompted an FDA safety review in May 2004 and revised product labeling to indicate that clinicians should avoid targeting Hb concentrations above 12 g/dL. Of the other five trials, survival appeared poorer with erythropoietic stimulant in	2 RCTs and 2 meta-analyses showed no change in survival with epoetin A(Han, 2008) or epoetin B (Aapro, 2006; Aapro, 2008a; Aapro, 2008b) but the authors noted that the latter was underpowered to detect a difference; One multicenter RCT of epoetin A found a decrease in median survival, which resulted in early termination of the study (Wright, 2007). A new review reported that epoetin has been associated with reduced transfusion requirements and also with an increase in the risk for venous thromboembolism (VTE) and a decrease in survival rate. (Fenner and Ganser, 2008).	(See reference to FDA Medwatch Revised Box Label above)	One of the experts judged the conclusion to still be valid but provided a new reference (Fenner and Ganser, 2008). The remaining three judged it no longer valid and made the following comments: "There are several new trials with evidence of harm, but nearly all were stopped early by DSMBs." Another expert stated: "Package Inserts 2008. Not related to hemoglobin level. 51 RCTs - meta-analysis, decreased survival withESAs. Trials that included survival as 1st or secondary outcomes; (14 trials with 5,785	Conclusion is probably out of date and this portion of the CER may need updating based on new data and the majority of expert opinion.

Legend: DSMB: Data safety monitoring board; ESA: Erythropoiesis stimulating agent; Hb: Hemoglobin; ODAC: Oncology Drug Advisory Committee; QoL: Quality of life; RCT: Randomized controlled trial; TEE: Thromboembolic event; VTE: Venous thromboembolism

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts:	Conclusion from SCEPC
three and better in two, but most results were not statistically significant. Analysis of mortality in all 40 trials shows no overall benefit of darbepoetin or epoetin on survival. Neither higher than recommended target Hb nor any other single patient- or treatment-related factor explained why some trials showed a detriment in survival and others did not.			patients)-hazard ratio for mortality =1.18(1.04, 1.35). (Samaras, 2008 [RAND unable to locate reference]) "No longer valid: New Evidence: As mentioned previously, 5 new studies (4 darbepoetin and 1 epoetin) showed evidence of tumor progression or worse survival in some patient populations although indication or dose of ESAs or Hb used was not compared with current product labeling. FDA analysis of Hb achieved (as opposed to target) presented at March 2008 ODAC meeting raised concerns about Hb<12 as target and resulted in labeling change that Hb target should be to avoid a transfusion."	
For other adverse events, reporting is incomplete, representing less than one-third of patients. Studies did not use consistent definitions of events and severity. Overall, adverse events were more frequent with epoetin or darbepoetin than control, but pooled results did not show statistically significant differences.	According to an updated systematic review of 57 studies by Bohlius and colleagues (the authors of this review), treatment with epoetin or darbepoetin increased the risk of thromboembolic events; although uncertainty remains regarding their effect on survival, caution is advised on their use with thrombogenic chemotherapeutic agents or in patients at high risk for thromboembolic events (Bohlius., 2006). A systematic review of Phase 3 trials assessing mortality associated with the use of ESAs to treat	No new information.	One expert considered the conclusion still valid. Two did not and noted the following: "1.57-fold increased risk of VTE. (Bohlius, 2006)" "Several new meta-analyses have been published with statistically significant	Conclusion is possibly out date and this portion of the CER may need updating based on differing expert opinion.

Legend: DSMB: Data safety monitoring board; ESA: Erythropoiesis stimulating agent; Hb: Hemoglobin; ODAC: Oncology Drug Advisory Committee; QoL: Quality of life; RCT: Randomized controlled trial; TEE: Thromboembolic event; VTE: Venous thromboembolism

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts:	Conclusion from SCEPC
	anemia among cancer patients found an increased risk of VTE and mortality (Bennett, 2008).		worsening in survival reported in Bennett, 2008."	
Key Question 2: How do alternative dosing strategies affect the comparative efficacy and safety of epoetin and darbepoetin?				
For each of the following pairs of dosing strategies, one large trial reported no statistically significant difference between strategies: fixed-dose compared to dose based on weight, one trial each for epoetin and darbepoetin; fixed-dose epoetin administered weekly vs. thrice weekly; fixed dose epoetin administered weekly vs. every 3 weeks; and darbepoetin using an initial loading dose versus constant weight-based dosing regimens. The remaining 14 trials were too small to interpret.	Two RCTs compared the effect of administering darbepoetin with and without iron (sodium ferric gluconate or IV iron) on hematopoietic response to darbepoetin and transfusion rate among patients with Hb≤11: both studies found that iron co-administration improved hematopoietic response to darbepoetin (Pedrazzoli, 2008; Bastit, 2008), and one found decreased requirement for transfusions (Bastit, 2008).	(See reference to FDA Medwatch Revised Box Label above)	Two experts considered the conclusion still valid; two said they do not know.	Conclusion is still valid and this portion of the CER does not need updating.
Key Question 3: How do alternative thresholds for initiating treatment or alternative criteria for discontinuing therapy or duration of therapy affect the efficacy and safety of erythropoietic stimulants?				
Three unblinded randomized trials, not yet published, compared using erythropoietic stimulant therapy soon after mild anemia developed vs. delaying treatment until Hb had fallen below a predefined	One RCT (probably one of the ones originally reported as not yet published) found greater effects on Hb, QoL, and productivity when treatment was initiated early (baseline Hb 10-12 g/dL) (Straus, 2006). A systematic review of 11 RCTs comparing early and late erythropoietic intervention reported	(See reference to FDA Medwatch Revised Box Label above)	One expert said the conclusion is probably still valid. One said it is not valid and provided the following comment" "Package inserts. No specific trigger or target	Conclusion is probably out of date and this portion of the CER may need updating based on new evidence and the majority of expert opinion.

Legend: DSMB: Data safety monitoring board; ESA: Erythropoiesis stimulating agent; Hb: Hemoglobin; ODAC: Oncology Drug Advisory Committee; QoL: Quality of life; RCT: Randomized controlled trial; TEE: Thromboembolic event; VTE: Venous thromboembolism

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts:	Conclusion from SCEPC
threshold of moderate anemia. Comparisons were ~11 g/dL vs. 9 g/dL; ~11 g/dL vs. 10 g/dL; and ~13 g/dL vs. 10 g/dL. All patients in the mild anemia arms were treated with an erythropoietic stimulant; of patients in whom treatment was delayed until moderate anemia developed, 19 percent, 63 percent, and 44 percent, respectively, were treated with erythropoietic stimulant. Transfusion was more frequent when treatment was delayed until moderate anemia developed, but the difference was not statistically significant in any study. One trial reported a statistically significant increase in TEE among patients who were treated for mild anemia compared with those who were treated for moderate anemia.	improved clinical benefit (in terms of Hb and transfusion incidence) from early treatment initiation (Lyman, 2006).		hemoglobin level is advised." One expert said the conclusion is no longer valid and provided the following evidence: "As mentioned previously, FDA analysis of Hb achieved (as opposed to target) presented at March 2008 ODAC meeting raised concerns about Hb<12 as target and resulted in labeling change that Hb target should be to avoid a transfusion."	
Key Question 4: Are any patient characteristics at baseline or early hematologic changes useful to select patients or predict responses to treatment with erythropoietic stimulants?				
Available evidence does not identify any single patient factor as clinically useful to guide treatment decisions. Potential predictive factors, measured at baseline (e.g., serum erythropoietin level or observed/predicted ratio [O/P ratio], serum ferritin) or early after starting treatment (e.g., Hb increase, serum ferritin, reticulocyte increase), were found to have either weak ability or no ability to	A phase-III multi-center RCT compared the effect of darbepoetin to placebo in patients with active cancer who were not receiving or planning to receive cytotoxic chemotherapy or myelosuppressive radiotherapy. Although transfusion incidence decreased non-significantly, cardiovascular events, TEE, and mortality increased, and long-term survival decreased (Smith, 2008). Survival varied by sex, tumor type, and geographic region but these effects disappeared w/sensitivity analysis.	(See reference to FDA Medwatch Revised Box Label above)	One expert deemed the conclusion still valid. A second said that it is probably not valid and provided the following evidence "Contra-indicated in patients receiving potentially curative therapy. Package insert. Breast, lungs and head and neck cancers may be particularly risky. ODAC 2008."	Conclusion is possibly out of date and this portion of the CER may need updating, based on differing expert opinion.

Legend: DSMB: Data safety monitoring board; ESA: Erythropoiesis stimulating agent; Hb: Hemoglobin; ODAC: Oncology Drug Advisory Committee; QoL: Quality of life; RCT: Randomized controlled trial; TEE: Thromboembolic event; VTE: Venous thromboembolism

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts:	Conclusion from SCEPC
discriminate between responders and nonresponders. Seven algorithms combining multiple factors, potentially more useful to predict Hb response, are each currently supported only by one study. The largest of these studies do not report sufficient predictive ability for any algorithm to establish clinical utility for selecting treatment.				
Are there new data that could inform the key questions that might not be addressed in the conclusions? One expert provided additional comments: The problem for doing a systematic review on this aspect of the evidence is that nearly all the new studies were terminated early by DSMBs because of safety concerns, well before they reached accrual targets. As a result, it seems unlikely to me that repeating the literature-based analyses with the added data would be any more conclusive than before. But another important issue here, and partly the reason why IPD meta-analysis seems the best approach going forward, is that an overall, across-the-board conclusion for all oncology patients may be misleading. The big advantage of IPD analysis in this particular situation is that, for each outcome, results can be evaluated separately for early- and advanced-stage patients, and separately for each of the most common malignancies.				

Legend: DSMB: Data safety monitoring board; ESA: Erythropoiesis stimulating agent; Hb: Hemoglobin; ODAC: Oncology Drug Advisory Committee; QoL: Quality of life; RCT: Randomized controlled trial; TEE: Thromboembolic event; VTE: Venous thromboembolism

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CER 4. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis

For this assessment, a limited literature search was conducted for the years 2005-2008. This search included the five generalist journals listed in the Methods and five specialty journals (as recommended by the subject matter experts): Rheumatology, Journal of Pain, British Journal of Rheumatology, Journal of Rheumatology, and Arthritis and Rheumatology. The search identified 49 titles, of which all were obtained as abstracts for further review. Fourteen full text articles were obtained and then abstracted. Thirty five articles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance.

We consulted the project lead, three members of the TEP, and two additional experts for their assessments. Of these 6 individuals, 4 responded.

Table 2.4 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.4 CER 4. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis: Are the conclusions still valid?

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
Key Question 1: What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements? How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use? (Note: The only benefits considered under this question are improvements in osteoarthritis symptoms from long-term use. Evidence of harms associated with NSAID use includes long-term studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.)				
There are no clear differences between various nonaspirin, nonselective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac) in efficacy for pain relief or improvement in function.	No new evidence.	No new information.	All experts agreed the conclusion is still valid. One expert states the conclusion needs to exclude acetaminophen and non-acetylated salicylates.	Conclusion is still valid and this portion of the CER does not need updating.
It is not clear whether celecoxib has fewer potential harms than nonselective NSAIDs when used longer than 3-6 months.	The Chan study is summarized below.	No new information.	One expert noted that you would need a large long-term trial to have enough power to examine this question, and s/he hasn't heard of any studies that have done this. One expert noted that in a new RCT (Chan, 2007) in patients with prior GI bleeding, celecoxib plus a proton pump inhibitor (PPI) was safer than an NSAID plus PPI. One expert noted that a study has shown that etoricoxib has fewer harms (Multinational Etoricoxib and Diclofenac Arthritis	Conclusion is probably out of date and this portion of the CER may need updating based on new data and expert opinion.

Legend: ADAPT: Alzheimer's Disease Anti-inflammatory Prevention Trial; CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; CV: cardiovascular; CVD: cardiovascular disease; DMSO: dimethyl sulfoxide; GI: gastrointestinal; H2: histamine-2, HR: hazard ratio; MEDAL: Multinational Etoricoxib and Diclofenac Arthritis Long-term; OA: osteoarthritis; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; RA: rheumatoid arthritis; RCT: randomized controlled trial; TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial; VIGOR: Vioxx Gastrointestinal Outcomes Research; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
			Long-term [MEDAL] program). [Note: This study was included in the original CER] One expert noted that the conclusion needs to better account for celecoxib's dose and depends on whether aspirin is added. [Note: Those issues are addressed below]	
Celecoxib is associated with an increased risk of myocardial infarction. Most of the CV events with celecoxib were reported in two large polyp-prevention trials.	In a large cohort study, the relative risk of cardiovascular events in patients started on celecoxib compared to non users of NSAIDs was not significantly increased; however in subgroup analysis, several patient characteristics increased the risk for some CV events (Solomon DH, 2008) In a pooled analysis of 6 placebo-controlled RCTs, a differential risk of cardiovascular events was seen based on dosing regimen with the lowest hazard ratio in the 400 mg/day dose group (HR 1.1 with 95% CI 0.6 to 2.0) and the highest in the 400 mg twice a day dose group (HR 3.1) **(**Solomon SD, 2008).	No new information.	One expert thinks there may have been some data published from some Alzheimer's prevention trials that were consistent with the original conclusion. One expert noted increased risk compared with placebo, but assumed SD Solomon's 2008 paper suggests that low dose in low-risk individuals is ok.	Conclusion is still valid and this portion of the CER does not need updating.
Etoricoxib is associated with fewer GI adverse events (perforations, symptomatic ulcers, and bleeds) than nonselective NSAIDs. Reviews of RCTs suggest that etoricoxib has a similar CV safety profile compared to other NSAIDs, with the possible exception of naproxen. Definitive conclusions are not possible	Studies of etoricoxib vs. diclofenac in RA and OA reinforced the lower incidence of GI adverse events, but found no difference in serious complicated GI events. CV event incidence was similar, but studies found the 90 mg dose of etoricoxib to be associated with a significantly increased incidence of hypertension-related adverse events (Baraf, 2007; Laine, 2007; Cannon, 2006).	Etoricoxib: No new FDA information.	Three experts agreed the conclusion is still valid. One expert believes etoricoxib increases uncomplicated GI adverse events and appears to raise CV events.	Conclusion is possibly out of date and this portion of the CER may need updating based on diversity of expert opinion.

Legend: ADAPT: Alzheimer's Disease Anti-inflammatory Prevention Trial; CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; CV: cardiovascular; CVD: cardiovascular disease; DMSO: dimethyl sulfoxide; GI: gastrointestinal; H2: histamine-2, HR: hazard ratio; MEDAL: Multinational Etoricoxib and Diclofenac Arthritis Long-term; OA: osteoarthritis; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; RA: rheumatoid arthritis; RCT: randomized controlled trial; TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial; VIGOR: Vioxx Gastrointestinal Outcomes Research; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
because of small numbers of CV events.				
Results from one large trial found fewer adverse GI events with lumiracoxib than with naproxen and ibuprofen. Too few events have been reported in RCTs to accurately assess CV risk associated with lumiracoxib.	No new evidence.	Lumiracoxib refused approval by FDA 10/2007; Lumiracoxib was withdrawn from the Canadian market in 10/2007. Australia and New Zealand have also withdrawn lumiracoxib. Ibuprofen 3/2/2006 Revised label to add a boxed warning to address possible CV risks as well as known GI risks.	One expert agreed the conclusion is still valid; however, s/he suggests there may be new evidence about liver risk.	Conclusion is out of date and this portion of the CER needs updating since lumiracoxib is not FDA approved and has been withdrawn from the market of several countries.
Meloxicam - There were no significant differences in risks of serious GI events or CV risk.	No new evidence.	No new information.	Three experts agreed the conclusion is still valid. One expert suggests new McGettigan and Singh study (ACR abstract). [Note: The McGettigan study was included in the original CER; The Singh abstract was not found in our literature search]	Conclusion is still valid and this portion of the CER does not need updating.
Nabumetone or etodolac - There was insufficient evidence to make reliable judgments about relative GI safety and no evidence on CV safety.	No new evidence.	Etodolac 1/18/2006 - Revised label to add a boxed warning to address possible CV risks as well as known GI risks.	Experts agreed the conclusion is still valid	Conclusion is out of date and this portion of the CER needs updating to reflect change in labeling due to addition of FDA boxed warning label.
No clear difference in GI safety was found among nonselective NSAIDs at commonly used doses.	No new evidence.	No new information.	Experts agreed the conclusion is still valid	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
The CV safety of naproxen is moderately superior to that of any COX-2 selective NSAID.	No new evidence.	Naproxen Active FDA Safety Alert 12/2004- added the risk of cardiovascular and cerebrovascular events.	Three experts agreed the conclusion is still valid One expert states CV safety of naproxen depends on how it is taken; data from ADAPT (Alzheimer's Disease Anti-inflammatory Prevention Trial) show diclofenac is worse.	Conclusion is still valid and this portion of the CER does not need updating.
The CV safety of nonselective NSAIDs other than naproxen (data primarily on ibuprofen and diclofenac) was similar to that of COX-2 selective NSAIDs.	No new evidence.	No new information	Three experts agreed the conclusion is still valid. One expert stated that CV safety of nonselective NSAIDs should separate the coxibs-lumping them is problematic.	Conclusion is still valid and this portion of the CER does not need updating.
Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds compared to placebo or nonuse when given in long-term prophylactic doses. There is insufficient evidence to assess the balance of GI and CV safety of higher dose aspirin as used for pain relief compared with nonaspirin NSAIDs.	No new evidence.	Aspirin: No new information.	Experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Almost no data are available on CV safety for salsalate.	No new evidence.	Salsalate: No new information. .	Expert agreed the conclusion is still valid; one has unpublished data.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: ADAPT: Alzheimer's Disease Anti-inflammatory Prevention Trial; CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; CV: cardiovascular; CVD: cardiovascular disease; DMSO: dimethyl sulfoxide; GI: gastrointestinal; H2: histamine-2, HR: hazard ratio; MEDAL: Multinational Etoricoxib and Diclofenac Arthritis Long-term; OA: osteoarthritis; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; RA: rheumatoid arthritis; RCT: randomized controlled trial; TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial; VIGOR: Vioxx Gastrointestinal Outcomes Research; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
All NSAIDs and COX-2 inhibitors can cause or aggravate hypertension, congestive heart failure (CHF), edema, and impaired renal function	One study found etoricoxib 90 mg/d more likely than diclofenac to cause hypertension related adverse events (Baraf, 2007).	No new information.	One expert has a paper in press at Archives Int Med showing differences in acute kidney injury across agents.	Conclusion is possibly out of date and this portion of the CER may need updating based on upcoming publication of new evidence.
Among currently marketed NSAIDs, only diclofenac was associated with a significantly higher rate of liver-related discontinuations compared with placebo.	No new evidence.	Diclofenac 1/25/2006 - Revised label to add a boxed warning to address possible cardiovascular risks as well as known gastrointestinal risks.	Three experts agreed the conclusion is still valid. One expert suggests Lumiracoxib also was associated with liver problems in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), (in press). [Note: Lumiracoxib was not approved for use in an FDA decision in 10/2007; it was withdrawn from the Australian and Canadian market due to concerns about liver problems]	Conclusion is still valid and this portion of the CER does not need updating.
Uncertainty remains regarding the comparative tolerability of salsalate and nonselective NSAIDs.	No new evidence.	Salsalate: No new information.	Experts agreed the conclusion is still valid	Conclusion is still valid and this portion of the CER does not need updating.
Acetaminophen is modestly inferior to NSAIDs for pain and function. Compared with NSAIDs, acetaminophen had fewer GI side effects and serious GI complications. Acetaminophen may be	No new evidence.	Acetaminophen: No new information.	Experts agreed the conclusion is still valid	Conclusion is still valid and this portion of the CER does not need updating.

Legend: ADAPT: Alzheimer's Disease Anti-inflammatory Prevention Trial; CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; CV: cardiovascular; CVD: cardiovascular disease; DMSO: dimethyl sulfoxide; GI: gastrointestinal; H2: histamine-2, HR: hazard ratio; MEDAL: Multinational Etoricoxib and Diclofenac Arthritis Long-term; OA: osteoarthritis; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; RA: rheumatoid arthritis; RCT: randomized controlled trial; TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial; VIGOR: Vioxx Gastrointestinal Outcomes Research; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
associated with modest increases in blood pressure and renal dysfunction.				
One good-quality, prospective observational study found an increased risk of CV events with heavy use of acetaminophen that was similar to the risk associated with heavy use of NSAIDs.	No new evidence.	Acetaminophen: No new information.	One expert agreed the conclusion is still valid and noted the existing data were either from Nurses Health Study or Physicians Health Study so only a large, well-designed observational study could possibly call those results into question.	Conclusion is still valid and this portion of the CER does not need updating.
Glucosamine and chondroitin were generally well tolerated and no serious adverse events were reported in clinical trials.	In a large 6-month RCT of knee OA, glucosamine and chondroitin sulfate did not decrease pain significantly; however, in a secondary analysis, there was a suggestion of improvement in those with moderate to severe pain. (Clegg, 2006). Additionally, one RCT comparing glucosamine, acetaminophen, and placebo in knee OA found glucosamine more effective in reducing pain than placebo while acetaminophen did not demonstrate a significant improvement in functional status. (Herrero-Beaumont, 2007).	No new information.	Experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
We found no studies evaluating the GI or CV safety of alternative dosing strategies (such as alternate day dosing, once daily versus twice daily dosing, or periodic drug holidays). The risk of GI bleeding increases with higher doses of nonselective NSAIDs.	In a pooled analysis of 6 placebo controlled RCT, a differential risk of cardiovascular events were seen based on dosing regimen with lowest hazard ratio in the 400 mg a day dose (HR 1.1 with 95% CI 0.6 to 2.0), intermediate with 200 mg po BID and highest in 400 mg po BID dose (HR 3.1) (Solomon, 2008).	No new information.	Experts agreed the conclusion is still valid.	Conclusion is possibly out of date and this portion of the CER may need updating based on new data.
Higher doses of celecoxib were associated with increased CV risk, but could not determine the effects of dose on CV risk associated	No new information.	No new information.	Experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: ADAPT: Alzheimer's Disease Anti-inflammatory Prevention Trial; CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; CV: cardiovascular; CVD: cardiovascular disease; DMSO: dimethyl sulfoxide; GI: gastrointestinal; H2: histamine-2, HR: hazard ratio; MEDAL: Multinational Etoricoxib and Diclofenac Arthritis Long-term; OA: osteoarthritis; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; RA: rheumatoid arthritis; RCT: randomized controlled trial; TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial; VIGOR: Vioxx Gastrointestinal Outcomes Research; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
with rofecoxib due to low numbers of events at lower doses. Most trials of nonselective NSAIDs involved high doses.				
Key Question 2: Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups of patients? *** Demographic subgroups include age, sex, and race.** *** Coexisting diseases include hypertension, edema, ischemic heart disease, heart failure; peptic ulcer disease; history of previous bleeding due to NSAIDs.** *** Concomitant medication use includes anticoagulants.**				
GI and CV complication rates are higher among older patients and those with predisposing comorbid conditions, but there is no evidence that the relative safety of different NSAIDs varies according to baseline risk. Compared to nonuse of NSAIDs, one additional death per 1 year of use occurred for every 13 patients treated with rofecoxib, 14 with celecoxib, 45 with ibuprofen, and 24 with diclofenac in one large, population-based observational study of high-risk patients with acute myocardial infarction. There is no evidence that the comparative safety or efficacy of specific selective or nonselective NSAIDs varies depending on age, gender, or racial group, although data are sparse.	One study found predisposing patient characteristics to be age greater than or equal to 80 years, hypertension, prior MI, prior CVD, rheumatoid arthritis, chronic renal disease and COPD (Solomon DH, 2008).	No new information.	Three experts agreed the conclusion is still valid ; one cites Solomon DH, 2008. One expert was not clear on which studies support these recommendations. The same expert responded that the conclusion statement, "There is no evidence that the comparative safety or efficacy of specific selective or nonselective NSAIDs varies depending on age, gender, or racial group, although data are sparse" is odd.	Conclusion is still valid and this portion of the CER does not need updating.
Among patients who had a recent episode of upper GI bleeding, there is good evidence that rates of	This risk may be reduced by the use of a COX2 plus a PPI as the rate of recurrent GI bleed in a RCT of 441 patients was 0% compared with 8.9% for those on celecoxib alone with a median follow	No new information.	Experts agreed the conclusion is still valid. One cites Chan, 2007.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: ADAPT: Alzheimer's Disease Anti-inflammatory Prevention Trial; CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; CV: cardiovascular; CVD: cardiovascular disease; DMSO: dimethyl sulfoxide; GI: gastrointestinal; H2: histamine-2, HR: hazard ratio; MEDAL: Multinational Etoricoxib and Diclofenac Arthritis Long-term; OA: osteoarthritis; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; RA: rheumatoid arthritis; RCT: randomized controlled trial; TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial; VIGOR: Vioxx Gastrointestinal Outcomes Research; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
recurrent ulcer bleeding are high (around 5 percent after 6 months) in patients prescribed celecoxib or a nonselective NSAID plus a PPI.	up of 13 months (Chan, 2007).			
Concomitant use of anticoagulants (e.g., warfarin) and any nonselective NSAID increases the risk of GI bleeding three- to sixfold compared to anticoagulants alone. Reliable conclusions about the safety of selective NSAIDs used with anticoagulants are not possible due to flaws in existing observational studies, although there are case reports of serious bleeding events, primarily in the elderly.	No new evidence.	No new information.	Experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
There was no difference in rates of ulcer complications between celecoxib and nonselective NSAIDs in the subgroup of patients who took aspirin. Concomitant low-dose aspirin use increased the rate of endoscopic ulcers in both patients on celecoxib and those on nonselective NSAIDs. Rofecoxib plus low-dose aspirin or ibuprofen alone were associated with similar risks of endoscopic ulcers which were significantly	Etoricoxib was less likely to cause than uncomplicated GI complications than diclofenac in patient on low dose aspirin (Laine, 2007).	No new information.	One expert noted this seems to be an area of substantial interest as celecoxib is trying to keep market share, and there are at least some studies looking at endoscopic outcomes. One expert states “need to re-review aspirin in MEDAL. vs. aspirin in TARGET.” [Note: The MEDAL study was included in the original CER; In the original CER the	Conclusion is possibly out of date and this portion of the CER may need updating based on expert opinion.

Legend: ADAPT: Alzheimer’s Disease Anti-inflammatory Prevention Trial; CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease; COX-2: cyclooxygenase-2; CV: cardiovascular; CVD: cardiovascular disease; DMSO: dimethyl sulfoxide; GI: gastrointestinal; H2: histamine-2, HR: hazard ratio; MEDAL: Multinational Etoricoxib and Diclofenac Arthritis Long-term; OA: osteoarthritis; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; RA: rheumatoid arthritis; RCT: randomized controlled trial; TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial; VIGOR: Vioxx Gastrointestinal Outcomes Research; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
higher than those for placebo (6 percent) or aspirin alone. Compared to nonuse of aspirin, concomitant aspirin use did not ameliorate the increased risk of vascular events associated with COX-2 selective NSAIDs.			TARGET study was included however the TARGET study indicated by the expert was not found in the original CER.	
Key Question 3: What are the comparative effects of coprescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?				
Consistent evidence found coprescribing of PPIs to be associated with the lowest rates of endoscopically detected duodenal ulcers relative to gastroprotective agents. Coprescribing of misoprostol is associated with similar rates of endoscopically detected gastric ulcers as coprescribing of PPIs. While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of perforation, obstruction, or bleeding, there is a high rate of withdrawals due to adverse GI symptoms.	Now new evidence.	No new information.	Three experts agreed the conclusion is still valid One expert stated that the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study and Chan studies should be reviewed.	Conclusion is still valid and this portion of the CER does not need updating.
The risk of endoscopic duodenal ulcers for standard-dose H2 blockers was lower than placebo, similar to misoprostol, and higher than omeprazole. Standard dosages of H2 blockers were associated with no reduction of risk for gastric ulcers relative to placebo.	No new evidence.	No new information.	Experts agree the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
Double (full) dose H2 blockers were associated with a lower risk of endoscopic gastric and duodenal ulcers relative to placebo. It is unknown how full-dose H2 blockers compare to other antiulcer medications.				
Key Question 4: What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations? Topical preparations include: capsaicin, diclofenac, ibuprofen, ketoprofen, and salicylate.				
Topical NSAIDs were similar to oral NSAIDs for pain relief in trials primarily of patients with osteoarthritis of the knee, with topical diclofenac (often with dimethyl sulphoxide [DMSO], a drug not approved for use in humans in the United States). Topical ibuprofen was superior to placebo in several trials. Consistent evidence from good-quality trials, systematic reviews, and observational studies found topical NSAIDs to be associated with increased local adverse events compared with oral NSAIDs. Total adverse events and withdrawal due to adverse events were similar. Data from one good-quality trial found topical NSAIDs superior to oral NSAIDs for GI events, including severe	This is further supported by a meta-analysis of topical diclofenac which suggested equivalent efficacy compared to oral diclofenac (Towheed, 2006). It was also shown superior to placebo in another study (Niethard, 2005). The updated search identified one RCT of topical ibuprofen that combined with a patient preference study found that advice to use topical ibuprofen versus oral ibuprofen had equivalent effects on pain as measured by the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scale. In this study, oral ibuprofen had more minor adverse events such as changes in serum creatinine (Underwood, 2008).	No new topical NSAIDs approved.	Experts agreed the conclusion is still valid. One expert noted: “a UK study of topical ibuprofen still had not been published last time I checked but was due any time; there may also be new studies of topical diclofenac. I thought I heard of a topical NSAID approved in the US but I am not positive about that”. [Note: The Underwood study summarized is the UK topical NSAID study referred to]	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	Summary of SCEPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 1 TEP Member, 2 Other Experts	Conclusion from SCEPC
events, and changes in hemoglobin. Topical salicylates were no better than placebo in higher quality placebo-controlled trials. Compared to placebo, one additional patient achieved pain relief for every eight that used topical capsaicin in a good-quality meta-analysis, but capsaicin was associated with increased local adverse events and withdrawals due to adverse events.				

Are there new data that could inform the key questions that might not be addressed in the conclusions?

A systematic review and meta-analysis of tramadol or tramadol/acetaminophen use in osteoarthritis found modest benefits with the medication, with 1 in 8 discontinuing therapy because of side effects (Cepeda, 2007).
A recent systematic review of randomized controlled trials did not find any evidence of efficacy for vitamin A, C, E or selenium for the treatment of any type of arthritis including osteoarthritis (Canter, 2007).

One expert noted: I think one big question is whether the combination of naproxen + PPI is safer (from CV and GI risk standpoint) compared to celecoxib or a different nonselective, but I don't know if anyone has gone so far as to conduct a head-to-head trial (though several experts are already recommending the naproxen + PPI combo). The topical NSAID area is likely to be one of the hotter ones. There isn't exactly new evidence, but there has been varying interpretation of the NIH glucosamine trial. It hinges on whether a post-hoc subgroup analysis provides any reliable information. We thought it provided some information; others have completely dismissed it.

Another comments: There is no mention of recent negative trials for glucosamine and chondroitin sulfate. Assume that other than topicals - non oral meds not included (ie no mention of acupuncture/hyaluronic acid…..)

Another expert notes: I don't see any statement about COX2 effectiveness compared with other NSAIDs- was this not a conclusion of the panel? The first conclusion just deals with moderately selective Cox2 inhibitors. There is large RCT that suggests etoricoxib and celicoxib are equal in efficacy and side effect profile (Bingham, 2007).

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CER 6. Efficacy and Comparative Effectiveness of Off-label Uses of Atypical Antipsychotics

For this CER, which was produced by the SCEPC, a full literature search was conducted for the years 2006-2008. The search identified 1,502 titles, of which 261 were obtained in full text for further review. The remaining titles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance. Of the 261 selected for further review, 38 were abstracted into an evidence table (Attachment II). The remaining articles were rejected because they had already been included in the earlier report or did not include a comparison of interest.

We consulted the original content expert and primary reviewer, 4 members of the TEP, and one additional expert for their assessments. Of these 6 individuals, four responded.

Table 2.5 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.5 CER 6. Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics: Are the conclusions still valid?

Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
Key Question 1: What are the leading off-label uses of atypical antipsychotics in the literature?				
The most common off-label uses of atypical antipsychotics found in the literature were treatment of depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, Tourette's syndrome, autism, and agitation in dementia. In October 2006, risperidone was approved for use in autism.	There are several new RCTs of atypicals for anorexia nervousa and bulimia (Mondraty, 2005; Bissada, 2008; Spettique, 2008). Court (2008) published a systematic review in Eating Disorders which included four RCTs.	No new information.	All experts agreed still valid.	Conclusion is still valid, but AHRQ may wish to expand scope to anorexia depending on sponsor and public interest.
Key Question 2: What does the evidence show regarding the effectiveness of atypical antipsychotics for off-label indications, such as depression? How do atypical antipsychotic medications compare with other drugs for treating off-label indications?				
There is a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes in dementia patients. The clinical benefits must be balanced against side effects and potential harms.	a) CATIE-AD found that olanzapine and risperidone improved NPI total score and BPRS (Brief Psychiatric Rating Scale) hostile suspiciousness factor. There were no significant differences between antipsychotics and placebo on cognition, function, care needs, or quality of life, except for worsened functioning with olanzapine (Sultzer, 2008). b) New RCT shows quetiapine 200 mg	In August 2008, FDA ordered a new boxed warning for all typical antipsychotics: Increased mortality in elderly patients with dementia-related psychosis.	Two experts agreed still valid. One expert cited additional trials that support efficacy in dementia patients: Streim, 2008 (aripiprazole); Mintzer, 2007 (aripiprazole); Sultzer, 2008 (olanzapine). Two experts did not comment.	Conclusion is possibly out of date and this portion of the CER may need updating. Although no experts felt the conclusion was out of date, we found new studies that reported olanzapine and quetiapine effective and two new meta-analyses.

Legend: AE: Adverse Event; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impressions Scale; EPS: Extrapyramidal Side Effects; HAM-D: Hamilton Depression Score; MADRAS: Montgomery Asberg Depresson Rating Scale; NPI: Neuropsychiatric Inventory; PANNS: Positive and Negative Syndrom Scale; RCT: Randomized Controlled Trial; VA: Veterans Administration

Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
	associated with significant improvements in PANNS-EC, CGI-C compared to placebo (Zhong, 2007). c) New meta-analysis shows effect sizes of atypical antipsychotics for behavioral problems in dementia are medium, and there are no statistically or clinically significant differences between them and placebo (Yury, 2007). d) Head to head RCT shows quetiapine and risperidone equally effective and well tolerated (Rainer, 2007). e) New systematic review on dementia symptoms shows olanzapine and risperidone effective compared with placebo. Short-term AEs similar to placebo. Risperidone had advantage over haldol in EPS. Evidence for other atypicals too limited to assess (Carson, 2006). f) New RCT found aripiprazole 10 mg/day was efficacious and safe for psychosis associated with AD, significantly improving psychotic symptoms, agitation, and clinical global impression (Mintzer, 2007). g) In another new RCT in nursing home residents with AD and psychosis, aripiprazole did not confer specific benefits for the treatment of psychotic symptoms; but psychological and behavioral symptoms, including agitation, anxiety, and depression, were improved with aripiprazole, with a low risk of AEs (Stein, 2008). h) A new RCT in elderly patients with organic brain disease (N= 15) showed no difference between risperidone and placebo, as measured by PANSS items (Naber, 2007).			

Legend: AE: Adverse Event; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impressions Scale; EPS: Extrapyramidal Side Effects; HAM-D: Hamilton Depression Score; MADRAS: Montgomery Asberg Depresson Rating Scale; NPI: Neuropsychiatric Inventory; PANNS: Positive and Negative Syndrom Scale; RCT: Randomized Controlled Trial; VA: Veterans Administration

Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
For SRI-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone at 8 weeks.	a) Aripiprazole approved by FDA for adjunctive tx in unipolar, non-psychotic depression after two new RCTs (Marcus, 2008; Berman, 2007). b) New RCT of risperidone augmentation showed higher odds of remitting (OR = 3.33) than placebo at 4 weeks (Keitner, 2008). [Original CER included only trials of 8 weeks or more.] c) New RCT shows olanzapine/ fluoxetine combination effective at 8 weeks (Thase, 2007). d) Meta-analysis of 10 clinical trials finds patients on adjunct atypicals significantly more likely to experience remission or clinical response than those on adjunct placebo. No studies on aripiprazole or ziprasidone were included. The new meta-analysis used "remission rate" (% of patients improving a certain amount on HAM-D or MADRAS) as the outcome, while original CER used the continuous score. Also, they included one 4-week trial and one 6-week trial; the original CER excluded these as too short in duration. e) RCT of risperidone augmentation show a significant reduction in depression symptoms, substantial increase in remission and response, compared to augmentation with placebo at 6 weeks (Gharabawi, 2007).	In November 2007, aripiprazole was FDA approved as adjunctive treatment for major depressive disorder.	One expert did not know. One expert noted: a study in bipolar depression showing efficacy of olanzapine + fluoxetine over fluoxetine alone (Thase, 2007); 2 RCTs showing quetiapine monotherapy is superior to placebo in bipolar depression monotherapy (cited in Papakostas); and now FDA has approved apriprazole for acute bipolar depression. Two experts did not comment.	Conclusion is probably out of date and this portion of the CER may need updating based on the new FDA approval, plus new literature and expert opinion.
In patients with major depressive disorder with psychotic features, olanzapine and olanzapine plus fluoxetine were compared with placebo for 8 weeks in 2 trials. There was a benefit for	No contradictory evidence.	No new information.	Three experts agreed still valid; one of these experts suggested additional trials showing efficacy of olanzapine. One did not comment.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AE: Adverse Event; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impressions Scale; EPS: Extrapyramidal Side Effects; HAM-D: Hamilton Depression Score; MADRAS: Montgomery Asberg Depresson Rating Scale; NPI: Neuropsychiatric Inventory; PANNS: Positive and Negative Syndrom Scale; RCT: Randomized Controlled Trial; VA: Veterans Administration

Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
olanzapine alone.				
For bipolar depression, olanzapine and quetiapine were superior to placebo in one study for each drug, but data are conflicting in two other studies that compared atypical antipsychotics to conventional treatment.	Two new RCTs found aripriprazole not significantly more effective in bipolar depression than placebo at 8 weeks (Thase, 2008).	In October 2006 quetiapine was FDA approved for major depressive episodes associated with bipolar disorder.	One expert noted FDA approval of quetiapine for bipolar depression. Another expert mentioned a study in bipolar depression showing efficacy of olanzapine + fluoxetine over fluoxetine alone and two RCTs showing quetiapine monotherapy is more effective than placebo in bipolar depression. (These were included in the original CER).	Conclusion is still valid and this portion of the CER does not need updating. New RCTs did not show a benefit for aripiparazole, and the studies suggested by the expert were already included in the original CER.
We identified 12 trials of risperidone, olanzapine, and quetiapine used as augmentation therapy in patients w/ OCD who were resistant to standard treatment (nine trials were sufficiently similar clinically to pool). Atypical antipsychotics have a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy for OCD patients who fail to adequately respond to SRI therapy. There were too few studies of olanzapine augmentation to permit separate pooling for this drug.	New head-to-head RCT showed both risperidone and olanzapine more effective than placebo, but no significant differences between the two drugs (Maina, 2008). A new RCT (Savas, 2008) showed that quetiapine is better than ziprasidone for augmentation therapy in OCD (Savas, 2008).	No new information.	Two experts agreed still valid. One of them noted the following new studies: Drug Neuropsych (15, 585-6) showed efficacy of SSRIs plus aripiprazole; a new study in Clinical Drug Investigation showed that quetiapine is better than ziprasidone for augmentation therapy in OCD (Savas, 2008); a new study in European Journal of Psychiatry showed that olazapine is equal to risperidone for augmentation therapy in OCD (Maina, 2008). Two experts did not comment.	Conclusion is possibly out of date and this portion of the CER may need updating due to publication of aripiprazole trial. The results from the two new head to head trials could be added to the pooling performed in the original CER.
We found four trials of risperidone and two trials of olanzapine of at least 6 weeks duration in	A new meta-analysis (Pae, 2008) including data from seven RCTs showed that atypicals may have a beneficial effect in the treatment of	No new information.	One expert noted the following: Int Clin Psychopharm Meta analysis of 7 RCTs (Pae, 2008) showed atypicals more effective than placebo, but only due to increase in intrusive symptoms.	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
patients with PTSD. There were three trials enrolling men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. There were three trials of olanzapine or risperidone as monotherapy for women with PTSD; the evidence was inconclusive regarding efficacy.	PTSD, as indicated by the changes from baseline in Clinician Administered PTSD Scale total scores. The symptom of 'intrusion' was mainly responsible for this significance. The original CER qualitatively summarized six of the trials separately for women and men. The Pae meta-analysis pools the male and female studies together.		All experts agreed still valid.	
We identified five trials of atypical antipsychotic medications as treatment for borderline personality disorder & one trial as treatment for schizotypal personality disorder. Three RCTs each w/ no more than 60 subjects provide evidence that olanzapine is more effective than placebo & may be more effective than fluoxetine in treating borderline personality disorder. The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small.	An RCT of ziprasidone failed to show benefit in borderline personality disorder (Pascual, 2008).	No new information.	Our experts do not know this area well.	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in one small trial.	No new evidence.	No new information.	No expert comment on this issue.	Conclusion is still valid and this portion of the CER does not need updating.
Aripiprazole was more effective than placebo for the treatment of borderline personality in one small trial.	18-month follow up of the original trial shows significant improvement at 18 months (Nickel, 2007).	No new information.	No expert comment on this issue.	Conclusion is still valid and this portion of the CER does not need updating.
We found four trials of risperidone and one of ziprasidone for treatment of Tourette's syndrome. Risperidone was more effective than placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three remaining trials. The one available study of ziprasidone showed variable effectiveness compared to placebo.	No new evidence.	No new information.	No expert comment on this issue.	Conclusion is still valid and this portion of the CER does not need updating.
Two trials support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism.	Another trial showed that (non-autistic) children who respond to initial treatment with risperidone would benefit from continuous long-term treatment (Reyes, 2006).	No new information.	No expert comment on this issue.	Conclusion is still valid and this portion of the CER does not need updating.
Key Question 3: What subset of the population would potentially benefit from off-label uses?				
Other than specific populations listed in the finding for Key Question 2, there was insufficient information to answer this question. Therefore, it is included as a topic for future research.	No new evidence.	No new information.	Experts do not know of new information.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AE: Adverse Event; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impressions Scale; EPS: Extrapyramidal Side Effects; HAM-D: Hamilton Depression Score; MADRAS: Montgomery Asberg Depresson Rating Scale; NPI: Neuropsychiatric Inventory; PANNS: Positive and Negative Syndrom Scale; RCT: Randomized Controlled Trial; VA: Veterans Administration

Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
Key Question 4: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics?				
Olanzapine patients are more likely to report weight gain than those taking placebo, other atypical antipsychotics, or conventional antipsychotics.	No new evidence.	No new information.	Three experts agreed still valid. The fourth feels there is weight gain with other atypicals and cites Schneider, 2006 (Catie-AD). However, that study was included in our original AE analyses and pooled results suggested olanzapine patients gain more weight.	Conclusion is still valid and this portion of the CER does not need updating.
In a recently published meta-analysis death occurred in 3.5 percent of dementia patients randomized to receive atypical antipsychotics vs. 2.3 percent of patients randomized to receive placebo. The difference in risk for death was small but statistically significant. Sensitivity analyses did not show evidence for differential risks for individual atypical antipsychotics. In another recently published meta-analysis of six trials of olanzapine in dementia patients, differences in mortality between olanzapine and risperidone were not statistically significant, nor were differences between olanzapine and conventional antipsychotics.	a) A new meta-analysis of six RCTs of risperidone regarding mortality in elderly dementia patients showed 4.0% mortality with risperidone versus 3.1% with placebo (relative risk 1.21, 95% CI 0.71-2.06) during tx or within 30 days or tx discontinuation (Haupt, 2006). b) Another study assessed short-term mortality in a population-based cohort of elderly people in British Columbia who were prescribed conventional or atypical antipsychotic medications. Within the first 180 days of use, 1822 patients (14.1%) in the conventional drug group died, compared with 2337 (9.6%) in the atypical drug group (mortality ratio 1.47, 95% CI 1.39-1.56). Multivariable adjustment resulted in a 180-day mortality ratio of 1.32 (1.23-1.42) (Schneeweiss, 2007). c) Death rates for incident (N=16,634) and prevalent (N=9,831) users of various antipsychotics, carbamazepine, and sodium valproate age 65+ were compared. Haloperidol was consistently associated with increased risk of death compared with olanzapine (RR for incident users 2.26, 95% CI 2.08 – 2.47). Risperidone (RR 1.23, 95% CI: 1.07 – 1.40) was also associated with increased risk of death compared to olanzapine in incident users (Hollis, 2007).	In August 2008, FDA ordered a new boxed warning for all typical antipsychotics: Increased mortality in elderly patients with dementia-related psychosis.	Three experts agreed still valid or did not know. The fourth noted that recent studies of atypicals vs conventionals show a higher risk possible with conventionals.	While the conclusion is still valid, the strength of evidence supporting the conclusion has increased and therefore this may possibly need updating.

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Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
	d) A new cohort study of medical records from the Tennessee Medicaid program found that current users of atypical antipsychotics had a rate of sudden cardiac death twice that of those who didn't use such drugs and similar to those who took haloperidol or thiordazine. (Ray, 2009).			
In our pooled analysis of three RCTs of elderly patients with dementia, risperidone was associated with increased odds of cerebrovascular accident compared to placebo. This risk was equivalent to 1 additional stroke for every 31 patients treated in this patient population (i.e., number needed to harm of 31). The manufacturers of risperidone pooled four RCTs and found that cerebrovascular adverse events were twice as common in dementia patients treated with risperidone as in the placebo patients. In a separate industry-sponsored analysis of five RCTs of olanzapine in elderly dementia patients, the incidence of cerebrovascular adverse events was three times higher in olanzapine patients than in placebo patients.	a) Retrospective cohort study with N >40,000 used a logistic regression model to show that relative to those who received no antipsychotics, community dwelling elderly newly dispensed an atypical were 3.2 times more likely, and those who received a conventional antipsychotic were 3.8 more likely, to develop any serious event during the first 30 days (Rochon, 2008; Gill, 2007). b) Retrospective cohort study of VA data on patients age 65+ (N = 10,615) who began outpatient treatment with psyc meds following a dementia diagnosis showed that those taking antipsychotics had significantly higher mortality rates (22.6% to 29.1%) than patients taking non-antipsychotic meds (14.6%). Adjusted mortality risks for atypicals were similar to those for conventional antipsychotics. The proportions of patients taking antipsychotics who died from cerbrovascular, cardiovascular, or infectious causes were not higher than rates for those taking other psyc meds (Kales, 2007).	No new information.	Two experts agreed still valid. Two others did not comment.	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
We pooled three aripiprazole trials and four risperidone trials that reported extrapyramidal side effects (EPS) in elderly dementia patients. Both drugs were associated with an increase in EPS.	No new evidence.	No new information.	One expert agreed still valid. One other noted that EPS was reported with olanzapine (Schneider, 2006). That study was already included in our CER. Two others did not comment.	Conclusion is still valid and this portion of the CER does not need updating.
Ziprasidone was associated with an increase in EPS when compared to placebo in a pooled analysis of adults with depression, PTSD, or personality disorders.	No new evidence.	No new information.	Three experts agreed still valid. No comment from another.	Conclusion is still valid and this portion of the CER does not need updating.
Risperidone was associated with increased weight gain compared to placebo in our pooled analyses of three trials in children/adolescents. Odds were also higher for gastrointestinal problems, increased salivation, fatigue, EPS, and sedation among these young risperidone patients.	No new evidence.	No new information.	Two experts agreed still valid. Two others did not comment.	Conclusion is still valid and this portion of the CER does not need updating.
Compared to placebo, all atypicals were associated with sedation in multiple pooled analyses for all psychiatric conditions studied.	No new evidence.	No new information.	Two experts agreed still valid. Two others did not comment.	Conclusion is still valid and this portion of the CER does not need updating.
Key Question 5: What are the appropriate dose and time limit for off-label indications?				

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Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
There was insufficient information to answer this question. Therefore, it is included as a topic for future research	No new evidence.	No new information.	One expert agreed still valid. Three others did not comment.	Conclusion is still valid and this portion of CER does not need updating.
Are there new data that could inform the key questions that might not be addressed in the conclusions?	**Glucose / Diabetes:** Sacher (2008) reports a small RCT where olanzapine but not ziprasidone lead to a decrease in whole body insulin sensitivity in response to a hyperinsulinemic euglycemic challenge in healthy adults. Bayesian data-mining of FDA adverse events reporting system (DuMouchel, 2008) showed consistent and substantial differences between atypicals in reporting ratios re glycemic effects, especially life-threatening ones. Low association: ziprasidone, aripriprazole, and risperidone; medium association: quetiapine, and strong association: olanzapine. A VA retrospective cohort analysis (Duncan, 2007) showed that in patients without a random plasma glucose of >=160 mg/dl before medication exposure (n=1394), treatment with olanzapine, risperidone, or a typical antipsychotic was associated with an incidence of new diabetes-level hyperglycemia of 78.7 cases per 1,000 individuals exposed per year. Olanzapine was associated with a greater rate of developing at least one fasting glucose measurement of >=200 than risperidone (OR = 2.14). In a systematic review of 17 pharmacoepidemiologic studies (Ramaswamy, 2006) olanzapine, but			Any new Comparative Effectiveness Review on atypical antipsychotics should assess glucose issues in the harms section, due to the number of recently published cohort analyses revealing glycemic effects.

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Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
	not risperidone, was associated with significantly increased risk of new-onset diabetes. Of nine studies comparing relative risk of diabetes with olanzapine and risperidone, six demonstrated significantly greater risk with olanzapine. A retrospective study of schizophrenia patients at Mass General (Henderson, 2007) showed that the incidence of diabetes presenting as diabetic ketoacidosis was higher than in the general hospital population and differed across drugs (olanzapine, 0.8%, risperidone, 0.2%, no incidence with ziprasidone or quetiapine). A retrospective analysis of diabetes risk in elderly patients with dementia in seven olanzapine clinical trails (Micca, 2006) showed that risk of diabetes was not significantly associated with antipsyc treatment. **Pituitary tumors**: Sarfman (2006) analyzed the FDA AERS and found that risperidone had the highest adjusted reporting ratios for hyperprolactinemia, galactorrhea, and pituitary tumor among the antipsychotics, and one of the highest scores for all drugs in the database. **Cholesterol:** Using MediCal data, Olfson (2006) estimated the relative risk of developing hyperlipidemia after treatment with antipsychotics compared to no antipsychotic treatment. 12,133 incident cases of hyperlipidemia were matched to 72,140 control subjects. Compared with no antipsyc meds, tx			

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Conclusions From CER Executive Summary	SC EPC Literature Search	FDA/Health Canada	Expert Opinion EPC Investigator, 3 TEP Members	Conclusion from SC EPC
	with risperidone (OR 1.56, 95% CI 1.43 – 1.64), quetiapine (OR 1.52, 95% CI 1.40 – 1.65), olanzapine (OR 1.56, 95%CI 1.47 – 1.67) and ziprasidone (OR 1.40, CI 1.19 – 1.65) were associated with increased risk of hyperlipidemia, as were conventional antipsychotics (OR 1.26, 95% CI 1.14 – 1.39). **Muscle toxicity**: Waring (2006) reviewed case notes from 64 consecutive patients admitted after olanzapine overdose. Serum creatine kinase was > 5 times the upper limit of normal in 17% of patients, and there was a dose-dependent relationship. No patients developed renal failure. **New drug:** Paliperidone-ER, first atypical with extended release formulation approved by FDA for schizophrenia (Lautneschlager, 2008; Yang, 2007; Owen, 2007; Howland, 2007).			

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CER 7. Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression

For this assessment, a full literature search was conducted for the years 2000-2008 using the PubMed and PsychInfo search platforms. The search identified 2,836 titles, of which 376 were obtained in full text for further review. The remaining titles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance. Of those selected for further review, 31 were abstracted into an evidence table (Attachment II). The remaining articles were rejected because they had already been included in the earlier report or did not include a comparison of interest.

We consulted the project lead and three additional subject matter experts for their assessments. Of these four individuals, three responded.

Table 2.6 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

As this report was being prepared, a new meta-analysis appeared that assessed the comparative effectiveness of 12 second-generation antidepressants (Cipriani et al., 2009). This analysis included data from 117 RCTs and used indirect comparison methods to conclude that escitalopram and sertraline are superior to the other drugs in both efficacy and acceptability. However, in a letter of response, the authors of the AHRQ CER point out that the indirect methods used portray a degree of precision in the results that is not present on direct comparisons. Our assessment of this new meta-analysis agrees with theirs: we do not judge this new analysis as indicating necessarily that CER #7 is out of date.

Table 2.6 CER 7. Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: Are the conclusions still valid?

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
Key Question 1: **1a. For adults with major depressive disorder (MDD), dysthymia, or subsyndromal depressive disorders, do commonly used medications for depression differ in efficacy or effectiveness in treating depressive symptoms?**				
The relative risk (RR) of response was significantly greater for escitalopram than for citalopram.	Two placebo-controlled trials and a head-to-head superiority study show escitalopram was numerically better than citalopram in reducing Montgomery-Åsberg Depression Rating Scale (MADRS). Meta-analysis of 5 clinical trials (3 placebo-controlled trials, 1 head-to-head superiority study, and 1 long-term non-inferiority study) showed statistically significant differences in favor of escitalopram in terms of reducing MADRS and increasing response (Clancon, 2007).	No new information.	Two experts agreed the conclusion is still valid. One expert noted that s/he does not know.	Conclusion is still valid and this portion of the CER does not need updating.
Fluoxetine vs. paroxetine: We did not find any statistically significant differences in effect sizes on the Hamilton Rating Scale for Depression (HAM-D) or response rates between fluoxetine and paroxetine. Paroxetine led to a higher rate of responders than fluoxetine.	An analysis of 12 randomized controlled trials (RCTs) of patients with depressive disorder, comparing paroxetine and fluoxetine, found inconsistent results across efficacy outcomes (Katzman, 2007).	No new information.	Three experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Fluoxetine vs. sertraline: Patients on sertraline had an additional, statistically nonsignificant treatment effect of a 0.75-point reduction (95-percent CI, –0.45-1.95) on the HAM-D scale compared with patients on fluoxetine. The relative risk of response was significantly greater for sertraline than for fluoxetine.	No new evidence.	No new information.	Three experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Fluoxetine vs. venlafaxine: Patients on venlafaxine had an additional, statistically nonsignificant treatment effect of a 1.31-point reduction on the HAM-D scale compared with patients on fluoxetine. The relative risk of response was significantly greater for venlafaxine than for fluoxetine.	A direct comparison of venlafaxine vs. fluoxetine among patients with major depressive disorder, followed up for 1 year, found no significant difference in time to rehospitalization (Lin, 2008). A meta-analysis of 34 RCTs, comparing	No new information.	One expert agreed the conclusion is still valid. One expert said the conclusion is no longer valid based on 2 new head-to-head trials of venlafaxine vs. fluoxetine: the	Conclusion is possibly out of date and this portion of the CER may need updating. Although we found only one new conflicting RCT, methods and inclusion criteria of

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
	venlafaxine to fluoxetine, found venlafaxine is statistically superior to fluoxetine (Nemeroff, 2008).		pooled estimate would most likely lose statistical significance. One expert said s/he does not know - but that this finding needs to be reviewed as there have been additional RCTs in venlafaxine (unsure of comparator).	new meta-analysis (Nemeroff, 2008) should be reviewed.
Findings from indirect comparisons yielded no statistically significant differences in response rates. The precision of some of these estimates was low, leading to inconclusive results with wide confidence intervals.	Indirect comparison of escitalopram vs. venlafaxine XR, using 10 placebo-controlled studies, and two direct comparison studies found escitalopram was non-inferior to venlafaxine XR (indirect comparison: mean -0.02, 95% CI -0.16 to infinity; direct comparison: mean: 0.23, 95% CI: -0.01 to infinity). The results were consistent after controlling age, gender repartition and severity at baseline (Eckert, 2006).	No new information.	Three experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Eighteen studies indicated no statistical differences in efficacy with respect to health-related quality of life (HRQOL).	No new evidence.	No new information.	Three experts agreed the conclusion is still valid. One expert said s/he did not know. "I am unaware of important new direct evidence but there are new data on adverse effects including GI bleeding, osteoporosis. New data on sexual dysfunction, new data on effect on pain which could be incorporated into models to estimate effects on health-related quality of life."	Conclusion is still valid and this portion of the CER does not need updating. New data on adverse events (suggested by one expert) is covered in key question 4.
Seven studies funded by the maker of mirtazapine reported that mirtazapine had a significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline.	No new evidence.	No new information.	Two experts agreed the conclusion is still valid. One expert said s/he does not know.	Conclusion is still valid and this portion of the CER does not need updating.
We identified no head-to-head trials for dysthymia. In placebo-controlled trials, significant differences in population characteristics make the evidence	No new evidence.	No new information.	One expert said the conclusion is still valid. One expert said s/he does not	Conclusion is still valid and this portion of the CER does not need updating.

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
insufficient to identify differences between treatments.			know- "Evidence is sparse. Need periodic lit searches to identify any new study." One expert said s/he does not know.	
The only head-to-head evidence for treating patients with subsyndromal depression came from a nonrandomized, open-label trial comparing citalopram with sertraline. This study did not detect any differences in efficacy. Findings from two placebo-controlled trials were insufficient to draw any conclusions about the comparative efficacy and effectiveness.	No new evidence.	No new information.	Two experts agreed the conclusion is still valid. One expert said s/he does not know.	Conclusion is still valid and this portion of the CER does not need updating.

Are there new data that could inform the key questions that might not be addressed in the conclusions?

A pooled analysis of 9 RCTs, comparing duloxetine with placebo for 8-9 weeks, found duloxetine produced significantly greater baseline-to-endpoint mean change than placebo in HAM-D17 total score, Maier and retardation subscales, and the Clinical Global Impressions-Severity of Illness scale in mild (HAM-D17: < or =19; n=682), moderate (HAM-D17: between 19 and 25, n=1099), or severe (HAM-D17: > or =25; n=446) groups. Effective sizes were largest in the most severely depressed patients (Shelton, 2007).

An analysis of 62 RCTs of patients with depressive disorder, comparing paroxetine vs. placebo or other antidepressants (amisulpride, amitriptyline, bupropion, clomipramine, doxepin, fluvoxamine, fluoxetine, imipramine, lofepramine, mianserin, mirtazapine, moclobemide, maprotiline, nefazodone, nortriptyline, sertraline, tianeptine, venlafaxine), found paroxetine yielded consistently and significantly better remission (rate difference [RD]: 10%, 95% CI 6 to 14), clinical response (RD: 17%, 95% CI 7 to 27), and symptom reduction (effect size: 0.2, 95% CI 0.1 to 0.3) than placebo. No consistent and significant difference was observed between paroxetine and other antidepressants (Katzman, 2007).

A prospective, 24-week open label study of 170 patients with major depressive disorder, comparing venlafaxine vs. paroxetine, found venlafaxine was comparable with paroxetine on response rate and remission, whereas paroxetine produced significantly higher remission rates at weeks 4, 8, 16, 20, 24 when remission was defined as HAM-D =5. Conclusion: Venlafaxine treatment was similar to paroxetine according to the typical efficacy measures. However, the authors feel that paroxetine might be superior to venlafaxine if the stricter remission criterion is used (Wu, 2007).

A meta-analysis of 34 RCTs, comparing venlafaxine and selective serotonin reuptake inhibitors SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram), found venlafaxine had higher intention to treat (ITT) remission rate than the SSRIs as a group (the overall difference is 5.9%, 95% CI 0.038 to 0.081; p<0.001). The number needed to treat (NNT) to benefit is 17 (95% CI 12-26). The difference vs. fluoxetine was significant (6.6%, 95% CI 0.030 to 0.095); smaller difference vs. paroxetine, sertraline, and citalopram were not significant. Venlafaxine therapy is statistically superior to SSRI as a class, but only to fluoxetine individually. The clinical significance of the modest advantage seems limited to the broad grouping of major depressive disorder (Nemeroff, 2008).

1b. If a patient has responded to one agent in the past, is that agent better than current alternatives at treating depressive symptoms?

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
We did not find any efficacy evidence regarding this question.	No new evidence.	No new information.	One expert said the conclusion is still valid. One expert responded "there is no new information to my knowledge."	Conclusion is still valid and this portion of the CER does not need updating.
Key Question 2: **2a. For adults with a depressive syndrome, do antidepressants differ in their efficacy or effectiveness for maintaining response or remission (i.e., preventing relapse or recurrence)?**				
Three head-to-head RCTs suggest that no substantial differences exist between fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine, regarding relapse. Twenty-one placebo-controlled trials support the general efficacy and effectiveness of most second-generation antidepressants for preventing relapse or recurrence. No evidence exists for duloxetine.	A review of 5 placebo-controlled acute-phase studies found most of the relapse rate during new-generation antidepressant continuation treatment may be due to relapse in patients who were not true drug responders (Zimmerman, 2007). A meta-analysis of 1,833 outpatients with major depressive disorder found the HAMD-sub-1-sub-7 remission rate was 40.3% for duloxetine, 38.3% for 2 SSRIs (paroxetine or fluoxetine), and 28.4% for placebo. Active treatments were superior to placebo. The difference between duloxetine and SSRIs was not statistically significant. Duloxetine therapy was significant more effective than therapy with the 2 SSRIs for patients with more severe depression, with remission rates of 35.9% vs. 28.6% (P=0.046) (Thase, 2007). An update of the original report, using four head-to-head trials and 23 placebo-controlled trials from 1980-2007, did not find statistically difference in relapse or recurrence prevention between duloxetine and paroxetine, fluoxetine and sertraline, and trazodone and venlafaxine. Compared with placebo, the class of second-generation antidepressants had a relatively large effect size that persists over time. The number of patients needed to treat is 5 (95% CI: 4-6)	No new information.	Two experts agreed the conclusion is still valid. One expert said s/he does not know.	Conclusion is possibly out of date and this portion of the CER may need updating to include evidence for duloxetine.

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
	(Hansen, 2008).			
2b. For adults receiving antidepressant treatment for a depressive syndrome that either has not responded (acute phase) or has relapsed (continuation phase) or recurred (maintenance phase), do alternative antidepressants differ in their efficacy or effectiveness?				
One head-to-head efficacy study and two effectiveness studies provide conflicting evidence on differences among second-generation antidepressants in treatment-resistant depression. The efficacy study suggests that venlafaxine is modestly more effective than paroxetine. A good-quality effectiveness study suggests that no substantial differences exist among bupropion SR, sertraline, and venlafaxine XR, but a fair-quality effectiveness study suggests that venlafaxine is modestly more effective than citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline.	A review of 5 randomized comparative studies (3 RCTs and 2 randomized open label studies) and 9 non-randomized non-comparative studies (2 switch studies, 5 open label switch studies, 1 post-hoc analysis, and 1 open case study) of >5,000 patients with treatment resistant depression supports the use of venlafaxine as a common switch agent following initial antidepressant failure (Dunner, 2007). An 8-week double-blind, placebo controlled trial of elderly patients with recurrent major depressive disorder comparing duloxetine vs. placebo, found duloxetine significantly improved cognition, depression and some pain measures. Hamilton depression scale response (37.3% vs. 18.6%) and remission (27.4% vs. 14.7%) rates at endpoint were significantly higher for duloxetine than placebo (Raskin, 2007).	No new information.	One expert agreed the conclusion is still valid. Two experts said they do not know.	Conclusion is still valid and this portion of the CER does not need updating.
Key Question 3: **3a. Do medications differ in their efficacy and effectiveness in treating the depressive episode?**				
Antidepressant medications do not differ substantially in antidepressive efficacy for patients with MDD and anxiety symptoms.	A prospective cohort study of 6,719 adult patients with depressive syndrome and associated with anxiety symptoms, treated with venlafaxine XR for 24 weeks, found venlafaxine XR was associated with significant decrease in the scores in the HAM-D depression rating and HAM-A anxiety rating (Benassar, 2006).	No new information.	Three experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
3b. Do medications differ in their efficacy and effectiveness in treating the accompanying symptoms?				
One fair-quality head-to-head trial reported no statistically significant difference between fluoxetine and sertraline for treating depression in patients with psychomotor retardation. The same study found that sertraline was more efficacious than fluoxetine for treating depression in patients with psychomotor agitation.	A meta-analysis of 44 placebo-controlled trials of patients with Parkinson's disease and depression found a modestly positive and significant effect size result with SSRIs on motor function (d=0.34, p<0.05) (Frisina, 2005).	No new information.	Two experts agreed the conclusion is still valid. One expert said s/he does not know.	Conclusion is possibly out of date and this portion of the CER may need to be updated to add points regarding treatment of Parkinson's symptoms and pain (see below).
Are there new data that could inform the key questions that might not be addressed in the conclusions? An analysis of 10 double blind head-to-head trials of patients with major depressive disorder found bupropion and the SSRIs appear to be equally effective in treating insomnia in depression (Papakostas, 2007). A pooled analysis of 9 RCTs, comparing duloxetine with placebo for 8-9 weeks, found mildly (HAM-D17: < or =19; n=682) and severely (HAM-D17: > or =25; n=446) depressed patients with duloxetine exhibited significant reduction in Visual Analog Scale overall pain severity. (Shelton, 2007) An 8-week double-blind, placebo controlled trial of elderly patients with recurrent major depressive disorder, comparing duloxetine vs. placebo, found duloxetine significantly improved Visual Analogue Scale scores for back pain and time in pain while awake vs. placebo (Raskin, 2007).				
Key Question 4: For adults with a depressive syndrome, do commonly used antidepressants differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to nausea, diarrhea, headache, tremor, daytime sedation, decreased libido, failure to achieve orgasm, nervousness, insomnia, and more severe events including suicide.				
Constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence were commonly and consistently reported adverse events. On average, 61 percent of patients in efficacy trials experienced at least one adverse event. Nausea and vomiting were found to be the most common reasons for discontinuation in efficacy studies. Overall, second-generation antidepressants have similar adverse events profiles.	An update of the original report, using four head-to-head trials and 23 placebo-controlled trials from 1980-2007, found the most common adverse event due to treatment of second generation antidepressants (including duloxetine, paroxetine, fluoxetine, sertraline, trazodone and venlafaxine) in continuation- and maintenance-phase studies was headache, followed by nausea (weighted mean incidence=15.5% and 7.4%, respectively). Compared with the incidence of adverse events in acute-phase studies, the relative incidence during long-term treatment was slightly lower (Hansen, 2008).	No new information.	Three experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
	In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, among 2,876 patients with major depression, ratings of side effect frequency, intensity, and burden, as well as the number of serious adverse events, were significantly greater in the anxious depression group than those with nonanxious depression (Fava, 2008). A retrospective cohort study of elderly patients prescribed SSRIs found the risk of poisoning during SSRI use was higher than nonuse. The adjusted hazard ratio (95% CI) of poisoning was higher during SSRI use vs. nonuse (1.16 [1.07 to 1.25]) and varied between SSRI agents from 0.93 (0.74 to 1.16) for fluoxetine to 1.45 (1.23 to 1.71) for fluvoxamine (Rahme, 2008). Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), found nausea was the only AE with an incidence greater than or equal to 10% and 5 percentage points greater than with placebo during short-term treatment. In general, AEs of escitalopram were mild to moderate in severity (Baldwin, 2007).			
Discontinuation syndromes (e.g., headache, dizziness, nausea) occurred in 0 to 86 percent of patients. Paroxetine and venlafaxine had the highest incidence of this problem, and fluoxetine the lowest incidence.	Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), found, compared with paroxetine, escitalopram resulted in significantly fewer discontinuation symptoms (average increase in Discontinuation Emergent Signs and Symptoms Scale of 1.6 vs. 3.9, $p<0.01$) (Baldwin, 2007).	No new information.	Three experts agreed the conclusion is still valid.	Conclusion is possibly out of date and this portion may need updating. New analyses should be reviewed for methods, inclusion criteria, funding source.

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
Overall discontinuation rates did not differ significantly between SSRIs as a class and bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine. In the case of venlafaxine compared with SSRIs, higher discontinuation rates because of adverse events appear to be balanced by lower discontinuation rates because of lack of efficacy.	An analysis of the Medical Expenditure Panel Survey for 1996-2001 found 42.4% of patients discontinued antidepressant therapy during the first 30 days. 27.6% of the patients continued antidepressant treatment for more than 90 days. Antidepressant discontinuation during the first 30 days was more common among Hispanics (53.8%) than non-Hispanics (43.7%), patients with few than 12 years of education than those with 12 or more years of education (Olfson, 2006). A prospective cohort study of 6,719 adult patients with depressive syndrome and associated with anxiety symptoms, treated with venlafaxine XR for 24 weeks, found 81.8% of patients completed 24 weeks of treatment (Roca, 2006). An analysis of 62 RCTs found controlled-release paroxetine had significantly fewer dropouts due to adverse events than immediate-release paroxetine (RD: 5%, 95% CI 0.1 to 11). No other difference found between paroxetine and other antidepressants (amisulpride, amitriptyline, bupropion, clomipramine, doxepin, fluvoxamine, fluoxetine, imipramine, lofepramine, mianserin, mirtazapine, moclobemide, maprotiline, nefazodone, nortriptyline, sertraline, tianeptine, venlafaxine) (Katzman, 2007). Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), the 8 week withdrawal rate due to AEs was higher with escitalopram than with placebo (7.3% vs. 2.8%, p<0.001) but lower than with paroxetine (6.6% vs. 9.0%; p<0.01) or venlafaxine (6.1% vs. 13.2%,	No new information.	Three experts agreed the conclusion is still valid.	Conclusion is possibly out of date and this portion may need updating based on new analysis showing lower drop out rate with escitalopram.

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
	p<0.01) (Baldwin, 2007).			
Bupropion is associated with a lower incidence of sexual dysfunction than fluoxetine, paroxetine, and sertraline. In head-to-head trials, paroxetine consistently had higher rates of sexual dysfunction than comparators (fluoxetine, fluvoxamine, nefazodone, and sertraline).	Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), found AEs related to sexual dysfunction were similarly frequent with escitalopram and citalopram, but were higher with paroxetine (Baldwin, 2007).	No new information.	Three experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
The existing evidence on the comparative risk for rare but severe adverse events, such as suicidality, seizures, cardiovascular events (i.e., elevated systolic and diastolic blood pressure and elevated pulse/heart rate), hyponatremia, hepatotoxicity, and serotonin syndrome, is insufficient to draw firm conclusions.	A matched case-control study with Medicaid beneficiaries did not find antidepressant drugs are statistically associated with suicide attempts (OR: 1.10 95% CI 0.86-1.39) or suicide deaths (OR 0.90, 95% CI: 0.52-1.55) in adults. However, in children and adolescents, antidepressant drugs were significantly associated with suicide attempts (OR, 1.52, 95% 1.12-2.07) and suicide deaths (OR, 15.62; 95% CI, 1.65-infinity) (Olfson, 2006). A comparison of before and during 12 weeks of antidepressant treatment in 437 elderly patients with major depression found 7.8% with emergent suicidality, 12.6% with persistent suicidality, and 15.6% with resolved suicidality. Rates of emergent suicidality didn't differ significantly between paroxetine-and nortriptyline-treated patients (Szanto, 2007). A observational cohort study in Denmark found patients who continued treatment with antidepressants had a decreased rate of	07/2006 SSRIs Active FDA Safety Alert "increased risk for Persistent Pulmonary Hypertension in babies born to mothers who took selective serotonin reuptake inhibitors (SSRIs) and increased risk for Serotonin Syndrome in patients who use SSRIs and triptans together". 07/2006 Serotonin-norepinephrine reuptake inhibitors (SNRIs) Active FDA Safety Alert "increased risk for Serotonin Syndrome in patients who use SSRIs and triptans together".	Three experts agreed the conclusion is still valid.	Conclusion is possibly out of date and this portion of the CER may need updating based on new U.K. cohort study of over 200,000 patients.

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
	suicide compared to those who purchased antidepressant once (rate ratio: 0.31, 95% CI: 0.26-0.36). The rate of suicide decreased consistently with the number of prescriptions (Sondergard, 2007). A retrospective cohort study with 219,099 UK patients found venlafaxine was associated with an increased risk of attempted suicide, compared to citalopram, fluoxetine and dothiepin. For completed suicides, unadjusted and adjusted hazard ratio for venlafaxine compared with citalopram were 2.44 (95% 1.12 to 5.31) and 1.70 (95% CI 0.76-3.80), for venlafaxine compared with fluoxetine were 2.85 (95% CI 1.37 to 5.94) and 1.63 (95% CI 0.74 to 3.59) (Rubino, 2007). A retrospective cohort study of elderly patients prescribed SSRIs found the risk of suicide death was not higher during periods of SSRI use vs. nonuse. The adjusted risk of suicide death was not higher during SSRI use vs. nonuse (hazard ratio (95% CI)): any SSRI=0.64 (0.38 to1.07), paroxetine=0.71 (0.37 to 1.35), citalopram=1.16 (0.59 to 2.25), and sertraline=0.38 (0.16 to 0.93) (Rahme, 2008). An evaluation of 12 placebo controlled trials of MDD patients, comparing duloxetine vs. placebo didn't find significant difference in the incidence of suicide-related events (Acharya, 2006). Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), did not find significant differences between escitalopram and placebo in incidence of suicidal behavior,			

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
	measured by self-harm and suicidal thoughts. The incidence of cardiovascular events with escitalopram was similar to that with placebo (Baldwin, 2007). An open-label study of 62 patients aged 60+ with major depressive disorder, treated with venlafaxine XR for 12 weeks, found 24% (95% CI 7.3% to 40.7%) of initially normotensive participants and 54% (95% CI 34.3% to 74%) of those with preexisting hypertension experienced an increase in blood pressure. 29% (95% CI 14.6% to 43.4%) developed orthostatic hypotension. 2 experienced a clinically significant increase in QTc interval. 1 participant reported new-onset mild dizziness, 4 reported new-onset tachycardia or palpitation. Overall, 17 unique participants (28.8%, 95% CI 17.3% to 40.4%) experienced a new-onset cardiovascular problem. Systematic monitoring of cardiovascular parameters during treatment with venlafaxine-XR should be strongly recommended, especially in the elderly (Johnson, 2006).			
Are there new data that could inform the key questions that might not be addressed in the conclusions? An analysis of US nationally representative prescription database found adherence was better with the once daily bupropion XL than with the twice-daily bupropion SR formulation (Stang, 2007).				
Key Question 5: How do the efficacy, effectiveness, or harms of treatment with antidepressants for a depressive syndrome differ for the following subpopulations: *** Elderly or very elderly patients;** ***Other demographic groups (defined by age, ethnic or racial groups, and sex);** *** Patients with medical comorbidities (e.g., ischemic heart disease, cancer)?**				
No major differences in efficacy and effectiveness exist among second-generation antidepressants in elderly or very elderly populations. Indirect evidence suggests that efficacy among second-generation antidepressants does not differ between men and women.	An analysis of 10 double blind head-to-head trials of patients with major depressive disorder found no age-related difference in efficacy between bupropion and the SSRIs. There is greater improvement in efficacy in anxious/somatic symptoms of depression among women during SSRIs treatment than men (Papakostas, 2007).	07/2006 SSRIs Active FDA Safety Alert "increased risk for Persistent Pulmonary Hypertension in babies born to mothers who took selective serotonin reuptake inhibitors (SSRIs) and increased risk for Serotonin Syndrome in patients	Two experts agreed the conclusion is still valid. One expert responded that s/he does not know.	Conclusion should be updated to include new data on racial/ethnic populations.

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
	Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), found the risk of AEs due to escitalopram was no higher in special patient populations, such as the elderly or those with hepatic dysfunction (Baldwin, 2007). An open-label study of 62 patients aged 60+ with major depressive disorder, treated with venlafaxine XR for 12 weeks, found 24% (95% CI 7.3% to 40.7%) of initially normotensive participants and 54% (95% CI 34.3% to 74%) of those with preexisting hypertension experienced an increase in blood pressure. 29% (95% CI 14.6% to 43.4%) developed orthostatic hypotension. 2 experienced a clinically significant increase in QTc interval. 1 participant reported new-onset mild dizziness, 4 reported new-onset tachycardia or palpitation. Overall, 17 unique participants (28.8%, 95% CI 17.3% to 40.4%) experienced a new-onset cardiovascular problem. Systematic monitoring of cardiovascular parameters during treatment with venlafaxine-XR should be strongly recommended, especially in the elderly (Johnson, 2006). An analysis of the Medical Expenditure Panel Survey for 1996-2001 found antidepressant discontinuation during the first 30 days was more common among Hispanics (53.8%) than non-Hispanics (43.7%) (Olfson, 2006). A randomized study of 727 patients with nonpsychotic major depressive disorder and taking any of the following: sustained-release bupropion hydrochloride, sertraline hydrochloride, or extended release	who use SSRIs and triptans together".		

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
	venlafaxine hydrochloride, found remission was more likely among whites. Intolerance was less likely for Hispanic participants (Rush, 2008). An analysis of STAR*D patients with nonpsychotic major depressive disorder, treated with citalopram up to 14 weeks, found Black, and to a lesser extent Hispanic patients, had a poorer response to citalopram than white patients. After adjusting for baseline differences, the remission rates seemed to be more similar on the HAM-D, but remained worse for blacks on the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Lesser, 2007). A meta-analysis of 7 double-blind placebo controlled trials of patients with MDD who received duloxetine found no significant difference in duloxetine's treatment effect between African-American and Caucasian patients. Discontinuation rates due to adverse events did not differ significantly between African-Americans and Caucasians. No adverse event led to discontinuation in more than one African-American patient. The rate of occurrence of AEs did not differ significantly between two groups (Bailey, 2006). A clinical trial of 35 adult cancer outpatients with depression, during chemotherapy, found sertraline could significantly decrease mean depression scores, analyzed by Hospital Anxiety and Depression Scale (HADS) and MADRS scales, HADS anxiety scores. No severe adverse effects were observed (Torta, 2008). A meta-analysis of 44 placebo-controlled			

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 1 TEP Member, 1 Other Expert	Conclusion from SC EPC
	trials of patients with Parkinson's disease and depression found SSRIs produced a robust antidepressant effect on moderately depressed Parkinson's patients (d=0.44, p< 0.05). A modestly positive and significant effect size result was observed with SSRIs on motor function (d=0.34, p<0.05), and there were no significant side effects (d=-0.002, p=0.50). These results show that SSRIs can be used to treat depression without the fear of worsening PD (Frisina, 2005).			
Are there new data that could inform the key questions that might not be addressed in the conclusions? Additional comments: A new drug (Desvenlafaxine, *Pristiq*) has been FDA approved for the treatment of MDD in adults. This drug is not included in the current MMA report. To my knowledge, no head-head trials comparing desvenlafaxine to other second-generation antidepressants exist yet Scope could be broadened to include antipsychotics.				

Legend: CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRQOL: health-related quality of life; ITT: intention to treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report; RCT: randomized controlled trial; RD: rate difference; RR: relative risk; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; STAR*D: Sequenced Treatment Alternatives to Relieve Depression

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CER 9. Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease

For this assessment, a limited literature search was conducted for the years 2006-2008. This search included the five generalist journals listed in the Methods and four specialty journals (as recommended by the subject matter experts): Circulation; Journal of the American College of Cardiology; Heart; American Journal of Cardiology. The search identified 252 titles, of which 42 were obtained in full text for further review. The remaining titles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance. Of the 42 selected for further review, all were abstracted into an evidence table (Attachment II). An additional 7 articles were included at the suggestion of the experts.

We consulted the project leader and 4 additional subject matter experts for their assessments. Of these 5 individuals, four responded. Importanlty, the project leader indicated that AHRQ was already supporting an individual patient-level data meta-analysis to better refine estimates of comparative effectiveness for subgroups of patients. This meta-analysis was recently published and, in the view of the project leader, constitutes the update (Hlatky et al, 2009).

Table 2.7 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.7 CER 9. Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease: Are the conclusions still valid?

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions: EPC Investigator, 3 Other Experts	Conclusion from SC EPC
Key Question 1 **1a: In patients with ischemic heart disease and angiographically proven single or multi-vessel disease, what is the effectiveness of PCI compared with CABG in reducing the occurrence of adverse objective outcomes and improving subjective outcomes?**				
There were no significant differences in procedural survival when trials were subdivided into balloon-era and stent-era studies or into single vessel-disease and multi-vessel-disease patient populations. Procedural survival for both percutaneous coronary interventions (PCI) and coronary artery bypass graft (CABG) was high for both procedures and did not differ significantly. In large registries, procedural survival has increased significantly over time. Short-term procedural survival after PCI generally exceeded that of CABG in both earlier and more recent time intervals.	Hannan, 2008 found, based on the NY State Registry, no difference in procedural mortality. (Data from this registry were already included in the evidence report and the new report was not significantly different from the prior one.) Takagi, 2008 found no difference in survival between the procedures, based on a meta-analysis of 4 of the included randomized controlled trials (RCT)s of multi-vessel disease.	No new information.	Three experts judge this conclusion as still being valid. One expert is unsure whether the data from the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) or the Stent or Surgery (SoS) Trials are included. These both favor CABG and do not seem to be reflected in this statement. [SoS was included in original CER.]	Conclusion is still valid and this portion of the CER does not need updating.
Freedom from procedural strokes: was significantly higher after PCI than after CABG.	No new evidence.	No new information.	All four experts judge this conclusion to still be valid.	Conclusion is still valid and this portion of the CER does not need updating.
Freedom from procedural myocardial infarctions was not assessed in a consistent fashion across trials RCTs,	No new evidence.	No new information.	Three experts judge this conclusion as still being valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: ARTS: Arterial Revascularization Therapy Study; AWESOME: Angina With Extremely Serious Operative Mortality Evaluation; BARI: Bypass Angioplasty Revascularization Investigation ; BARI-2D: Bypass Angioplasty Revascularization Investigation 2 Diabetes trial; BMS: bare metal stent; CABG: coronary artery bypass graft; COURAGE: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation**;** DES: drug-eluting stent; LAD: left anterior descending artery; LIMA: left internal mammary artery; LM: left main descending artery; PCI: percutaneous coronary intervention; QoL: quality of life; RCT: randomized controlled trial; SF: Short Form; SoS: Stent or Surgery; STICH: Surgical Treatment for IschemiC Heart failure; STS: Society of Thoracic Surgeons; SYNTAX: Synergy Between PCI With Taxus and Cardiac Surgery

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts	Conclusion from SC EPC
and there was significant heterogeneity in this outcome. The pooled PCI-CABG difference was small and not statistically significant.			One expert believes the key challenge is the definition across the modalities. Current approaches, as used in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) seem reasonable. This is, however, probably not a clearly important outcome in the era of very sensitive biomarkers. NOTE: COURAGE compared PCI + optimal medical therapy with optimal medical therapy. No CABG was conducted in the study.	
1b: Over what period of time are the comparative benefits of PCI and CABG sustained?				
Long-term survival across all RCTs between 1 and 5 years of followup was similar in CABG-assigned and PCI-assigned patients, with less than 1-percent absolute PCI-CABG survival difference at each time point. The long-term survival difference between PCI and CABG was significantly different in the older RCTs that relied on balloon angioplasty, but not in the	A 6-year follow up study of the SoS) Trial and 5 year data from other RCTs show no difference in survival (Booth, 2008; Hlatky, 2008). The SoS Trial of patients with multivessel disease, comparing PCI with CABG, found a continuing survival advantage for patients managed with CABG at a median follow-up of 6 years (Booth, 2008). When the SoS data were added to the 5 year outcome data from the other PCI vs. surgery trials the overall pooled result was not significantly changed, which did not show a survival	No new information.	Three experts judged this conclusion as still being valid. One expert cited SoS trial was added to CER meta-analysis results (Booth, 2008). One expert cited additional support (Bravata, 2007). (This article was derived from the CER)	Conclusion is possibly out of date and this portion of the CER may need updating, due to differing expert opinion.

Legend: ARTS: Arterial Revascularization Therapy Study; AWESOME: Angina With Extremely Serious Operative Mortality Evaluation; BARI: Bypass Angioplasty Revascularization Investigation ; BARI-2D: Bypass Angioplasty Revascularization Investigation 2 Diabetes trial; BMS: bare metal stent; CABG: coronary artery bypass graft; COURAGE: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation**;** DES: drug-eluting stent; LAD: left anterior descending artery; LIMA: left internal mammary artery; LM: left main descending artery; PCI: percutaneous coronary intervention; QoL: quality of life; RCT: randomized controlled trial; SF: Short Form; SoS: Stent or Surgery; STICH: Surgical Treatment for IschemiC Heart failure; STS: Society of Thoracic Surgeons; SYNTAX: Synergy Between PCI With Taxus and Cardiac Surgery

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts	Conclusion from SC EPC
more recent RCTs that employed coronary stents. Stent-era trials included more patients with single-vessel disease, however, and had shorter followup than balloon-era trials.	differences between CABG and PCI (Hlatky, 2008). A new report from the NY State Registry confirmed slightly improved survival with CABG at 18 months compared with PCI. (Data from this registry were already included in the evidence report and the new report was not significantly different from the prior one) (Hannan, 2008). Takagi, 2008 found no difference in survival between the procedures, based on a meta-analysis of 4 of the included RCTs of multi-vessel disease (Takagi, 2008).		One expert believes the conclusion is no longer valid based on SoS favoring CABG, and SYNTAX does so for the combined endpoint. Drug-eluting stents (DES) were not used in SoS, only bare metal stents (BMS).	
Freedom from angina was significantly greater after CABG than after PCI in randomized trials between 1 and 5 years post-procedure. Freedom from repeat revascularization was significantly greater after CABG than after PCI at 1 and 5 years. The gap between PCI and CABG in repeat revascularization procedures narrowed in more recent trials that used coronary stents. Freedom from myocardial infarction was small, 1 percent between 1 and 5 years after the procedure and did not achieve statistical significance.	No new evidence found for freedom from angina. A new report from the NY State Registry also confirmed a higher revascularization rate among stent recipients than CABG patients (Hannan, 2008). (Data from this registry were already included in the evidence report.) A meta-analysis of four of the included RCTs of multi-vessel disease found increased repeat revascularization after CABG than after PCI (Takagi, 2008). No new evidence found for freedom from myocardial infraction Initial analysis of the SYNTAX trial found, at 12 months, repeat revascularization was more frequent with PCI than CABG, while the increase in repeat revascularization for PCI compared to CABG was lower than in any prior trials. Stroke was more frequent in the CABG group. Combined	No new information.	One expert judged the conclusion is still valid One expert cited additional support (Bravata, 2007). (This article was derived from the CER) One expert believes this conclusion is the key. One expert judged the conclusion to be no longer valid. This expert cited the SYNTAX trial comparing multivessel stenting (including left main descending artery (LM)) vs. CABG. The trial found statistically	Conclusion is possibly out of date and this portion of the CER may need updating, due to differing expert opinion.

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts	Conclusion from SC EPC
	safety in terms of death, MI and stroke remained the same for PCI and CABG. Sub-analysis of patients with triple-vessel disease, overall 12-month Major Adverse Cardiovascular and Cerebrovascular Events (composite of death, stroke, MI, and repeat revascularization) rates were significantly higher in those who received PCI compared with CABG. The rates of MI and repeat revascularization were also higher in the PCI arm. (Walle, 2008; Feldman, 2008; Kahn, 2009)		greater MI rate vs. CABG in the subgroup of patients undergoing multivessel stenting.	
In general, quality-of-life scores improved to a significantly greater extent after CABG than after PCI between 6 months and 3 years of followup but equalized thereafter. The degree of improvement in quality of life was correlated with relief of angina.	Favarato, 2007 found the CABG group had greater improvements in Short Form (SF)36-measured quality of life (QOL) than the PCI group (Favarato, 2007).	No new information.	Three experts judged this conclusion to still be valid. One expert believes the conclusion is no longer valid. Registries support a slower rate of improvement in QoL in CABG than PCI, but the overall benefits favor CABG. Almost all of the differences in QoL at one year are attributable to restenosis – which is minimized in DES. Haven't seen recent registries with QoL outcomes comparing CABG and PCI in the DES era (Borkon, 2002).	Conclusion is possibly out of date and this portion of the CER may need updating, due to differing expert opinion.
Key Question 2: Is there evidence that the comparative effectiveness of PCI and CABG varies based on: 2a. Age, sex, race, or other demographic risk factors?				
There was little evidence from RCTs to gauge whether the comparative effectiveness of CABG and PCI varies according to patient or	No new evidence found for age, gender, race.	No new information.	Four experts judged this conclusion to still be valid. One expert cited	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts	Conclusion from SC EPC
provider characteristics. Older patients had more procedural complications from both PCI and CABG, especially stroke. Patients aged 65 years and older had lower long-term survival compared with younger patients. Roughly 27 percent of the patients in randomized trials were women, and their outcomes were similar to those among men in the trials that examined outcomes by gender. Outcomes after PCI and CABG according to race were analyzed only by the BARI (Bypass Angioplasty Revascularization Investigation) trial and registry, which found African-American patients had significantly lower overall survival, irrespective of treatment with PCI or CABG.			additional support (Lawrence, 2007).	
2b. Coronary disease risk factors, diabetes, or other comorbid disease?				
In large clinical registries, comparative survival after PCI or CABG varied significantly according to the extent of coronary disease. Survival was significantly better after PCI in patients with single-vessel disease that did not involve the proximal left anterior	A new report from the NY State Registry (Hannan, 2008) was similar to what was seen in other prior registries—namely that patients with more extensive disease had improved survival with CABG. (Data from this registry were already included in the evidence report.)	No new information.	Three experts judge the conclusion as not being valid anymore. One expert is working on a Technical Addendum to the original Evidence Report that is really a piece of original research –	Conclusion is probably out of date and this portion of the CER needs updating based on the majority of expert opinion.

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts	Conclusion from SC EPC
descending artery (LAD), and survival was significantly better after CABG in patients with extensive triple-vessel or left main disease. In analyses from large clinical registries of patients with middle spectrum CAD severity, there was no difference in survival after PCI or CABG.			namely a collaboration among all the large clinical trials to pool individual patient data and look very carefully at all the patient subgroup outcomes. One expert cited SYNTAX trial comparing evaluated multivessel stenting (including LM) vs. CABG. The trial didn't find statistically difference in survival in LM stenting vs. CABG and in multivessel stenting vs. CABG. One expert judges the conclusion as still being valid.	
Survival at 1 and 5 years in patients with diabetes was reported by six trials. The BARI trial reported a significant survival advantage for patients with diabetes assigned to CABG: 5-year survival of 80 percent with CABG vs. 65 percent with PCI. None of the other trials found as dramatic a difference in survival between patients with and without diabetes.	No new evidence other than possible new data from Stanford-UCSF EPC (Hlatky, 2008).	No new information.	All four experts judge this conclusion to still be valid. In July 2008, CER authors added SoS and Arterial Therapy Revascularization Study (ARTS) trials to their meta-analyses on diabetes patients. There was no difference in conclusions. (Hlatky, 2008) One expert reveals that Bypass Angioplasty Revascularization Investigation Type 2 Diabetes (BARI-2D- is a	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts	Conclusion from SC EPC
			program to study whether, in patients with Type 2 Diabetes, initial treatment with angioplasty or bypass surgery is better than initial treatment with a medical program) is to be released this year.	
In general, obesity was not consistently associated with significant differences in comparative effectiveness of PCI and CABG in the two trials that reported outcomes by body mass index.	No new evidence.	No new information.	Two experts agreed that the conclusion is no longer valid. One expert is working on a Technical Addendum to the original Evidence Report that is really a piece of original research – namely a collaboration among all the large clinical trials to pool individual patient data and look very carefully at all the patient subgroup outcomes. Two experts agreed that the conclusion is still valid.	Conclusion is possibly out of date and this portion of the CER may need updating, based on the expected availability of the individual patient level meta analysis that will have greater power to assess comparative effectiveness in subgroups.
2c. Angiographic-specific factors including, but not limited to, the number of diseased vessels amenable to bypass or stenting, vessel territory of stenoses (e.g., left main or anterior descending coronary arteries, right coronary artery, circumflex coronary artery), diffuse vs. focal stenoses, left ventricular function, or prior revascularization procedures?				
There was no significant difference in the comparative survival benefit when RCTs were subdivided into those enrolling patients with single-vessel proximal LAD disease and those enrolling patients	A new study based on the NY State Registry (Hannan, 2008) found no difference in procedural mortality. (Data from this registry were already included in the evidence report and the new report was not significantly different from the prior one.) Takagi, 2008 found no difference in survival	No new information.	All four experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts	Conclusion from SC EPC
with multi-vessel disease.	between the procedures, based on a meta-analysis of 4 of the included RCTs of multi-vessel disease (Takagi, 2008).			
In large clinical registries, comparative survival after PCI or CABG varied significantly with the extent of coronary disease, with better survival after PCI in patients with the least extensive coronary disease and better survival after CABG in patients with the most extensive disease.	No new evidence.	No new information.	Two experts agreed this conclusion is still valid. One expert cited additional support. (Lawrence, 2007) One expert suggested that the conclusions are no longer very relevant, given that PCI is almost universally done, when possible, among those with single vessel disease. One expert believes the conclusion is no longer valid and cites the SYNTAX trial comparing multivessel stenting (including LM) to CABG. The trial didn't find statistical difference in survival in LM stenting vs. CABG and in multivessel stenting vs. CABG	Conclusion is possibly out of date and this portion of the CER may need updating, due to differing expert opinion.
Most trials comparing PCI and CABG randomized patients with relatively preserved left ventricular function and a low prevalence of heart failure. The limited range of ejection fractions within the trials precludes a stringent test of	No new evidence for left ventricular function.	No new information.	All four experts agreed this conclusion as still valid. One expert mentioned that while not directly comparing PCI and CABG, the results of the	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts	Conclusion from SC EPC
whether the comparative effectiveness of PCI and CABG varies according to left ventricular function.			Surgical Treatment for IschemiC Heart failure (STICH) trial might be released this year (2009).	
2d. CABG-specific factors including, but not limited to, cardiopulmonary bypass mode (normothermic vs. hypothermic), type of cardioplegia used (blood vs. crystalloid), or use of saphenous vein grafts, single or bilateral internal mammary artery grafts, or other types of bypass grafts?				
Use of minimally invasive techniques: "Minimally invasive" surgery, which is performed through a small thoracotomy incision on a beating heart, was compared with PCI in eight small RCTs. These trials enrolled patients with single-vessel proximal LAD disease (predominantly or exclusively) and generally used PCI with stents as the comparator. These trials showed no significant differences in survival between PCI and CABG over a relatively short followup period.	No new evidence.	No new information.	All four experts agreed this conclusion is still valid. One expert noted that there are some new data favoring open procedures, not positive.	Conclusion is still valid and this portion of the CER does not need updating.
Standard CABG was used in all trials that enrolled patients with multi-vessel disease, with variable use of left internal mammary grafting, ranging from a low of 37 percent in the early GABI study to over 90 percent. The 1-year survival advantage for CABG vs. PCI increased along with the proportion of internal mammary artery grafts used, but this trend was not statistically	No new evidence.	No new information.	Three experts agreed this conclusion is still valid. One expert concludes the use of left internal mammary arteries (LIMAs) is now a quality indicator for the Society of Thoracic Surgeons (STS) and this does not seem as relevant an issue any more.	Conclusion is still valid and this portion of the CER does not need updating.

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 3 Other Experts	Conclusion from SC EPC
significant and not evident at 5 years.				
2e. Clinical presentation (e.g., stable angina or unstable angina based on New York Heart Association functional class I-IV, acute coronary syndrome, cardiogenic shock, acute myocardial infarction with or without ST elevation, or silent ischemia)?				
Comparative survival after PCI and CABG was not consistently different between patients with stable or unstable angina.	No new evidence.	No new information.	All four experts agreed this conclusion is still valid. One expert cited (Hochholzer, 2008).	Conclusion is still valid and this portion of the CER does not need updating.
2f. Adjunctive medical therapies, such as short-term intravenous or oral antiplatelet drugs, or long-term use of oral antiplatelet drugs?				
The RCTs did not report comparative effectiveness data based on the use of adjunctive medical therapy for PCI or CABG. It is uncertain whether patients who have undergone CABG are as likely as patients who have undergone PCI to comply with recommendations for long-term use of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins. There is relatively little evidence on this question from randomized trials; however, the Duke Database, a large observational registry of patients receiving both procedures, reports relatively similar use of evidence-based therapies after PCI and CABG.	No new evidence.	No new information.	All four experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

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2g. Process characteristics such as provider volume, hospital volume, and setting (e.g., academic vs. community)?				
There was considerable evidence that procedural outcomes of both CABG and PCI were significantly worse in low-volume hospitals and with low-volume operators. This relationship remained significant for PCI, even as procedural risk has been reduced by the availability of coronary stents and adjunctive therapy. The magnitude of association of procedural outcomes with volume of PCI and CABG may be only modest, however, at least among sufficiently experienced centers and operators.	No new evidence.	No new information.	Three experts agreed this conclusion is still valid. One expert believes the conclusion does not seem to be as important in the current era. Also of note, substantially more data have emerged supporting the use of PCI without onsite CABG. Not sure if that is relevant to this work.	Conclusion is still valid and this portion of the CER does not need updating.
2h. Prior PCI or CABG revascularization procedures?				
Most randomized trials excluded patients with prior CABG, but one randomized trial and several clinical registries have compared PCI with re-do CABG in patients with a prior CABG. In the AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) trial, patients with prior CABG were randomized to either re-do CABG or PCI. While procedural survival was	No new evidence.	No new information.	All four experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

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significantly lower in the patients assigned to CABG 3-year survival did not differ significantly. A similar pattern has been reported by 3 large clinical registry studies. Procedural mortality was higher for re-do CABG than for PCI, but survival at 5 to 6 years of followup did not differ significantly.				
Are there new data that could inform the key questions that might not be addressed in the conclusions? Additional comments: 1) Meta-analysis of PCI (mostly BMS) vs. CABG RCTs demonstrated lower revascularization rates and improved angina relief but increased stroke rate in CABG; no survival difference @ 10 yrs (including in diabetics). Ann Intern Med. 2007 Nov 20;147(10):703-16. (This article was derived from the CER) 2) Small cohort studies & meta-analyses demonstrate no early or midterm difference in the treatment of unprotected LM stenosis between PCI and CABG. Am J Cardiol. 2008 Jan 15;101(2):169-72., Am Heart J. 2008 Feb;155(2):274-83., J Am Coll Cardiol. 2008 Feb 5;51(5):538-45 *The remainder of new studies comparing PCI & CABG were case series or retrospective (generally single-center) cohort studies.				

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CER 10. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension

For this assessment, a limited literature search was conducted for the years 2006-2008. This search included the five generalist journals listed in the Methods and five specialty journals (as recommended by the subject matter experts): Stroke; Hypertension; Circulation; Journal of the American College of Cardiology; Heart; American Journal of Cardiology. The search identified 285 titles, of which 49 were obtained in full text for further review. The remaining titles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance. Of those selected for further review, 48 were abstracted. The remaining article was rejected because it had already been included in the earlier report or did not include a comparison of interest. Three additional articles were also included at the suggestion of the experts, for a total of 51.

We consulted the project lead and 4 additional subject matter experts (the report does not list the TEP composition) for their assessments. Of these 5 individuals, three responded.

Table 2.8 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.8 CER 10. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension: Are the conclusions still valid?

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions 3 Experts	Conclusion from SC EPC
Key Question 1. For adult patients with essential hypertension, how do ACEIs and ARBs differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes?				
ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension.	A large randomized controlled trial (RCT), ONTARGET, comparing telmisartan (an ARB) with ramipril (an ACEI), found slightly lower BP attained with telmisartan 80 than ramipril 10 over 4+ yrs of follow up. The ONTARGET study also showed noninferiority in BP-independent CV protection. The TRANSCEND Study showed no significant effect of ARB for primary or secondary prevention (ONTARGET Investigators, 2008).	No new information.	One expert cited 2 large randomized controlled trials (RCT) comparing telmisartan (an ARB) with ramipril (an ACEI), the ONTARGET and TRANSCEND trials. This study concludes slightly lower BP attained with Telmisartan 80 than Ramipril 10 over 4+ yrs of follow up ON TARGET study showed noninferiority in BP independent CV protection, TRANSCEND study showed no significant impact of ARB for primary or secondary prevention (ONTARGET Investigators, 2008). Two experts judged the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Due to insufficient numbers of deaths or major cardiovascular events in the included studies, it was not possible to discern any differential effect of ACEIs vs. ARBs for these critical	A case-control study of the association of ACEIs and aortic rupture in patients with AAA found that patients on ACEIs had lower risk of rupture than patients on ARBs, but this was not a statistically significant finding (OR 1.24; 0.71-2.18) (Hackam, 2006).	No new information.	One expert cited the ONTARGET and TRANSCEND trials (ONTARGET Investigators, 2008). Two experts judged the	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AAA: Abdominal aortic aneurysm; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker/antagonist; BP: Blood pressure; DIRECT: DIabetic REtinopathy Candesartan Trials; MI: Myocardial infarction; ONTARGET: ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; TRANSCEND: Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions 3 Experts	Conclusion from SC EPC
outcomes.	Two reviews evaluated the association of ARBs and myocardial infarction (MI) (Hall, 2007 and Strauss, 2007). Only one of these included any direct ACEI vs ARB comparison evidence. The evidence from this would neither change the conclusion or the quality rating for the risk of MI in this report. The ONTARGET trials showed slightly lower BP attained with Telmisartan 80 than Ramipril 10 over 4+ yrs of f/u. ON TARGET study showed noninferiority in BP-independent CV protection, TRANSCEND study showed no significant impact of ARB for primary or secondary prevention (ONTARGET Investigators, 2008).		conclusion is still valid .	
No differences were found in measures of general quality of life; this is based on 4 studies, 2 of which did not provide quantitative data.	No new evidence.	No new information.	Three experts judged the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
There was no statistically evident difference in the rate of treatment success based on use of a single antihypertensive, for ARBs compared to ACEIs. There were no consistent differential effects of ACEIs vs. ARBs on several potentially important clinical outcomes, including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, measures of LV mass or function, and progression of renal disease (either based on creatinine, GFR, or proteinuria). Relatively few	A network meta-analysis (which facilitates the inclusion of both direct and indirect comparison trials) to evaluate the incident diabetes in 22 clinical trials of antihypertensive drugs found that ARBs and ACEs are the antihypertensive agents least associated with incident hypertension but did not find a robust difference between the two (Elliott and Meyer, 2007).	No new information.	Three experts judged the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AAA: Abdominal aortic aneurysm; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker/antagonist; BP: Blood pressure; DIRECT: DIabetic REtinopathy Candesartan Trials; MI: Myocardial infarction; ONTARGET: ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; TRANSCEND: Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions 3 Experts	Conclusion from SC EPC
studies assessed these outcomes over the long term.				
Key Question 2: For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety, adverse events, tolerability, persistence, and adherence?				
ACEIs have been consistently shown to be associated with slightly greater risk of cough than ARBs. There was no evidence of differences in rates of other commonly reported specific adverse events to quantify.	A RCT comparing telmisartan with ramipril showed that telmisartan resulted in a lower rate of cough (1.1% vs. 4.2%, p <.001) than ramipril (ONTARGET Investigators, 2008).	No new information.	One expert identified a recent RCT with data on cough: Telmisartan (an ARB) had lower rate of cough (1.1% vs 4.2%, p <.001) than ramipril (ONTARGET Investigators, 2008). Three experts judged the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Angioedema was reported only in patients treated with ACEIs; however, because angioedema was rarely explicitly reported in the included studies, it was not possible to estimate its frequency in this population.	A RCT comparing telmisartan to ramipril showed that telmisartan had a lower rate of angioedema than ramipril (0.1% vs. 0.3%, p=.01) (ONTARGET Investigators, 2008).	No new information.	One expert identified a recent RCT with data on angioedema: telmisartan had a lower rate of angioedema than ramipril (0.1% vs 0.3%, p=.01) (ONTARGET Investigators, 2008) One expert did not know if the conclusion was still valid. One expert judged the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
ACEIs and ARBs have similar rates of adherence based on pill counts; this result may not be applicable outside the clinical trial setting. Rates of continuation with therapy	No new evidence.	No new information.	Three experts judged the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AAA: Abdominal aortic aneurysm; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker/antagonist; BP: Blood pressure; DIRECT: DIabetic REtinopathy Candesartan Trials; MI: Myocardial infarction; ONTARGET: ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; TRANSCEND: Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions 3 Experts	Conclusion from SC EPC
appear to be somewhat better with ARBs than with ACEIs; however, due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is unknown.				
Key Question 3: Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?				
Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs and ARBs for any particular patient subgroup.	DIRECT, a randomized controlled trial of the effects of candesartan vs. placebo on incidence and progression of retinopathy in Type 1 diabetics and on progression and regression of retinopathy in Type 2 diabetics showed that it reduced incidence but not progression in Type 1 diabetics (Sjølie, 2008), did not reduce progression in type 2 diabetics, and had a small but significant effect on regression in early disease stages (Chaturvedi, 2008).	8/29/2006, Losartan (Cozaar), Labeling Revision-Under the "PRECAUTIONS/Drug Interactions" subsection, add Lithium: As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists. 8/17/2007, DIOVAN (VALSARTAN) TABLET; ORAL, Labeling Revision- "USE IN PREGNANCY" warning, to update the pregnancy information, including increased risk of injury and death to the developing fetus and birth defects, based on a publication regarding the use of ACE inhibitors during the first trimester of pregnancy. 8/17/2006, ATACAND (CANDESARTAN CILEXETIL), Under "PRECAUTIONS, General," add Major Surgery/Anesthesia Hypotension may occur during major surgery and anesthesia in patients treated with angiotensin II receptor antagonists, including candesartan, due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.	One expert concludes DIRECT showed slight edge for ARB in diabetic retinopathy (Sjølie, 2008; Chaturvedi, 2008). Three experts judged the conclusion is still valid.	Conclusion is possibly out of date and this portion may need updating, based on new FDA data about possible adverse events.

Legend: AAA: Abdominal aortic aneurysm; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker/antagonist; BP: Blood pressure; DIRECT: DIabetic REtinopathy Candesartan Trials; MI: Myocardial infarction; ONTARGET: ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; TRANSCEND: Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions 3 Experts	Conclusion from SC EPC
Are there new data that could inform the key questions that might not be addressed in the conclusions? **Additional comments:** 1) Meta-analysis suggesting increase in adverse events with combination of ACEI/ARB vs ACEI alone in patients with heart failure (Phillips, 2007). 2) Small case series showed slowing of progressive aortic root dilation in Marfan's patients on ARB (Brooke, 2008). 3) One expert states: Unaware of any new head-to-head comparisons in the treatment of essential hypertension that would impact these initial conclusions. I am not an expert in this area and it is possible that I may be unaware of some new evidence, but I doubt it. 4) The ONTARGET study (ONTARGET Investigators, 2008), the largest trial comparing ACE-I (ramipril) with ARB (telmisartan) and both with respect to cardiovascular events, demonstrated no difference, again supporting the above conclusions.				

Legend: AAA: Abdominal aortic aneurysm; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker/antagonist; BP: Blood pressure; DIRECT: DIabetic REtinopathy Candesartan Trials; MI: Myocardial infarction; ONTARGET: ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; TRANSCEND: Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease

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CER 11. Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults

For this assessment, a limited literature search was conducted for the years 2006-2008. This search included the five generalist journals listed in the Methods and four specialty journals (as recommended by the subject matter experts): Arthritis and Rheumatism; Journal of Rheumatology; British Journal of Rheumatology; and Annals of Rheumaticologic Disease. The search identified 364 titles, of which 57 were obtained in full text for further review. The remaining titles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance. Of the 57 selected for further review, 26 were abstracted. The remaining articles were rejected because they had already been included in the earlier report or did not include a comparison of interest.

We consulted the project lead, four peer reviewers, and one additional subject matter expert for their assessments. Of these six individuals, three responded.

Table 2.9 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.9 CER 11. Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults: Are the conclusions still valid?

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 OtherExperts	Conclusion from SC EPC
Key Question 1: For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission?				
The data show no differences in radiographic outcomes over 2 years for leflunomide and methotrexate (MTX). One systematic review that included a meta-analysis of two RCTs suggested that higher proportions of patients on MTX than on leflunomide met the American College of Rheumatology (ACR) 20-percent improvement criteria at 1 year but statistical significance was lost at 2 years.	No new evidence.	No new information found.	No opinions provided by experts.	Conclusion is still valid and this portion of the CER does not need updating.
In three studies, patients on etanercept had a faster onset of action than patients on infliximab, although no differences in effectiveness were apparent between the two agents.	No new evidence.	No new information found.	One expert judged this conclusion was still valid with this comment: “New evidence exists—so far only in abstract form and relates to etanercept with respect to rituximab (I think). There is no new evidence for infliximab.”	Conclusion is still valid and this portion of the CER does not need updating.
Adjusted indirect comparisons indicate that anakinra has lower efficacy than anti-Tumor Necrosis Factor (TNF) drugs.	No new evidence (suggested citation was included in previous CER).	No new information found.	One expert judged this conclusion providing a reference in support (Zink, 2005).	Conclusion is still valid and this portion of the CER does not require updating.
One prospective cohort study enrolled a population who failed initial RA treatment. After 12 months, patients on biologic Disease Modifying Antirheumatic Drugs (DMARDs) had almost four times higher odds of achieving functional independence percent and almost two times higher odds of achieving remission than patients on synthetic DMARDs.	No new results found. (Suggested article did not meet the CER's inclusion criteria as it was not a meta-analysis and included studies that were themselves reviewed in the CER).	No new information found.	Two experts agreed this conclusion was still valid with these comments: “New evidence supporting this, perhaps changing estimates slightly, but general conclusions unchanged.” – MSA. “Lots more on remission-more than I can list; see review by Sesin and Bingham, 2005.”	Conclusion is still valid and this portion of the CER does not need updating.
Combination strategies of one or more synthetic DMARDs with corticosteroids have better outcomes than synthetic DMARD monotherapy.	Several articles were found which affect this conclusion. An RCT with 508 subjects combination therapy with MTX+sulfasalazine+prednisone was superior to MTX monotherapy in improvement of functional ability, quality of life and radiographic	No new information found.	One expert judged this conclusion was still valid, citing an article for support (Hetland, 2008).	Conclusion is possibly out of date and this portion of the CER may need updating due to new studies which may

Legend: DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; anti-TNF: anti-Tumor Necrosis Factor; ACR20/50/70: American College of Rheumatology 20/50/70-percent improvement criteria; DAS28: Disease Activity Score shortform;

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 OtherExperts	Conclusion from SC EPC
	outcomes (Allaart, 2007). A double-blind RCT with 160 patients, cyclosporine had equivocal role in combination with intraarticular betamethasone and MTX; improving ACR20 and ACR-N scores, but not ACR50, ACR70, remission rates, or radiographic changes. (Hetland, 2006; Hetland, 2008). In an unblinded RCT the combination of cyclosporine and leflunomide was better than monotherapy with either alone for ACR50 at 12 months (80% for combination vs. 40% and 42% for cyclosporine and leflunomide respectively, p=0.001), though Disease Activity Score (DAS)28 scores were not significantly different. (Karanikolas 2006). An RCT of 44 patients demonstrated that MTX+intravenous methylprednisone was superior to MTX monotherapy in reducing magnetic resonance imaging (MRI)-detected synovitis and bone edema as well as ACR20/50/70 and remission at 52 weeks (Durez, 2007).			change the strength of the conclusion. .
Overall, combination therapy of biologic DMARDs and MTX achieved better clinical response rates than monotherapies.	The review found articles supporting this conclusion for many previously reviewed drugs: infliximab (Smolen, 2006; Smolen 2008), etanercept (Emery, 2008; van der Heijde, 2007) and rituximab (Mease, 2008). No new articles were identified for abatacept or adalimumab. There were several studies of biologics which have not been included in the CER previously. There was one trial of golimumab (an anti-TNF antibody) which improved ACR20 at 16 weeks (Kay, 2008). Two studies of tocilizumab (an IL-6 antagonist) which found a stronger effect for combination therapy with MTX than MTX monotherapy (Maini, 2006 and Genovese 2008). There was one study found of denosumab (a RANKL antagonist) with MTX which improved radiographic outcomes over MTX monotherapy (Cohen, 2008). One study was found regarding psoriatic arthritis, in which combination therapy of Alefacept (a T-cell activation inhibitor) with MTX improved ACR20 at 24 weeks compared to MTX monotherapy (Mease, 2006).	No new information found.	One expert judged this conclusion still valid, stating that there are multiple articles which support this conclusion and citing one (Smolen, 2008).	Conclusion is out of date and this portion of the CER needs updating because of studies on new drugs and new studies of previously reviewed drugs which will not change the general conclusion but will extend it to new drugs and better refine the estimate of benefit.

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 OtherExperts	Conclusion from SC EPC
A combination of etanercept with sulfasalazine did not achieve better outcomes than etanercept monotherapy.	No new evidence.	No new information found.	No opinions provided by experts.	Conclusion is still valid and this portion of the CER does not need updating.
Key Question 2: For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to improve functional capacity or quality of life?				
Patients on MTX had less improvement in functional status and health-related quality of life than patients taking leflunomide.	No new evidence.	No new information found.	One expert thought this conclusion valid but with this comment: "Personally, data is weak that differences are important." One expert stated they did not know.	Conclusion is still valid and this portion of the CER does not need updating.
Existing head-to-head evidence (three RCTs) supports no differences in efficacy between MTX and sulfasalazine by ACR 20,DAS, and functional capacity.	No new evidence.	No new information found.	One expert stated that they did not know.	Conclusion is still valid and this portion of the CER does not need updating.
Greater improvements in functional capacity and quality of life were found with combination therapies (adalimumab, infliximab, or etanercept plus MTX) than with MTX alone.	Several new studies were found that supported this conclusion: adalimumab (Kimel, 2008 and Bejarano, 2008.), infliximab (Allaart, 2007). Additionally, one study supported this conclusion for a drug (rituximab) which had not previously been reviewed in by the CER (Mease, 2008).	No new information found.	One expert judged this conclusion still valid, stating: "New evidence exists but I don't have the references in mind."	Conclusion is possibly out of date and this portion of the CER may need updating, based on a new study about a previously included drug that had not been studied.
Key Question 3: For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects?				
No differences in tolerability were reported for leflunomide, MTX, and sulfasalazine. Discontinuation rates because of adverse events did not differ among leflunomide, MTX, or sulfasalazine.	No new evidence.	No new information found.	No opinions provided by experts.	Conclusion is still valid and this portion of the CER does not need updating.
Biologic DMARDs were generally well tolerated in efficacy studies. Injection site reactions were substantially higher in patients using anakinra than in patients on adalimumab or etanercept.	No new evidence.	No new information found.	One expert felt that this conclusion was no longer valid, stating: "Higher, yes, but not clear about SUBSTANTIALLY higher."	Conclusion is possibly out of date and this portion of the CER may need updating, based on diversity of expert opinion.
Combination studies involving two synthetic DMARDs, including sulfasalazine andMTX, vs. one DMARD showed no differences in withdrawal	One article was found supporting this conclusion (Allaart, 2007).	No new information found.	One expert stated that s/he did not know if this conclusion was still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; anti-TNF: anti-Tumor Necrosis Factor; ACR20/50/70: American College of Rheumatology 20/50/70-percent improvement criteria; DAS28: Disease Activity Score shortform;

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 OtherExperts	Conclusion from SC EPC
rates because of adverse events. Combination studies including prednisone with one or more DMARDs also had no differences in discontinuation rates between groups.				
Biologic combination vs. monotherapy: One RCT did not detect any synergistic effects of a combination treatment of etanercept and anakinra compared with etanercept monotherapy. The incidence of serious adverse events, however, was substantially higher with the combination treatment (14.8 percent vs. 2.5 percent; P = NR).	No new evidence.	No new information found.	One expert felt that this conclusion was still valid, stating: "Another study showed 7.3% serious infections vs. 4.3% (not sure of numbers but something like that) and also found that abatacept plus Tumor Necrosis Factor Inhibitors is associated with more serious infections."	Conclusion is possibly out of date and this portion of the CER may need updating based on diversity of reviewer opinion: one expert recalled studies that were not found on our targeted search.
A combination treatment of two biologic DMARDs can lead to substantially higher rates of severe adverse events than biologic DMARD monotherapy. The evidence, is limited to combinations of anakinra plus etanercept and abatacept plus anakinra, adalimumab, etanercept, or infliximab	No new evidence.	No new information found.	No opinions provided by experts.	Conclusion is still valid and this portion of the CER does not need updating.
No differences in adverse events were found between combinations of biologic and synthetic.	No new evidence.	No new information found.	One expert felt this conclusion was invalid, stating: "I'm not sure if this is mis-stated. Combination of biologics have a much higher rate of adverse events-i.e., infections-than combinations of synthetic DMARDS. This evidence was already present at the time the review was written." One expert did not know.	This conclusion should possibly be reworded to make clear exactly what comparisons are being made.
In general, no statistically significant differences in adverse events existed between combinations of biologic and synthetic DMARDs and synthetic DMARD monotherapy. Studies, however, were too small to assess reliably differences in rare but severe adverse events. An exception was a study with high-dose infliximab plus MTX therapy, which led to a statistically significantly higher rate of serious infections than MTX monotherapy.	Three clinical trials which did not find statistically significant differences (Allaart, 2007; Durez, 2007; Kay, 2008). The suggested article is a review from 2004 which was not a meta-analysis and did not meet criteria of the original CER (Khanna, 2004).	No new information found.	One reviewer felt this conclusion was out of date, stating: "This is true for clinical trials, but indirect comparisons and cohort studies show greater incidence of serious adverse events, mostly infections with biologic therapies." Another reviewer felt this conclusion was still valid, adding that he thought this was also true of CHF and providing a reference (Khanna, 2004).	Conclusion is probably out of date and this portion of the CER may need updating based on new data and diversity of expert opinion that might change the conclusion.

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 OtherExperts	Conclusion from SC EPC
Key Question 4: What are the comparative benefits and harms of drug therapies for rheumatoid arthritis and psoriatic arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities?				
No comparative evidence exists on psoriatic arthritis (PsA) for any drugs.	No new evidence.	No new information found.	One reviewer felt this conclusion was still valid, stating: "There is some weak evidence from cohort data that there are no differences. Not important enough to modify review I think" and provided a reference (Gratacos 2007). One reviewer did not know.	Conclusion is still valid and this portion of the CER does not need updating.
For RA the strength of evidence for age, sex, and comorbidities is very weak.	No new evidence.	No new information found.	No opinions provided by experts.	Conclusion is still valid and this portion of the CER does not need updating.
A combination of either adalimumab plus MTX or infliximab plus methotrexate in patients with early, aggressive RA who were methotrexate naive led to better clinical and radiographic outcomes than MTX monotherapy.	Two trials supporting this conclusion for infliximab were reported (Goekoop-Ruiterman, 2007; Allaart 2007) and two for adalimumab (Bejarano, 2008; Kimel, 2008).	No new information found.	One reviewer felt this conclusion was still valid, and noted that he though this evidence also existed for adalimumab.	Conclusion is still valid and this portion of the CER does not need updating.

Are there new data that could inform the key questions that might not be addressed in the conclusions?

One expert comments that some of our team members were involved in updating a lit scan (from 7/06 through 12/17/07) for Targeted Immune Modulators. This scan included 5 additional RCTS for rheumatoid arthritis, but only one head to head trial (DeFilippis LA et al etanercept vs. infliximab, N=32). There were 3 psoriatic arthritis studies but they were compared with placebo.

One expert comments that most of the new data relates to the use of other biologic therapies. The review will probably need to be updated in the near future for agents such as Rituximab, abatacept, and the new products currently being evaluated for approval.

Other findings from the targeted literature search:
Use of glucocorticoids:
- Intra-articular glucocorticoids in combination with MTX were better than MTX alone, at 52 weeks: ACR20 85% vs. 68% (p=0.02) ACR-N 80% vs. 54.5% (p=0.025); HAQ 0.3 vs. 0.4 (p<0.001); DAS28 not significant. Larsen score not significant. (Hetland 2006)
- MTX+infliximab superior to MTX+intravenous methylprednisone for reducing MRI-detected synovitis and bone edema. They had equivalent effects on ACR20,50,70 and remission at 52 weeks. (Durez 2007).

Risk of Acute Myocardial Infarction (AMI)
- A nested case-control analysis with cohort of 107,908 subjects found synthetic DMARDs (including MTX) were associated with reduced risk of AMI (RR 0.8). Glucocorticoids had increased risk. Biologic DMARDs had no effect (Suissa, 2006).

Step up vs. parallel therapy (addresses question in initial CER, page 7)
- Step up therapy (sulfasalazine, MTX, hydroxychloroquine) equally efficacious to parallel therapy in early rheumatoid arthritis (Saunders, 2008).
- Parallel therapy (sulfasalazine, MTX, prednisone) had faster onset then step up therapy (Allaart, 2007; Goekoop-Ruiterm, 2008).
- Parallel therapy (sulfasalazine, MTX, hydroxychloroquine, prednisolone) better than step up therapy (Makinen, 2007).

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Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions: EPC Investigator, 2 OtherExperts	Conclusion from SC EPC
Therapies not included in initial CER: -Tacrolimus (T cell inhibitor) superior to mizoribine (T cell blocker) with 28 week ACR20 of 48% compared to 10% (Kawai, 2006). - A 2 year RCT found ACR50 response in 40% of patients on Doxycycline+MTX compared to 12% patients on MTX alone (O'Dell, 2006).				

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CER 12. Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis

For this assessment, a limited literature search was conducted for the years 2005-2008. This search included the five generalist journals listed in the Methods and four specialty journals (as recommended by the subject matter experts): Bone; Journal of Bone Mineral Research; Osteoporosis International; and Endocrine Reviews. The search identified 549 titles, of which 160 were obtained in full text for further review. The remaining titles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance. Of the 160 selected for further review, 42 were abstracted into a table. The remaining articles were rejected because they had already been included in the earlier report or did not include a comparison of interest.

We consulted the project lead, four members of the TEP, and one of the peer reviewers for their assessment. Of these six individuals, four responded.

Table 2.10 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.10 CER 12. Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Are the conclusions still valid?

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
Key Question 1: What are the comparative benefits in fracture reduction among and also within the following treatments for low bone density: *** Bisphosphonate medications, specifically alendronate, risedronate, etidronate, ibandronate, pamidronate, and zoledronic acid.** *** Calcitonin.** *** Calcium.** *** Estrogen for women.** *** Parathyroid hormone (PTH).** *** Selective estrogen receptor modulators (SERMs), specifically raloxifene and tamoxifen.** *** Testosterone for men.** *** Vitamin D.** *** Combinations of above.** *** Exercise in comparison to above agents.**				
There is good evidence that alendronate, etidronate, ibandronate, risedronate, calcitonin, 1-34 PTH, and raloxifene prevent vertebral fractures.	No new evidence.	No new information.	Four experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
There is good evidence that risedronate and alendronate prevent both nonvertebral and hip fractures.	Pooled analysis of 8 RCTs found dose response of annual cumulative exposure to oral ibandronate and decrease in non-vertebral fracture (Cranney, 2008).	No new information.	Four experts agreed this conclusion is still valid.	Conclusion is possibly out of date and this portion of the CER may need updating due to addition of ibandronate.
There is good evidence that zoledronic acid prevents vertebral and nonvertebral fractures and fair evidence that it prevents hip fractures.	Once-a-year intravenous (iv) zoledronic acid prevented vertebral and non-vertebral fractures in post-menopausal women as well as new hip fractures in hip fracture patients in the HORIZON trial (Black, 2007).	No new information.	Three experts agreed this conclusion is still valid. One expert referred to HORIZON trial.	Conclusion is still valid and this portion of the CER does not need updating.
There is evidence from one RCT that 1-34 PTH prevents nonvertebral fractures.	Evidence from a meta-analysis that 1-34 PTH alone or in combination with bisphosphonates prevents nonvertebral fractures (Vestergard, 2007).	No new information.	Four experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
There is good evidence that estrogen is associated w/ a reduced incidence of vertebral, nonvertebral, and hip fractures.	No new evidence.	No new information.	Four experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
There are no data from RCTs on the effect of testosterone on prevention of fractures.	No new evidence.	No new information.	Four experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
There is good evidence that there is no difference between calcium alone and placebo in preventing vertebral, nonvertebral, hip, and wrist fractures in postmenopausal women.	Meta-analysis of 17 trials showed both calcium alone and calcium + vitamin D reduced incidence of fractures of all types (Tang, 2007).	No new information.	Three experts agreed this conclusion is still valid.	Conclusion is possibly out of date and this portion of the CER may need updating. The new meta-analysis should be assessed for quality, inclusion criteria, etc.
Vitamin D has varying effects on fracture prevention, depending on dose, analogs, and population.	No new evidence.	No new information.	Four experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Based on limited data from head-to-head trials, superiority for the prevention of fractures has not been demonstrated for any agent within the bisphosphonate class.	A study comparing etidronate with alendronate and risedronate found no difference in preventing first incidence of any fracture (Mamdani, 2007) Studies purporting to show superiority of one agent over others were equivocal.	No new information.	Four experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Based on limited data from head-to-head trials, superiority for the prevention of vertebral fractures has not been demonstrated for bisphosphonates in comparison with calcitonin, calcium, or raloxifene.	No new evidence.	No new information.	Three experts agreed this conclusion is still valid. One expert questions existence of head-to-head comparisons of calcitonin with other agents for fracture prevention.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
Based on six head-to-head RCTs, there was no difference in fracture incidence between bisphosphonates and estrogen.	No new evidence.	No new information.	Three experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Are there new data that could inform the key questions that might not be addressed in the conclusions? **SC-EPC Literature Search –** A RCT comparing alendronate with teriparatide for the treatment of glucocorticoid-induced osteoporosis found that fewer new vertebral fractures occurred in the teriparatide group than in the alendronate group (0.6% vs. 6.1%, P = 0.004); the incidence of nonvertebral fractures was similar in the two groups (5.6% vs. 3.7%, P = 0.36) (Saag, 2007). A RCT compared the use of risedronate, 75 mg twice monthly, with that of daily risedronate (n=1229 postmenopausal women) on the secondary outcome of new vertebral fractures. At 1 year follow-up, the incidence of new fractures was the same in both groups (1%) (Delmas, 2008). 1 RCT and pooled data from 2 other RCTs found Strontium ranelate prevents vertebral fractures; 2 RCTs found strontium ranelate prevents nonvertebral fractures, including hip. This drug is not FDA-approved for osteoporosis.				
Key Question 2: How does fracture reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), prior fractures (prevention vs. treatment), age, gender, glucocorticoid use, and other factors (e.g., community dwelling vs. institutionalized, vitamin D deficient vs. not)?				
Alendronate, etidronate, ibandronate, risedronate, teriparatide, & raloxifene reduce the risk of fractures among high-risk groups, including postmenopausal women w/ osteoporosis.	No new evidence.	No new information.	Three experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating
Calcitonin has been demonstrated to reduce the risk of fracture among postmenopausal women.	No new evidence.	No new information.	Three experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Raloxifene prevents fractures in postmenopausal women at low risk for fracture.	No new evidence.	No new information.	Three experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
The effect of estrogen on fracture prevention for women at low risk is uncertain.	No new evidence.	No new information.	Two experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
Calcitonin, risedronate, and teriparatide reduce the risk of fracture among men.	No new evidence.	No new information.	Three experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
In subjects treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate.	A RCT comparing alendronate with teriparatide for the treatment of glucocorticoid-induced osteoporosis found that fewer new vertebral fractures occurred in the teriparatide group than in the alendronate group (0.6% vs. 6.1%, P = 0.004); the incidence of nonvertebral fractures was similar in the two groups (5.6% vs. 3.7%, P = 0.36) (Saag, 2007).	No new information	Three experts agreed this conclusion is still valid. One expert cited a head-to-head comparison of alendronate and teriparatide (Saag, 2007).	Conclusion is still valid and this portion of the CER does not need updating.
There is good evidence that tamoxifen does not prevent fractures among women at risk for breast cancer.	No new evidence.	No new information.	Three experts said they cannot assess whether the conclusion remains valid.	Conclusion is still valid and this portion of the CER does not need updating.
Reduction in fracture risk for subjects treated with alendronate, risedronate, or vitamin D has been demonstrated in populations at increased risk for fracture due to conditions that increase the risk of falling, including stroke with hemiplegia, Alzheimer's disease, and Parkinson's disease.	No new evidence.	No new information.	Three experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Are there new data that could inform the key questions that might not be addressed in the conclusions?
SC-EPC Literature Search –
One RCT found 1-34 PTH prevents spinal and other clinical fractures in women with severely reduced renal function (Miller, 2007).

One RCT found alendronate prevents vertebral, hip, and wrist fractures among postmenopausal women with osteoporosis across all age groups; risk reduction was greater in older women and in women at higher risk for fracture (Hochberg, 2005).

One RCT found alendronate more effective in postmenopausal women (at low, medium, and high risk for fracture) with elevated bone turnover (Bauer, 2006).

One RCT found raloxifene prevention of vertebral fractures in postmenopausal women was not affected by age, smoking status, physical activity, prior fracture history, diabetes, previous use of HRT or thyroid hormone, use of statins, weight loss, BMI, or fracture-specific summary risk score (Ensrud, 2008).

Prevention of fractures in women with severe osteoporosis by alendronate, risedronate, or raloxifene was independent of BMI, follow-up duration, number of prior fractures, treatment

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
modality, use of calcium/vitamin D, and compliance (Adami, 2008).				
Key Question 3: What are the adherence and persistence to medications for the treatment and prevention of osteoporosis, the factors that affect adherence and persistence, and the effects of adherence and persistence on the risk of fractures?				
Only 10 fracture trials reported rates of adherence to therapy. Five trials of calcium reported low rates of adherence. In two studies of daily oral bisphosphonates, more than 80 percent of patients took at least 70 percent of the drug. The other three trials reported high rates of adherence with risedronate therapy.	No new evidence.	No new information.	One expert agreed this conclusion is still valid. One expert did not know. One expert stated "there may be new compliance trials that I do not know about."	Conclusion is still valid and this portion of the CER does not need updating.
There is evidence from 10 observational studies that real world adherence to therapy with alendronate, etidronate, risedronate, calcitonin, hormone replacement therapy (HRT), raloxifene, calcium, and vitamin D is poor among many postmenopausal women with osteoporosis.	No new evidence.	No new information.	Two experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
There is evidence from one observational study that adherence to therapy with alendronate and risedronate is poor in many chronic glucocorticoid users.	No new evidence.	No new information.	Two experts agreed the conclusion is still valid. One expert said that the conclusion is probably still valid, but does not know.	Conclusion is still valid and this portion of the CER does not need updating.
There is evidence from 12 observational studies that persistence with therapy with alendronate, etidronate, risedronate, calcitonin, HRT,	No new evidence.	No new information.	Two experts agreed the conclusion is still valid. One expert noted the conclusion is probably	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
raloxifene, calcium, and vitamin D is poor in many men and postmenopausal women with osteoporosis.			still valid but does not know.	
Based on evidence from observational studies, factors that affect adherence and persistence w/ medications include side effects of medications, absence of symptoms related to the underlying disease, comorbid conditions, ethnicity, socioeconomic status, & dosing regimens. Weekly users had higher persistence & adherence rates than daily users.	No new evidence.	4/22/08 New Dosage Regimen for ACTONEL (RISEDRONATE SODIUM) -approve the use of Actonel (risedronate sodium) 150 mg tablets as a once monthly dose to treat Postmenopausal Osteoporosis (PMO) (S-030).	Two experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
There is evidence from one RCT that postmenopausal women who are nonadherent to treatment with calcium have a higher risk of fracture than women who are adherent to therapy. There is evidence from RCTs and observational studies that postmenopausal women who are nonadherent to treatment with alendronate, risedronate, HRT, calcium, or calcitonin have a higher risk of fracture than women who are adherent to therapy. There is evidence from one observational study that postmenopausal women w/	An observational study showed that postmenopausal women who had poorer compliance with alendronate, risedronate, or raloxifene had an increased risk of fracture (Adami, 2006); however another observational study of women with severe osteoporosis found no association (Adami, 2008). One randomized controlled trial showed that postmenopausal women who persist with alendronate after 5 years prior treatment have lower risk of clinical vertebral fractures (Black, 2006); and another randomized controlled trial showed that persistence with risedronate results in lower risk for new vertebral fractures (Watts, 2008). Evidence from one RCT that lack of persistence with raloxifene after 4 years did not affect overall	No new information.	One expert agreed the conclusion is still valid. One expert responded that the conclusion is probably still valid but does not know. One expert said “Do Not Know - Not sure if there are new compliance trials.”	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
osteoporosis who are nonpersistent w/ alendronate and risedronate therapy have a higher risk of fracture than women persistent w/ these medications.	risk of nonvertebral fracture except among women at high risk (prevalent vertebral fracture) (Siris, 2005).			
Key Question 4: What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?				
There is good evidence that there are no differences in the rates of serious cardiac events among bisphosphonates, calcium, vitamin D, calcitonin, PTH, and placebo.	No new evidence.	No new information.	Three experts referred to findings below regarding atrial fibrillation (AF).	Conclusion is still valid and this portion of the CER does not need updating.
A significant increase in the risk of AF for zoledronic acid relative to placebo has been reported in one large RCT but not in another. A trend toward increased risk for alendronate relative to placebo has been reported in a single large RCT.	One population-based case control study in Denmark found no greater "ever use" of bisphosphonates among AF patients (Sorensen, 2008) but a population-based case control study of women in the US did find increased ever use of alendronate (Heckbert, 2008).	No new information.	One expert agreed the conclusion is still valid. One expert cites the HORIZON trial, which showed more episodes of serious AF in those treated with zoledronic acid than placebo, although mechanism not clear [Note: this study was included in the original CER and it did not show a difference in serious AF (Lyles, 2007)]. One expert cites the same 2 case-controlled studies (by Sorensen (2008) and by Heckbert (2008) as found in the SCEPC literature search.	Conclusion is possibly out of date and this portion of the CER may need updating due to new evidence and difference in expert opinion.

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
			One expert cites an increased risk of serious AF with some bisphosphonates (same references as above). One expert notes that observational case-control studies have reported conflicting data for alendronate.	
Relative to placebo, Raloxifene has an increased pooled risk for pulmonary embolism (PE), thromboembolic events, and mild cardiac events (including chest pain, palpitations, tachycardia, and vasodilation). Relative to placebo, the risk of PE for tamoxifen was elevated in one trial; the risk of thromboembolic events did not differ in this trial.	One randomized controlled trial of bazedoxifene vs. raloxifene among healthy postmenopausal women found an increased risk of vasodilation, leg cramps, and venous thromboembolism for both (Silverman, 2008).	No new information.	Three experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
In three placebo-controlled trials of estrogen that reported cerebrovascular accident, estrogen participants had higher odds than did participants who took a placebo. In the two trials that compared an estrogen-progestin combination with placebo, the combination participants had greater odds of stroke than did placebo patients. When four estrogen studies reporting thromboembolic events were pooled, estrogen participants had greater odds of reporting them than did placebo	No new evidence.	No new information.	Three experts agreed this conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
participants. Similar results were found when three studies comparing an estrogen-progestin combination with placebo were pooled.				
Esophageal ulcerations were reported in trials of all the bisphosphonates except zoledronic acid. The only significant difference from placebo was found in one trial in which etidronate participants had higher odds of esophageal ulcers.	No new evidence.	No new information.	Three experts agreed this conclusion is still valid. One expert did not know if the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Perforations, ulcerations, and bleeds (PUBs) were reported in trials of all the bisphosphonates except zoledronic acid. Etidronate participants had higher odds of PUBs than did placebo participants in three pooled studies. In two pooled trials of oral daily ibandronate, treated participants had lower odds of PUBs than did placebo participants.	No new evidence.	No new information.	Three experts agreed the conclusion is still valid. One expert responded the conclusion is probably still valid but did not know.	Conclusion is still valid and this portion of the CER does not need updating
We categorized conditions such as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as “mild upper gastrointestinal (GI) events.” Etidronate users had showed greater odds than for placebo participants. Pooled trials of pamidronate also showed greater odds for drug users than for placebo. Our pooled analyses found no difference between alendronate, ibandronate, risedronate, or zoledronic acid and placebo regarding	One study of postmenopausal women found 1-34 PTH increased risk for nausea (Greenspan, 2007).	No new information.	Three experts agreed the conclusion is still valid. One expert responded that the conclusion is probably still valid but did not know.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
mild upper GI events.				
In contrast, alendronate participants had higher odds of mild upper GI events than did etidronate participants in three pooled head-to-head trials. Alendronate participants also had higher odds of mild upper GI events in four head-to-head trials vs. calcitonin and four head-to-head trials vs. estrogen. Etidronate participants had higher odds of mild upper GI events in three head-to-head trials vs. estrogen.	A head-to-head comparison of raloxifene vs. alendronate found that diarrhea, nausea, and the need for a colonoscopy were greater in the alendronate group (Recker., 2007).	No new information.	Three experts agreed the conclusion is still valid. One expert responded that the conclusion is probably still valid but did not know.	Conclusion is still valid and this portion of the CER does not need updating.
Risedronate participants had lower odds of musculoskeletal events than did placebo participants in nine pooled trials. In three pooled trials, zoledronic acid participants had higher odds of these events than did placebo participants. In two head-to-head trials,[259, 354] alendronate participants had greater odds of these events than did participants taking PTH.	No new evidence.	FDA Safety Alert (1/7/08) "Highlight the possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in patients taking bisphosphonates" i.e. Alendronate, Risedronate, Etidronate, Ibandronate, Pamidronate, and Zoledronic Acid.	Two experts agreed the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
In five pooled trials of estrogen vs. placebo, estrogen participants had lower odds of breast cancer. Conversely, in three pooled studies of estrogen-progestin combination vs. placebo, treatment participants had higher odds of breast cancer.	No new evidence.	No new information.	Two experts agreed the conclusion is still valid. One expert was not sure whether the conclusion is still valid. One expert responded that the conclusion is probably still valid but	Conclusion is still valid and this portion of the CER does not need updating..

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
			did not know.	
One estrogen-progestin study showed that treated participants had lower odds of colon cancer than did placebo participants.	No new evidence.	No new information.	Two experts agreed the conclusion is still valid. One expert responded that the conclusion is probably still valid but did not know.	Conclusion is still valid and this portion of the CER does not need updating.
In three pooled studies of tamoxifen vs. placebo, tamoxifen participants had lower odds of breast cancer. Differences between raloxifene and placebo were not significant.	No new evidence.	Raloxifene is now FDA-approved for breast cancer prevention.	One expert agreed the conclusion is still valid. One expert was not sure if the conclusion is still valid. One expert noted that raloxifene is now FDA-approved for breast cancer prevention.	Conclusion is out of date and this portion of the CER needs updating due to raloxifene being approved for breast cancer prevention.
Estrogen participants had more gynecological problems (such as uterine bleeding) than placebo participants. The same was true for users of estrogen-progestin combination in three pooled trials. In three pooled trials, tamoxifen participants had greater odds of gynecological problems than did placebo patients.	No new evidence.	No new information.	Two experts agreed the conclusion is, still valid. One expert was not sure if the conclusion is still valid. One expert agreed that the conclusion is probably still valid but did not know.	Conclusion is still valid and this portion of the CER does not need updating.
Osteosarcoma was reported in only one study, a head-to-head trial of raloxifene vs. tamoxifen; differences between groups were not significant.	One case report described identification of osteosarcoma in the postmortem of a postmenopausal woman who had been taking PTH for osteoporosis and who died of cancer (Harper et al., 2007).	FDA Safety Alert (7/29/08) reported increased incidence of osteosarcoma in rats given teriparatide.	One expert agreed the conclusion is still valid. One expert responded that the conclusion is no longer valid: One reported case of osteosarcoma in human	Conclusion is possibly out of date and this portion of the CER may need updating due to new evidence and difference in expert opinion.

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator, 2 TEP Members, 1 Other Expert	Conclusion from SC EPC
			taking PTH – unclear if related to PTH One expert did not know.	
There are no data from osteoporosis trials that describe an association between bisphosphonates and the development of osteonecrosis. In case reports and case series articles, we found many cases of osteonecrosis of the jaw in cancer patients taking intravenous bisphosphonates. Cases involved pamidronate, zoledronic acid, and alendronate.	No new evidence.	No new information.	Two experts judge the conclusion is still valid. One expert states that data from Horizon trial provides info on osteonecrosis of the jaw. This trial was included in the original CER. There was one case in the placebo group and one in the treatment group – both cases resolved with surgery.	Conclusion is still valid and this portion of the CER does not need updating.
Are there new data that could inform the key questions that might not be addressed in the conclusions? **SC-EPC Literature Search –** One RCT of 1-34 PTH found an increased risk for hypercalciuria and hypercalcemia (Greenspan, 2007); another RCT in women with renal impairment found a decrease in mean glomerular filtration rate (Miller, 2007). 12/11/07 AREDIA (PAMIDRONATE DISODIUM) Labeling Revision - Add Warning: Deterioration in Renal Function Calcium+Vitamin D increased the risk of renal calculi among postmenopausal women at low risk for osteoporosis (Jackson, 2006). 3/20/08 Zometa (ZOLEDRONIC ACID) Patient Population Altered - approve the use of Zometa in pediatric patients with severe osteogenesis imperfecta.				

Legend: AF: atrial fibrillation; PE: pulmonary embolism; PTH: parathyroid hormone; PUBs: perforations, ulcerations, and bleeds; SERM: selective estrogen receptor modulator.

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CER 13. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer

For this assessment, a limited literature search was conducted for the years 2006-2008. This search included the five generalist journals listed in the Methods; and three specialty journals (as recommended by the subject matter experts): Journal of Urology, Journal of Clinical Oncology, and Cancer. The search identified 540 titles, of which 16 were obtained in full text for further review. The remaining titles were rejected because they were editorials, letters, or non-systematic reviews, or did not include topics of relevance. Of the 16 selected for further review, 11 were abstracted. The remaining articles were rejected because they had already been included in the earlier report or did not include a comparison of interest. An additional 7 articles suggested by the experts were also reviewed and included.

We consulted the project lead as well as three members of the TEP and two additional subject matter experts. Of these six individuals, five responded.

Table 2.11 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the SCEPC regarding the need for update.

Table 2.11 CER 13. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer: Are the conclusions still valid?

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 2 TEP Members 1 Other Expert	Conclusion from SC EPC
Key Question 1: What are the comparative risks, benefits, short- and long-term outcomes of the following therapies for clinically localized prostate cancer (e.g., Radical prostatectomy, including perineal and retropubic approaches, and open vs. laparoscopic vs. no lymphadenectomy, External beam radiotherapy, including standard therapy, and therapies designed to decrease exposure to normal tissues such as 3D conformal radiation therapy and Intensity Modulated Radiation Therapy, Interstitial brachytherapy, Cryosurgery, Expectant management ("watchful waiting"), and Hormonal therapy as primary therapy, adjuvant or neoadjuvant to other therapies)?				
No one therapy can be considered the preferred treatment for localized prostate cancer patient must make trade offs between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decision making. Patient satisfaction with therapy is high and associated with several clinically relevant outcome measures.	An observational cohort using Surveillance, Epidemiology and End Result (SEER) data from 44,630 patients (32, 022 receiving treatment, 12,607 in the observation group) found, at 12 years of follow up, that active treatment was associated with significantly better survival (adjusted hazard ratio [HR] of 0.69, 95% CI 0.66-0.72). Adjusted HR for specific treatment: radical prostatectomy 0.50 (91% CI 0.47- 0.53); radiation 0.81 (95% CI 0.78-0.85) (Wong, 2006). In the Scandinavian Prostate Cancer Group Study #4, 695 men with clinically localized prostate cancer were randomized to prostatectomy or watchful waiting (WW). At 12 years of follow up, the relative risk of death was decreased in the prostatectomy group: 0.65 (95% CI 0.45, 0.93); and there was a similar reduction in distant metastases (Bill-Axelson, 2008).	Not applicable.	Four experts agreed that a 12-year update of a previously included randomized trial of surgery versus watchful waiting (WW) is consistent with the original findings although it offers longer follow-up. While useful to describe, it is unlikely to dramatically alter findings (Bill-Axelson, 2008).	Conclusion is possibly out of date and this portion of the CER may need updating due to longer term follow up data.
Compared with men who used WW, men with clinically localized prostate cancer detected by methods other than prostate specific antigen (PSA) testing and treated with radical prostatectomy (RP) experienced fewer deaths from prostate cancer, marginally fewer deaths from any cause, and fewer distant metastases.	At 12 years follow-up, in the Scandinavian Prostate Cancer Group Study #4, the relative risk of death was decreased in the prostatectomy group: 0.65 (95% CI 0.45, 0.93); and there was a similar reduction in distant metastases (Bill-Axelson, 2008).	Not applicable.	One expert noted that the P value for overall survival is no longer statistically significant, although there are trends towards a benefit. No benefit was seen in men aged > 65 for overall, disease-specific survival or metastases. Another expert referred to Bill-Axelson, 2008.	Conclusion is probably out of date and this portion of the CER may need updating based on longer follow up data in the original study and expert opinion.

Legend: ADT: androgen deprivation therapy; EBRT: external beam radiotherapy; ED: erectile dysfunction; IMRT: intensity modulated radiation therapy; PIVOT Trial: Prostate cancer Intervention Versus Observation Trial; PSA: prostate specific antigen; RCT: randomized controlled trial; RP: radical prostatectomy; WW: watchful waiting

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 2 TEP Members 1 Other Expert	Conclusion from SC EPC
Radical prostatectomy vs. external beam radiotherapy (EBRT). One small older trial indicated that, compared with EBRT, RP was more effective in preventing progression, recurrence, or distant metastases in men with clinically localized prostate cancer detected by methods other then PSA testing.	An observational cohort (1,618 patients who received surgery, 702 who received external beam radiation, and 114 in the observation group) that found that, at 13 years of follow up, prostate cancer mortality among patients with clinically localized cancer was 2.2-3.8 times higher in patients receiving EBRT than in patients receiving surgery (Albertsen, 2007).	Not applicable.	One expert called attention to Albertsen, 2007, an observational population-based cohort "study, which showed a survival benefit to surgery over EBRT in certain risk groups. However, these are level II data."	Conclusion is possibly out of date and this portion of the CER may need updating based on new data that may change the conclusion.
The addition of neoadjuvant hormonal therapy to RP did not improve survival or cancer recurrence rates, defined by PSA recurrence, but increased AEs.	No new evidence.	Not applicable.	No expert response.	Conclusion is still valid and this portion of the CER does not need updating.
It is not known if using higher doses of EBRT by increasing either the total amount or type of radiation (e.g., via high-dose intensity modulated or proton beam or by adding brachytherapy) improves overall or disease-specific survival compared with other therapies. No EBRT regimen, whether conventional, high-dose conformal, dose fractionation, or hypofractionation, was superior in reducing overall or disease-specific mortality.	No new evidence.	Not applicable.	One expert agreed there was no new evidence. Two experts responded that they do not know. One cited two RCTs (Pollack, 2002 and Zietman, 2005), that demonstrated that higher dose radiation may decrease risk of PSA recurrence, which may change this conclusion. [Note: Both of these studies were included in the original CER] The other responded, "There are certainly no new level I trials showing that higher doses of EBRT are more effective than lower doses but the weight of observational cohorts and what appears to be better survival curves with more contemporary cohorts seem to favor higher doses being more effective, although the data are by no means conclusive in my opinion. However, I am reluctant to endorse the conclusion because, while the wording states 'it is not known,' this could be interpreted as 'it is unlikely that.' "	Conclusion is probably out of date and this portion of the CER may need updating based on new evidence and expert opinion.

Legend: ADT: androgen deprivation therapy; EBRT: external beam radiotherapy; ED: erectile dysfunction; IMRT: intensity modulated radiation therapy; PIVOT Trial: Prostate cancer Intervention Versus Observation Trial; PSA: prostate specific antigen; RCT: randomized controlled trial; RP: radical prostatectomy; WW: watchful waiting

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 2 TEP Members 1 Other Expert	Conclusion from SC EPC
Androgen deprivation therapy (ADT) combined with external beam radiotherapy (EBRT) (ADT + EBRT) may decrease overall and disease-specific mortality but increase adverse events (AEs) compared with EBRT alone in high-risk patients defined by PSA levels and Gleason histologic score. One RCT found that conformal EBRT combined with 6 months of ADT reduced all-cause mortality, disease-specific mortality, and PSA failure compared with conformal EBRT alone after a median followup of 4.5 years. There were significant increases in gynecomastia and impotence in the ADT + EBRT group compared with EBRT alone.	A RCT of 206 patients found, at a median of 7.6 years of follow up, that men receiving radiation therapy alone had a significant increase in overall mortality (HR = 1.8, 95% CI 1.1, 2.09) compared to men receiving radiation therapy plus androgen deprivation therapy. The effect was most pronounced in men with no or minimal comorbidities (D'Amico., 2008).	Not applicable.	Two experts agreed that the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
One small trial comparing different doses of supplemental EBRT, 20 Gy vs. 44 Gy, adjuvant to brachytherapy (103Pd) implant found no significant differences in the number of biochemical failure events and freedom from biochemical progression at 3 years. Preliminary results from one small trial comparing ^{125}I with ^{103}Pd brachytherapy found similar biochemical control at 3 years. There was a trend toward more radiation proctitis, defined as persistent bleeding, with ^{125}I.	No new evidence.	Not applicable.	Three experts agreed that the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
ADT with bicalutamide alone or in addition to RP or EBRT did not reduce cancer recurrence or mortality.	No new evidence.	Not applicable.	Three experts agreed that the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
When adjusting for baseline factors, erectile dysfunction (ED) was greater with RP compared to EBRT.	A prospective cohort study assessed 1201 patients at baseline and after receipt of radical prostatectomy, brachytherapy, or external beam radiation therapy. Distinct patterns-of-life changes were associated with each treatment; each affected sexuality, but patients receiving prostatectomy had greater decreases in sexuality and in spousal distress. Nerve-sparing operations were associated with better recovery of sexual function than procedures that were not nerve sparing (Sanda, 2008).	Not applicable.	One expert responded that it is likely there are additional population-based studies though these studies are unlikely to change the findings. One expert responded that recovery of sexual function depends on whether surgery was nerve-sparing or non-nerve-sparing (Sanda, 2008). One expert noted that he did not know, and added: "This is true up to 5 years after diagnosis, but it is difficult to say whether or not	Conclusion is possibly out of date and this portion of the CER may need updating based on a diversity of expert opinion.

Legend: ADT: androgen deprivation therapy; EBRT: external beam radiotherapy; ED: erectile dysfunction; IMRT: intensity modulated radiation therapy; PIVOT Trial: Prostate cancer Intervention Versus Observation Trial; PSA: prostate specific antigen; RCT: randomized controlled trial; RP: radical prostatectomy; WW: watchful waiting

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 2 TEP Members 1 Other Expert	Conclusion from SC EPC
			this is true beyond this. You need to put a time reference on this conclusion."	
No randomized trials evaluated cryosurgery and the majority of reports included patients with T3-T4 stages. Overall or prostate-cancer-specific survival was not reported. Progression-free survival in patients with T1-T2 stages ranged from 29 to 100 percent. AEs were often not reported but, when described, included bladder outlet obstruction (3 to 21 percent), tissue sloughing (4 to 15 percent), and impotence (40 to 100 percent). Outcomes may be biased by patient and provider characteristics.	Bill-Axelson study was summarized above (Bill-Axelson, 2008).	Not applicable.	One expert advised referring to Bill-Axelson, 2008 for updated analysis of the Scandinavian trial.	Conclusion is possibly out of date and this portion of the CER may need updating based on longer follow-up data from a seminal RCT.
Three reviews estimated the effectiveness and AEs of laparoscopic and robotic assisted prostatectomy. Median followup was 8 months. Laparoscopic RP had longer operative time but lower blood loss and improved wound healing compared with open retropubic RP. Results from eight nonrandomized reports suggested that total complications, continence rates, positive surgical margins, and operative time were similar for robotic assisted and open RP. Median length of hospital stay and median length of catheterization were shorter after robotic assisted RP than open RP.	An analysis of Medicare claims data (n=2702) of men undergoing minimally invasive prostatectomy or open prostatectomy found fewer perioperative complications in patients undergoing minimally invasive procedures (30% vs. 36 %) but higher rates of salvage therapy (28% vs. 9%) (Hu, 2008).	Not applicable.	One expert responded that new information is likely available from case series. Two experts cited a study that demonstrated higher risk of secondary therapies for patients undergoing minimally invasive RP (Medicare analysis) (Hu, 2008). One of these experts also cited reports from Europe indicating that, at least in pT3 patients, margin positive rates are higher in the laparoscopic group. [Note: We did not find this study in our limited literature search]	Conclusion is probably out of date and this portion of the CER may need updating based on new evidence and expert opinion.
There was no direct evidence that Intensity Modulated Radiation Therapy (IMRT) results in better survival or disease-free survival than other therapies for localized prostate cancer. Based on nonrandomized data, the absolute risks of clinical and biochemical outcomes (including tumor recurrence), toxicity, and quality of life after IMRT are comparable with conformal radiation. There is low-level evidence that IMRT provides at least as good a radiation dose to the prostate with less radiation to the surrounding tissues compared with conformal	No new evidence.	Not applicable.	One expert noted that there have been no RCTs. A meeting will be held with AHRQ this summer to consider planning a prospective cohort study to evaluate IMRT.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: ADT: androgen deprivation therapy; EBRT: external beam radiotherapy; ED: erectile dysfunction; IMRT: intensity modulated radiation therapy; PIVOT Trial: Prostate cancer Intervention Versus Observation Trial; PSA: prostate specific antigen; RCT: randomized controlled trial; RP: radical prostatectomy; WW: watchful waiting

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 2 TEP Members 1 Other Expert	Conclusion from SC EPC
radiation therapy.				
There were no data from randomized trials comparing HIFU (High Intensity Focused Ultrasound) with other primary treatment options. Biochemical progression-free survival rates of 66 to 87 percent and negative biopsy rates of 66 to 93 percent were reported from noncontrolled studies. The absolute risk of impotence and treatment-related morbidity appeared to be similar to other treatments. Followup duration was <10 years.	No new evidence.	Not applicable.	Two experts noted that the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Bother due to dripping or leaking of urine was more than six-fold greater in RP-treated men than in men treated with EBRT after adjusting for baseline factors. In a subgroup of men ages 70 and over, bother due to urine, bowel, or sexual dysfunction was 5.1, 2.4, and 2.8 times higher, respectively, for aggressive (RP/EBRT) vs. conservative (WW/ADT) therapy. Satisfaction with treatment was high, with less than 5 percent reporting dissatisfaction, unhappiness, or feeling terrible about their treatment, although the highest percent was among those treated with RP.	A prospective cohort study assessed quality-of-life domains in 1,201 patients and 625 spouses and reported distinct quality-of-life changes for different prostate cancer treatments (Sanda, 2008).	Not applicable.	One expert said that it is likely there are new case series and population-based cohort studies that might refine the estimates, although it has been only 1 year or so since the original CER was completed. One expert said that the difference between EBRT and RP in terms of dripping or leaking urine may not be as great as expressed here, especially with longer-term follow-up, and cited as examples Sanda, 2008 and Miller DC, et al, J Clin Oncol, 2005 (Miller, 2005).	Conclusion is possibly out of date and this portion of the CER may need updating based on expert opinion.
Key Question 2: How do specific patient characteristics, e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences (e.g., tradeoff of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these therapies, overall and differentially?				
No RCTs reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity, and most did not provide baseline racial characteristics. Available data were largely from case series. Few studies reported head-to-head comparisons, and there was limited adjustment for confounding factors. Modest treatment differences reported in some nonrandomized studies have not been consistently reported in well-powered studies. There was little evidence of a differential effect of treatments based on age. While differences	No new evidence.	Not applicable.	One expert stated that there was no new evidence. An RCT in the U.S. comparing surgery to watchful waiting in patients in whom prostate cancer was detected primarily by PSA and enrolling approximately 30% African-Americans is scheduled for completion in early 2010. One expert cited Bill-Axelson, 2005 (included in original report) and Bill-Axelson, 2008. As described above, the latter reports data from Scandinavian RCT that suggests strongly that	Conclusion is possibly out of date and this portion of the CER may need updating based on difference in expert opinion.

Legend: ADT: androgen deprivation therapy; EBRT: external beam radiotherapy; ED: erectile dysfunction; IMRT: intensity modulated radiation therapy; PIVOT Trial: Prostate cancer Intervention Versus Observation Trial; PSA: prostate specific antigen; RCT: randomized controlled trial; RP: radical prostatectomy; WW: watchful waiting

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 2 TEP Members 1 Other Expert	Conclusion from SC EPC
exist in the incidence and morbidity of prostate cancer based on patient age and there are differences in the treatments offered to men at different age ranges, few studies directly compared the treatment effects of different therapies across age groups. Most RCTs did not have age exclusion criteria. The mean/median age ranged from a low of 63 years for trials of RP to 72 years for trials of EBRT. Only one RCT provided subgroup analysis according to age. Results suggest that survival benefits of RP compared with WW may be limited to men under 65 years of age. Practice patterns from observational studies show that RP is the most common treatment option in younger men with localized prostate cancer.			benefits of local therapy are concentrated among men <65 years. One expert agreed that the conclusion is still valid.	
Key Question 3: How do provider/hospital characteristics affect outcomes overall and differentially (e.g., geographic region and volume)?				
Results from national administrative databases and surveys suggested that provider/hospital characteristics, including RP procedure volume, physician specialty, and geographic region, affect outcomes. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels.	No new evidence.	Not applicable.	One expert said that there is at least 1 study assessing volume and outcomes for radiation therapy and 1-2 additional studies for surgery. (Note: See below)	Conclusion is still valid and this portion of the CER does not need updating.
Surgeon RP volume was not associated with RP-related mortality and positive surgical margins. However, the relative risk of surgery-related complications adjusted for patient age, race, and comorbidity and for hospital type and location was lower in patients treated by higher volume surgeons. Urinary complications and incontinence were lower for patients whose surgeons performed more than 40 RPs per year. The length of hospital stay was shorter in patients operated on by surgeons who performed more RPs per year.	A cohort study of 7,765 prostate cancer patients treated with radical prostatectomy from 72 surgeons at major academic medical centers found a steep learning curve that did not plateau until approximately 250 operations had been performed. (Vickers, 2007).	Not applicable.	One expert noted that there is at least 1 study assessing volume and outcomes for radiation therapy and 1-2 additional studies for surgery. One expert said that recent data suggest that surgeon volume is also associated (inversely) with prostate cancer PSA and recurrence after radical prostatectomy (Vickers, 2007). One expert said he was not sure he agrees with this conclusion. “Specifically, I believe that there are now data from the Memorial group that volume correlates with margin status. However, everything else is true.”	Conclusion is probably out of date and this portion of the CER may need updating based on difference in expert opinion.

Legend: ADT: androgen deprivation therapy; EBRT: external beam radiotherapy; ED: erectile dysfunction; IMRT: intensity modulated radiation therapy; PIVOT Trial: Prostate cancer Intervention Versus Observation Trial; PSA: prostate specific antigen; RCT: randomized controlled trial; RP: radical prostatectomy; WW: watchful waiting

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 2 TEP Members 1 Other Expert	Conclusion from SC EPC
Surgery-related mortality and late urinary complications were lower and length of stay was shorter in hospitals that performed more RPs per year. Hospital readmission rates were lower in hospitals with greater volume. Teaching hospitals had a lower rate of surgery-related complications and higher scores of operative quality. Several studies found differences in treatment and outcome based on whether the patient was seen in an HMO (health maintenance organization) or fee-for-service organization and whether the patient was a Medicare beneficiary. Variability in the use of ADT was more attributable to individual differences among urologists than tumor or patient characteristics.	An analysis of SEER data for 82, 735 men with prostate cancer found use of ADT by urologists varied by characteristics of the urologist (Shahinian 2007).	Not applicable.	One expert noted that there is at least 1 study assessing volume and outcomes for radiation therapy and 1-2 additional studies for surgery. One expert also cited Shahinian, 2007 for additional details regarding ADT use among urologists.	Conclusion is possibly out of date and this portion of the CER may need updating based on expert opinion.
Key Question 4: How do tumor characteristics, e.g., Gleason score, tumor volume, screen vs. clinically detected tumors, and PSA levels, affect the outcomes of these therapies, overall and differentially?				
Little data exists on the comparative effectiveness of treatments based on PSA levels, histologic score, and tumor volume to identify low-, intermediate-, and high-risk tumors. We focused on baseline PSA levels and Gleason histologic score. The natural history of PSA-detected tumors is not known because few men remain untreated for a long period. One report assessed 20-year outcomes in the U.S. from men with prostate cancer detected prior to PSA testing and treated with WW. Histologic grade was associated with overall and prostate-cancer-specific survival. Men with low-grade prostate cancers had a minimal risk of dying from prostate cancer. Men with high-grade prostate cancers had a high probability of dying from their disease within 10 years of diagnosis, regardless of their age at diagnosis. Estimates from large ongoing screening trials suggest that PSA increases the time of detection by 5-15 years. Therefore, it is likely that men with PSA-detected tumors will have	No new evidence.	Not applicable.	Two experts agreed that the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.

Legend: ADT: androgen deprivation therapy; EBRT: external beam radiotherapy; ED: erectile dysfunction; IMRT: intensity modulated radiation therapy; PIVOT Trial: Prostate cancer Intervention Versus Observation Trial; PSA: prostate specific antigen; RCT: randomized controlled trial; RP: radical prostatectomy; WW: watchful waiting

Conclusions From CER Executive Summary	Summary of SC EPC Literature Search	FDA/Health Canada Info	Expert Opinions EPC Investigator 2 TEP Members 1 Other Expert	Conclusion from SC EPC
better 20-year disease-specific survival than this cohort.				
Based on very limited nonrandomized trial data, disease-specific survival was similar for men treated with EBRT or with RP in men with baseline PSA >10 ng/ml. Men with Gleason scores 8-10 were more likely to have biochemical recurrence than men with Gleason scores 2-6, regardless of type of treatment.	No new evidence.	Not applicable.	Two experts agree that the conclusion is still valid.	Conclusion is still valid and this portion of the CER does not need updating.
Are there new data that could inform the key questions that might not be addressed in the conclusions? Results of the longstanding PIVOT Trial should be available relatively soon, which will be the largest and most informative trial fo screening in the US and can be expected to influence the "expected management/watchful waiting" aspect of the CER. (Wilt, 2009)				

Legend: ADT: androgen deprivation therapy; EBRT: external beam radiotherapy; ED: erectile dysfunction; IMRT: intensity modulated radiation therapy; PIVOT Trial: Prostate cancer Intervention Versus Observation Trial; PSA: prostate specific antigen; RCT: randomized controlled trial; RP: radical prostatectomy; WW: watchful waiting

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ATTACHMENT II – Evidence Tables

CER 1 - Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
Key Question 1: What is the evidence of the comparative effectiveness of medical, surgical, and endoscopic treatments for improving objective and subjective outcomes in patients with chronic GERD?			
Medical therapy with PPIs and surgery (fundoplication) appeared to be similarly effective for improving symptoms and decreasing esophageal acid exposure. 10 percent to 65 percent of surgical patients still require medications. The limited data available did not support a significant benefit of fundoplication compared with medical therapy for preventing Barrett's esophagus or esophageal adenocarcinoma.	Yes	New Evidence: a) Multicenter RCT comparing laparoscopic antireflux surgery (LARS) vs esomeprazole were similarly effective and well-tolerated over 3 years.	b) Lundell, 2008 Gut
Of the three nonrandomized studies that compared an endoscopic procedure with laparoscopic fundoplication in patients with GERD documented by pH or	**Yes**	New Evidence: a) Comparison of endoscopic with laparoscopic fundoplication. Nonrandomized prospective study of 51 pts with persistent GERD comparing transesophageal endoscopic plication (TEP) with	a) Mahmood, 2006 AJG b) Domagk 2006 AJG

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
endoscopy, the longest followup was 8 months, and all three studies had significant bias that may invalidate the results. Two studies reported that more patients treated with laparoscopic fundoplication were satisfied with their results compared with those who had EndoCinchTM. One of these studies and a study of StrettaÒ also found less need for PPIs in patients who had fundoplication. Comparison of medical treatments with endoscopic procedures.		laparoscopic Nissen fundoplication (LNF) finds both techniques improved symptom score, acid regurgitation, quality of life, and reduced requirement for PPIs. Control of heartburn and acid reflux was better for LNF. TEP, like LNF, had comparable safety and efficacy. b) RCT comparing endoluminal gastroplasty (EndoCinch) with polymer injection (Enteryx) over 6 months demonstrates equal effectiveness in reducing PPI dosages and improving symptoms of pts.	
There was no head-to-head comparison of medical treatments with endoscopic treatments.	Yes	New Evidence: None	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
PPIs were superior to H2RAs in resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks. There was no difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for relief of symptoms at 8 weeks. No significant difference was found in the comparisons of esomeprazole 40 mg with lansoprazole 30 mg or pantoprazole 40 mg for relief of symptoms at 4 weeks. Similarly, there was no difference in the comparison of esomeprazole 20 mg with omeprazole 20 mg in relief of symptoms at 4 weeks.	**No**	New Evidence: a) Meta-analysis performed of 10 studies comparing rates of endoscopic healing, symptom relief, and adverse events of esomeprazole versus alternative PPIs in treatment of erosive esophagitis. Esomeprazole demonstrated a statistically significant improvement, but only modest clinical benefit in improved healing of erosive esophagitis at 8-weeks. Found no evidence of what is believed to be "clinically meaningful improvement in symptom relief" between PPIs b) Systematic review of RCTs in pts with reflux esophagitis demonstrates esomeprazole consistently has higher healing rates when compared with standard dose PPIs at 4 and 8 weeks. c) RCT of pts with erosive esophagitis comparing PPI maintenance therapy demonstrates esomeprazole 20 mg qday more effective than lansoprazole 15 mg qday in maintaining endoscopic/symptomatic mission in pts with healed erosive esophagitis d) RCT of GERD pts demonstrates famotidine 20 mg BID and omeprazole 20 mg qday were both effective in improving GERD symptoms, particularly non-erosive GERD disease over a period of 8 weeks. e) RCT of pts with erosive esophagitis demonstrates esomeprazole 40 mg super to pantoprazole 40 mg for healing of erosive esophagitis and providing resolution of associated heartburn at 4 and 8-weeks. f) RCT of pts with healed erosive esophagitis demonstrates esomeprazole 20 mg superior to pantoprazole 20 mg for maintenance therapy following healed erosive esophagitis and relief of GERD	a) Gralnek, 2006 CGH b) Edwards 2006 APT c) Devault 2006 CGH d) Wada, 2006 APT e) Labenz, 2005 APT f) Labenz, 2005 APT g) Fujiwara 2005, APT h) Fennerty, 2005 APT

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
		sytmpoms at 6 months. g) RCT of pts with NERD, found that in patients who are H pylori negative, omeprazole more effective than famotidine for control of GERD symptoms, but in H. pylori positive symptoms, similar efficacy was observed h) RCT of pts with moderate or severe erosive esophagitis demonstrates esomeprazole 40 qday heals EE faster and in more pts than lansoprazole 30 mg qda at 8 weeks. At 4 weeks, esomeprazole resolved heartburn in more pts than lansoprazole.	
New topic: Timing of treatment -"On-demand" vs "intermittent" vs "continuous" therapy	**X**	a) Systematic review of 17 studies. On-demaind PPI effective in long-term management of pts with NERD or mild and uninvestigated forms of GERD, but not in pts with severe erosive esophagitis. These studies include on-demand PPI vs. placebo and continuous PPI. b) Systematic review of the efficacy of intermittent and on-demand therapy with H2As and PPIs in pts with erosive esophagitis or symptomatic heartburn. Regarding intermittent therapy, neither PPIs or H2As were effective in maintaining control of esophagitis pts. In regards to on-demand therapy, PPIs may work in a proportion of non-erosive GERD pts. c) RCT of pts with erosive reflux esophagitis found that once daily esomeprazole 20 mg was better than "on-demand" for maintaining healed erosive esophagitis at 6 months. d) RCT of pts with NERD or low grade esophagitis demonstrates a slightly higher rate of symptom relief at 6 months with the continuous rabeprazole group versus the on-demand group. For overall quality of life, there was not difference between the groups. Daily consumption	a) Pace, 2007 APT b) Zacny, 2005 APT c) Sjostedt, 2005 APT d) Bour, 2005 APT e) Bigard, 2005 APT

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
		was lower for the on-demand treatment group. e) RCT of GERD pts demonstrates that at 6 months, on-demand treatment with lansoprazole in symptomatic pts after short-term, continuous treatment treatment is more effect than placebo in improving symptoms	
New topic: Laryngeal/pharyngeal symptoms attributed to GERD. Caveat: the cause and effect relationship of GERD and laryngophayngeal reflux remains unclear	**X**	a) Meta-analysis of 5 studies using high-dose PPIs for treatment of laryngeal or pharyngeal symptoms was no more effective than placebo in provident symptomatic improvement or resolution of laryngo-pharyngeal symptoms. b) RCT for of 39 pts with laryngopharyngeal reflux treated with pantoprazole vs. placebo. No difference in symptom improvement was found between the two groups. c) Systematic review and meta-analysis of RCTs of pts with chronic cough associated with GERD demonstrating use of PPI for treat has some effect in some adults, but is less universal than suggested in consensus guidelines on chronic cough.	a) Gatta, 2007 APT b) Wo, 2006 AJG c) Chang, 2006 BMJ
New topic: Acupuncture vs. doubling PPI dose	**X**	a) RCT of 30 patients with refractory heartburn. All pts on PPI once daily. If symptoms refractory to treatment, pts randomized to doubling PPI dose vs. acupuncture twice weekly. Adding acupuncture was more effective than doubling PPI dose in controlling GERD symptoms in this pt population	a) Dickman, 2007 APT
New topic: Double dose or change PPI	**X**	a) RCT of pts with persistent heartburn symptoms found switching pts to different PPI was as effective as increasing PPI dosage to twice daily for controlling heartburn symptoms.	a) Fass, 2006 CGH
New topic: Long-term prevention of erosive or ulcerative GERD relapse	**X**	a) RCT of pts with healthed erosive/ulcerative GERD found 5-year maintenance therapy with rabeprazole effective in preventing replase of erosive/ulcerative GERD. 20 mg better than 10 mg. Both better than placebo.	a) Caos, 2005 APT

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
New topic: New endoscopic techniques	X	a) Radiofrequency energy delivery allows reduction or discontinuation of PPI therapy in patients with PPI-dependent symptoms.	a) Coron, 2008 APT
New topic: AZD0865, potassium-competitive acid blocker	X	a) RCT comparing a potassium-competitive acid blocker (AZD0865) did not provide clinical benefit over esomeprazole in pts with nonerosive reflux disease b) RCT of three doses of potassium-competitive acid blocker (AZD0865) (25, 50, 75 mg) and esomeprazole 40 mg. At 4 weeks, healing rates of esophagitis similar to esomeprazole. No significant differences in heartburn control. AZD0865 at 75 mg demonstrated reversible increases in liver transaminases.	a) Dent, 2008 AJG b) Kahrilas, 2007 CGH
New topic: Nocturnal symptoms	X	a) RCT in GERD patients with nocturnal heartburn concludes single-dose rabeprzole 20mg increases intragastric pH more than pantoprazole 40mg qday. b) RCT in GERD patients with nocturnal symptoms, comparing immediate-release omeprazole 40 mg oral suspension, delayed release lansoprazole 30 mg capsules, and delayed-release esomeprazole 30 mg capsules. Omeprazole superior to lansoprazole and comparable to esomeprazole. c) RCT in erosive esophagitis patients on daily PPI with experience night-time heart burn. OTC ranitidine 75 mg demonstrated decrease in symptoms vs. placebo on day 3, but not on day 14. d) RCT of pts with nocturnal GERD demonstrates immediate-release omeprazole reduced nocturned gastric acidity better than delayed-release pantoprazole.	a) Warrington, 2007 APT b) Katz, 2007 APT c) Vakil, 2006 APT d) Castell, 2005 APT

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
For maintenance medical treatment of 6 months to 1 year, PPIs taken at a standard dose were more effective than those taken at a lower dose.	No new evidence found	New Evidence: None	
Laparoscopic fundoplication was as effective as open fundoplication for relieving heartburn and regurgitation, improving quality of life, and decreasing use of antisecretory medications. Almost 90 percent of patients who were followed for 5 or more years in both surgical arms reported improvement in symptoms.	No new evidence found	New Evidence: None	
Compared to sham, StrettaTM was more effective in improving symptoms of reflux and improving quality of life at 6 months and was associated with a decrease in the need for antisecretory medications. Improvement of esophageal pH exposure compared with sham could	No new evidence found	New Evidence: a) Compared to sham, endoscopic gastroplication using Endocinch device reduced acid-inhibitory drug use, improved GERD symptoms, and improved quality of life	a) Schwartz, 2007 Gut

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
not be demonstrated for StrettaTM.			
Key Question 2: Is there evidence that effectiveness of medical, surgical, and endoscopic treatments varies for specific patient subgroups?			
Patients on maintenance antireflux medications may have higher rates of esophagitis if they have any of the following factors: increased severity of esophagitis at baseline (pretreatment), younger age, and moderate to severe regurgitation.	No new evidence found	New Evidence: None	
There is no substantial evidence to support a difference in surgical outcome based on age, preoperative presence or severity of esophagitis, lower esophageal sphincter incompetence, or esophageal body hypomotility. Patients treated surgically who have a history of psychiatric disorders may have worse symptom and satisfaction outcomes than those without a significant psychiatric history.	No new evidence found	New Evidence: None	
New topic: Early response to therapy predicts complete resolution	X	a) Pooled analysis from three multicenter, double-blind trials of patients receiving PPI. Heartburn resolution during 1st week of PPI	a) Talley, 2006 APT

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
		therapy is the best predictor of treatment success at week 4.	
Key Question 3: What are the short- and long-term adverse effects associated with specific medical, surgical, and endoscopic therapies for GERD?			
Higher adverse event rates were described for PPIs than for H2RAs or placebo. The most commonly cited events for PPIs and H2RAs were headache, diarrhea, and abdominal pain.	No new evidence found	New Evidence: None	
The most commonly reported complications occurring intraoperatively or within 30 days after open fundoplication were the need for splenectomy, dysphagia, inability to belch, and inability to vomit. The most commonly reported complications for laparoscopic procedures were gastric or esophageal injury or perforation, splenic injury or splenectomy, pneumothorax, bleeding, pneumonia, fever, wound infections, bloating, and dysphagia. Major complications were generally reported at very low rates.	No new evidence found	New Evidence: None	
Frequently reported complications for endoscopic treatments(intraoperatively or	No new	New Evidence: None	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	References
within 30 days after the procedure included chest or retrosternal pain, gastrointestinal injury, bleeding, and short-term dysphagia. The frequency and types of complications varied with the different procedures. Serious complications, including fatalities, have also been described.	evidence found		
New topic: Rebound acid hypersecretion	X	a) Systematic review of 8 studies demonstrates no strong evidence for clinically relevant increased acid production after cessation of PPI therapy. Only 1 study included patients with reflux esophagitis and the remaining 7 studies enrolled healthy volunteers.	a) Gatta, 2007 APT
New topic: Risk of bacterial gastroenteritis	X	a) Case control study. Pts with acute bacterial gastroenteritis and compared with a control group without acute bacterial GE. Current PPI use was associated with increased risk of bacterial GE. H2A use not associated with increased risk. Caveat is that this is a heterogenous patient population, including some with GERD.	a) Rodriguez, 2007 CGH
Are there new data that could inform the key questions that might not be addressed in the conclusions?			

CER 3 - Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
COMPARATIVE EFFICACY AND SAFETY					
Hematologic Response					
(4) Pirker et al., 2008	Patients w/ extensive-stage small-cell lung cancer receiving first-line platinum-containing chemo (carboplatin or cisplatin + etoposide) (n=600)	Phase III RCT DA 300 ug, 1x/wk for 4 weeks, then every 3 weeks for up to 6 cycles chemo; patients observed until death or until end-of-study visit	Change in Hgb concn from baseline to end of chemo and overall survival	DA **maintained Hgb levels sign higher than placebo** ($p \leq 0.001$); Transfusion risk sign. ↓ (HR, 0.40, 95% CI, 0.29-0.55) No difference in survival (HR, 0.93, 95% CI, 0.78-1.11, p=0.431); DA assoc w/↑ thromboembolic events (9% vs. 5%)	Study reinforces benefit of erythropoesis stimulating agents (ESAs) in reducing transfusions but not improving survival
(8) Han et al., 2008	Patients w/ limited disease small-cell lung cancer (LD-SCLC) receiving two 28-day cycles cisplatin (30mg/m(2)) days 1 and 8 and irinotecan at a dose of 60 mg/m(2) (Days 1, 8, and 15) followed by two 21-day cycles of cisplatin at a dose of 60 mg/m(2) (Day 1) and etoposide at a dose of 100 mg/m(2) (Days 1-3) with concurrent twice-daily thoracic radiotherapy for a total of 45 days (n=76, but 15 of 36 amifostine pts did not get treatment)	Phase II RCT: amifostine (500mg) vs. epo-alpha (10,000IU sc 3x/wk)	Anemia and adverse events	Amifostine~↑febrile neutropenia (p=0.003); grade 2-3 nausea (p=0.03); grade 4 leukopenia (p=0.05); Grade 3 esophagitis in 30% of amifostine pts. vs. 9% of epo patients (P = .059). Epo associated with less grade 2-3 anemia (P = .031) and **lower decreases in Hgb during therapy** (P = .016). Median survival times for both treatment arms were comparable (22.6 months in the amifostine arm vs 25.6 months in the epoetin-alpha arm; P = .447)	Epo was more effective than amifostene in preventing severe anemia in LD-SCLC pts undergoing chemo-hyperfractionated radiotherapy
(15) Aapro et al., 2008b Breast Cancer-Anemia and the Value of Erythropoetin (BRAVE) study	Patients w/ metastatic breast cancer treated w/ anthracycline- and/or taxane-based chemo, Hb<12.9	Open-label multi-center RCT comparing EB (30,000U sc, Q1W, 24 wks	1°:Survival 2°: progression-free survival, transfusion- and severe anemia-free survival, Hb response, safety, and QoL 18 months followup	At follow-up Overall Survival: EB: 62/231 (27%) vs. Control: 63/232 (27%) No difference (hazard ratio [HR] = 1.07; 95% CI, 0.87 to 1.33, P = .522) Progression-free survival: no difference (HR = 1.07; 95% CI, 0.89 to 1.30, P = .448).	EB increased Hb in patients with initial Hb less than 12.9 g/dL. No difference was detected in overall survival but design may have precluded detection.

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				Transfusion- and severe anemia-free survival: significant ↑ compared with control (HR = 0.59; P = .0097). **Median Hb: EB↑ Hb (11.7 g/dL at baseline to 13.3 g/dL at 24 weeks) vs. no change with control (11.5 v 11.4 g/dL).** TEEs: EB->↑ TEEs cf. controls (13% v 6%; P = .012) with no difference in serious TEEs (4% v 3%). QoL: EB-> no significant improvement QoL in this study (in patients with a high baseline Hb value)	
(16) Wright et al., 2007	Patients with non-small cell carcinoma of the lung not curable with therapy and baseline Hb<12.1g/dl. (n=70: 300 intended but study stopped early)	Multicenter RCT: EA, sc, q1w, 12 weeks vs. placebo	Change in Functional Assessment of Cancer Therapy Anemia scores from baseline to 12 weeks; QOL, survival	EA decreased median survival (63 vs. 129 days, HR, 1.84, p=0.04), but **EA appeared to ↑ Hb**. Numbers too small to assess effect on QOL.	**EA's association with decreased survival led to early termination of study.**
(54) Wilkinson et al., 2006 UK	Ovarian cancer patients w/ Hb≤12 g/dl receiving platinum chemo (n=182)	Multicenter, open-label CCT: EA, 10,000-20,000 IU q3w plus best standard treatment (BST) vs. placebo+BST	Hb, transfusion rates, QOL	Hb: **EA group had 1.8g/dl increase by 4-6 weeks, significantly increased from baseline and significantly greater than BST alone through end of study (p<0.001).** Transfusion rate: Significantly fewer EA than BST patients required transfusion(s) after the first 4 weeks of treatment (7.9 vs 30.5%; P<0.001) QOL: EA->significant (P≤0.04) differences for all three median CLAS scores (Energy Level, Ability to Do Daily Activities, Overall QOL) and the median average CLAS score during chemotherapy	EA increased Hb, reduced transfusion use, and improved QOL in anemic ovarian cancer patients
(62) Razzouk et al., 2006	Children 5-18 yoa receiving myelosuppressive chemo	RCT EA 600-900 U/kg q1w vs. placebo, 16 wks	PedsQL-GCS: Patient and parent QOL (generic score [GS] and	Mean final values for GS total score (P = .763 among patients; P = .219 among parents) and CS domain	Study confirmed the tolerability and hematologic benefits

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
	for nonmyeloid malignancies (excluding brain tumors) who developed anemia (222)		cancer-specific [CS]), Hb, AE	scores (P≥0.238; P≥0.081, respectively) were not significantly different between treatment groups. **EPO-treated patients had greater increases in Hb overall (P = 0.002)** and were more likely to be transfusion free after 4 weeks (38.7% v 22.5%; P =0 .010). Change in Hb correlated with change in PedsQL-GCS total score in the EPO group (r = 0.242; P = .018), but not in the placebo group (r = 0.086; P = .430). AEs were comparable between treatment groups.	of once-weekly EPO in children with cancer. No significant difference in HRQOL between treatment groups, but a significant positive correlation was observed between Hb changes and HRQOL changes in the EPO group.
(63) Norager et al., 2006	Patients admitted to a hospital for planned surgery for colorectal cancer; anemia not an inclusion criterion (151)	RCT of DA 300 or 150 ug q1w vs. placebo depending on Hb status[?]	Post-op work capacity, QOL, fatigue, postural sway, change in Hb d.7 and 30	DA assoc with sign greater work capacity on d. 7 and 30 (p-0.03 for each) cf placebo. No diffs in fatigue, postural sway or QOL **Decrease in Hb: DA significantly reduced the decrease in Hb on d.7 (p<0.01) and resulted in earlier return to pre-op Hb (p<0.01)** cf. placebo.	Perioperative DA treatment improved postoperative work capacity and Hb concentrations, but had no effect on postoperative fatigue, postural sway, QoL and muscle strength
Transfusion Rate					
(2) Smith et al., 2008	Patients with active cancer and anemia (how defined?), not receiving or planning to receive cytotoxic chemotherapy or myelosuppressive radiotherapy (n not reported in abstract)	Phase III multi-center RCT comparing Darbepo alpha (DA) to placebo: 6.75 ug/kg every 4 weeks (Q4W) for up to 16 weeks	Need for transfusion in wks 5-17; adverse events; survival (over 2-year followup)	DA assoc with non-statistically significant ↓ in # transfusions; DA assoc. with stat. sign. ↑ in cardiovascular and thromboembolic events, deaths in first 16 wks. Sign.↓ long-term survival (p=0.22) Survival effect varied by sex, tumor type, geographic region and disappeared w/sensitivity analysis*	Study does not support use of DA in this subset of cancer patients w/ anemia
(4) Pirker et al., 2008	Patients w/ extensive-stage small-cell lung cancer receiving first-line platinum-containing chemo (carboplatin or	Phase III RCT DA 300 ug, 1x/wk for 4 weeks, then every 3 weeks for up to 6 cycles chemo; patients observed until	Change in Hgb concn from baseline to end of chemo and overall survival	DA maintained Hgb levels sign higher than placebo (p≤0.001); Transfusion risk sign. ↓ (HR, 0.40, 95% CI, 0.29-0.55) No difference in survival (HR, 0.93,	Study reinforces benefit of erythropoesis stimulating agents (ESAs) in **reducing**

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
	cisplatin + etoposide) (n=600)	death or until end-of-study visit		95% CI, 0.78-1.11, p=0.431); DA assoc w/↑ thromboembolic events (9% vs. 5%)	**transfusions** but not improving survival
(54) Wilkinson et al., 2006 UK	Ovarian cancer patients w/ Hb≤12 g/dl receiving platinum chemo (n=182)	Multicenter, open-label CCT: EA, 10,000-20,000 IU q3w plus best standard treatment (BST) vs. placebo+BST	Hb, transfusion rates, QOL	Hb: EA group had 1.8g/dl increase by 4-6 weeks, significantly increased from baseline and significantly greater than BST alone through end of study (p<0.001). Transfusion rate: Significantly fewer EA than BST patients required transfusion(s) after the first 4 weeks of treatment (7.9 vs 30.5%; P<0.001) QOL: EA->significant (P≤0.04) differences for all three median CLAS scores (Energy Level, Ability to Do Daily Activities, Overall QOL) and the median average CLAS score during chemotherapy	EA increased Hb, **reduced transfusion use**, and improved QOL in anemic ovarian cancer patients
(62) Razzouk et al., 2006	Children 5-18 yoa receiving myelosuppressive chemo for nonmyeloid malignancies (excluding brain tumors) who developed anemia (222)	RCT EA 600-900 U/kg q1w vs. placebo, 16 wks	PedsQL-GCS: Patient and parent QOL (generic score [GS] and cancer-specific [CS]), Hb, AE	Mean final values for GS total score (P = .763 among patients; P = .219 among parents) and CS domain scores (P≥0.238; P≥0.081, respectively) were not significantly different between treatment groups. EPO-treated patients had greater increases in Hb overall (P = 0.002) and were **more likely to be transfusion free after 4 weeks** (38.7% v 22.5%; P =0 .010). Change in Hb correlated with change in PedsQL-GCS total score in the EPO group (r = 0.242; P = .018), but not in the placebo group (r = 0.086; P = .430). AEs were comparable between treatment groups.	Study confirmed the tolerability and hematologic benefits of once-weekly EPO in children with cancer. No significant difference in HRQOL between treatment groups, but a significant positive correlation was observed between Hb changes and HRQOL changes in the EPO group.
(70) Glaspy et al., 2006 (also appears below for KQ2)	Patients≥18yoa w/ a nonmyeloid malignancy (most commeon were lung, breast, GI) with	RCT cf. DA 200ug q2w vs. EA 40,000U q1w up to 16 wks, with identical dose adjustment rules	Incidence of RBC transfusion; Definition of non-inferiority was that upper 95% CI limit	**Transfusion incidence** from week 5 to the end of the treatment phase (the primary end point) was 21% in the DA group and 16% in the EA group;	Study shows comparable efficacy of DA Q2W and EA QW. Less frequent

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
	≥8wks planned chemotherapy, and anemia (Hb≤11g/dl) (1,220, 1209 of whom received ≥1 dose of a study drug)		of observed difference in transfusions between groups was <11.5%, based on treatment effect observed in placebo controlled EA studies	noninferiority was concluded because the upper 95% CI limit of the difference between groups (10.8%) was below the prespecified noninferiority margin. Sensitivity analyses using alternate statistical methods and analysis sets yielded similar results. HB, QOL, and AEs did not differ between therapies.	dosing offers potential benefits for patients, caregivers and health care providers.
(74) Aapro et al., 2006 UK	Cancer patients (56% hematological cancers and 44% solid tumors) (1,413)	Meta-analysis of 9 RCTs EB: median initial dose 30,000IU/wk	Survival, disease progression, TEE and TEE-mortality	Survival (0-6mos) for EB same as control (0.31 vs. 0.32 deaths/pt-year) Mortality risk: no difference (RR 0.97, 95% CI: 0.69, 1.36; P = 0.87) Risk of rapidly progressive disease significantly reduced for EB (RR 0.78, 95% CI: 0.62, 0.99; P = 0.042). TEE: slightly increased risk for EB (5.9% vs 4.2% of patients) TEE-related mortality: no difference	Epoetin beta provided a slight beneficial effect on tumour progression and did not impact on early survival or thromboembolic-related mortality
Thromboembolic events					
(14) Aapro et al., 2008a UK	Patients with cancer (65% solid tumors; 35% non-myeloid hematological malignancies) (n=2297) Subgroup analysis on patients w/ baseline Hb≤11g/dl (EORTC treatment guidelines)	Meta-analysis of 12 RCTs Epo-beta (EB)	Survival, tumor progression, thromboembolic events (TEEs)	Mortality: no effect overall (HR=1.13; 95% CI: 0.87, 1.46; P=0.355) No effect in patients with baseline Hb≤11g/dl (HR=1.09; 95% CI: 0.80, 1.47; P=0.579). Tumor Progression: A trend for a beneficial effect overall (HR=0.85; 95% CI: 0.72, 1.01; P=0.072) and in patients with an Hb≤11 (HR=0.80; 95% CI: 0.65, 0.99; P=0.041). TEEs: EB->↑TEEs vs. controls (7% vs 4%); however, TEEs-related mortality was similar in both groups (1% each)	EB had no negative effect on survival, tumor progression, or **TEEs-related mortality**
(15) Aapro et al., 2008b Breast Cancer-Anemia and the Value of Erythropoetin	Patients w/ metastatic breast cancer treated w/ anthracycline- and/or taxane-based chemo,	Open-label multi-center RCT comparing EB (30,000U sc, Q1W, 24 wks	1°:Survival 2°: progression-free survival, transfusion- and severe anemia-free	At follow-up Overall Survival: EB: 62/231 (27%) vs. Control: 63/232 (27%) No difference (hazard ratio [HR] = 1.07;	EB increased Hb in patients with initial Hb less than 12.9 g/dL. No difference

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
(BRAVE) study	Hb<12.9		survival, Hb response, safety, and QoL 18 months followup	95% CI, 0.87 to 1.33, P = .522) Progression-free survival: no difference (HR = 1.07; 95% CI, 0.89 to 1.30, P = .448). Transfusion- and severe anemia-free survival: significant ↑ compared with control (HR = 0.59; P = .0097). Median Hb: EB↑ Hb (11.7 g/dL at baseline to 13.3 g/dL at 24 weeks) vs. no change with control (11.5 v 11.4 g/dL). **TEEs: EB->↑ TEEs cf. controls (13% v 6%; P = .012) with no difference in serious TEEs (4% v 3%**). QoL: EB-> no significant improvement QoL in this study (in patients with a high baseline Hb value)	was detected in overall survival but design may have precluded detection.
(74) Aapro et al., 2006 UK	Cancer patients (56% hematological cancers and 44% solid tumors) (1,413)	Meta-analysis of 9 RCTs EB: median initial dose 30,000IU/wk	Survival, disease progression, TEE and TEE-mortality	Survival (0-6mos) for EB same as control (0.31 vs. 0.32 deaths/pt-year) Mortality risk: no difference (RR 0.97, 95% CI: 0.69, 1.36; P = 0.87) Risk of rapidly progressive disease significantly reduced for EB (RR 0.78, 95% CI: 0.62, 0.99; P = 0.042). TEE: slightly increased risk for EB (5.9% vs 4.2% of patients) TEE-related mortality: no difference	Epoetin beta provided a slight beneficial effect on tumour progression and did not impact on early survival or thromboembolic-related mortality
QOL					
(54) Wilkinson et al., 2006 UK	Ovarian cancer patients w/ Hb≤12 g/dl receiving platinum chemo (n=182)	Multicenter, open-label CCT: EA, 10,000-20,000 IU q3w plus best standard treatment (BST) vs. placebo+BST	Hb, transfusion rates, QOL	Hb: EA group had 1.8g/dl increase by 4-6 weeks, significantly increased from baseline and significantly greater than BST alone through end of study (p<0.001). Transfusion rate: Significantly fewer EA than BST patients required transfusion(s) after the first 4 weeks of treatment (7.9 vs 30.5%; P<0.001)	EA increased Hb, reduced transfusion use, **and improved QOL** in anemic ovarian cancer patients

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				QOL: EA->significant (P≤0.04) differences for all three median CLAS scores (Energy Level, Ability to Do Daily Activities, Overall QOL) and the median average CLAS score during chemotherapy	
(62) Razzouk et al., 2006	Children 5-18 yoa receiving myelosuppressive chemo for nonmyeloid malignancies (excluding brain tumors) who developed anemia (222)	RCT EA 600-900 U/kg q1w vs. placebo, 16 wks	PedsQL-GCS: Patient and parent QOL (generic score [GS] and cancer-specific [CS]), Hb, AE	Mean final values for GS total score (P = .763 among patients; P = .219 among parents) and CS domain scores (P≥0.238; P≥0.081, respectively) were not significantly different between treatment groups. EPO-treated patients had greater increases in Hb overall (P = 0.002) and were more likely to be transfusion free after 4 weeks (38.7% v 22.5%; P =0 .010). Change in Hb correlated with change in PedsQL-GCS total score in the EPO group (r = 0.242; P = .018), but not in the placebo group (r = 0.086; P = .430). AEs were comparable between treatment groups.	Study confirmed the tolerability and hematologic benefits of once-weekly EPO in children with cancer. No significant difference in HRQOL between treatment groups, but a significant positive correlation was observed between Hb changes and HRQOL changes in the EPO group.
(63) Norager et al., 2006	Patients admitted to a hospital for planned surgery for colorectal cancer; anemia not an inclusion criterion (151)	RCT of DA 300 or 150 ug q1w vs. placebo depending on Hb status[?]	Post-op work capacity, QOL, fatigue, postural sway, change in Hb d.7 and 30	DA assoc with sign greater work capacity on d. 7 and 30 (p-0.03 for each) cf placebo. No diffs in fatigue, postural sway or QOL Decrease in Hb: DA significantly reduced the decrease in Hb on d.7 (p<0.01) and resulted in earlier return to pre-op Hb (p<0.01) cf. placebo.	Perioperative DA treatment improved postoperative work capacity and Hb concentrations, but had no effect on postoperative fatigue, postural sway, QoL and muscle strength
Tumor Response and/or Progression					
(14) Aapro et al., 2008a UK	Patients with cancer (65% solid tumors; 35% non-myeloid hematological	Meta-analysis of 12 RCTs Epo-beta (EB)	Survival, tumor progression, thromboembolic events (TEEs)	Mortality: no effect overall (HR=1.13; 95% CI: 0.87, 1.46; P=0.355) No effect in patients with baseline	EB had no negative effect on survival, **tumor progression**, or TEEs-related

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
	malignancies) (n=2297) Subgroup analysis on patients w/ baseline Hb≤11g/dl (EORTC treatment guidelines)			Hb≤11g/dl (HR=1.09; 95% CI: 0.80, 1.47; P=0.579). Tumor Progression: A trend for a beneficial effect overall (HR=0.85; 95% CI: 0.72, 1.01; P=0.072) and in patients with an Hb≤11 (HR=0.80; 95% CI: 0.65, 0.99; P=0.041). TEEs: EB->↑TEEs vs. controls (7% vs 4%); however, TEEs-related mortality was similar in both groups (1% each)	mortality
(74) Aapro et al., 2006 UK	Cancer patients (56% hematological cancers and 44% solid tumors) (1,413)	Meta-analysis of 9 RCTs EB: median initial dose 30,000IU/wk	Survival, disease progression, TEE and TEE-mortality	Survival (0-6mos) for EB same as control (0.31 vs. 0.32 deaths/pt-year) Mortality risk: no difference (RR 0.97, 95% CI: 0.69, 1.36; P = 0.87) Risk of rapidly progressive disease significantly reduced for EB (RR 0.78, 95% CI: 0.62, 0.99; P = 0.042). TEE: slightly increased risk for EB (5.9% vs 4.2% of patients) TEE-related mortality: no difference	Epoetin beta provided a slight beneficial effect on tumour progression and did not impact on early survival or thromboembolic-related mortality
Survival					
(8) Han et al., 2008	Patients w/ limited disease small-cell lung cancer (LD-SCLC) receiving two 28-day cycles cisplatin (30mg/m(2)) days 1 and 8 and irinotecan at a dose of 60 mg/m(2) (Days 1, 8, and 15) followed by two 21-day cycles of cisplatin at a dose of 60 mg/m(2) (Day 1) and etoposide at a dose of 100 mg/m(2) (Days 1-3) with concurrent twice-daily thoracic radiotherapy for a total of	Phase II RCT: amifostine (500mg) vs. epo-alpha (10,000IU sc 3x/wk)	Anemia and adverse events	Amifostine~↑febrile neutropenia (p=0.003); grade 2-3 nausea (p=0.03); grade 4 leukopenia (p=0.05); Grade 3 esophagitis in 30% of amifostine pts. vs. 9% of epo patients (P = .059). Epo associated with less grade 2-3 anemia (P = .031) and lower decreases in Hgb during therapy (P = .016). Median survival times for both treatment arms were comparable (22.6 months in the amifostine arm vs 25.6 months in the epoetin-alpha arm; P = .447)	Epo was more effective than amifostene in preventing severe anemia in LD-SCLC pts undergoing chemo-hyperfractionated radiotherapy

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
	45 days (n=76, but 15 of 36 amifostine pts did not get treatment)				
(14) Aapro et al., 2008a UK	Patients with cancer (65% solid tumors; 35% non-myeloid hematological malignancies) (n=2297) Subgroup analysis on patients w/ baseline Hb≤11g/dl (EORTC treatment guidelines)	Meta-analysis of 12 RCTs Epo-beta (EB)	Survival, tumor progression, thromboembolic events (TEEs)	Mortality: no effect overall (HR=1.13; 95% CI: 0.87, 1.46; P=0.355) No effect in patients with baseline Hb≤11g/dl (HR=1.09; 95% CI: 0.80, 1.47; P=0.579). Tumor Progression: A trend for a beneficial effect overall (HR=0.85; 95% CI: 0.72, 1.01; P=0.072) and in patients with an Hb≤11 (HR=0.80; 95% CI: 0.65, 0.99; P=0.041). TEEs: EB->↑TEEs vs. controls (7% vs 4%); however, TEEs-related mortality was similar in both groups (1% each)	EB had no negative effect on **survival**, tumor progression, or TEEs-related mortality
(15) Aapro et al., 2008b Breast Cancer-Anemia and the Value of Erythropoetin (BRAVE) study	Patients w/ metastatic breast cancer treated w/ anthracycline- and/or taxane-based chemo, Hb<12.9	Open-label multi-center RCT comparing EB (30,000U sc, Q1W, 24 wks	1°:Survival 2°: progression-free survival, transfusion- and severe anemia-free survival, Hb response, safety, and QoL 18 months followup	At follow-up Overall Survival: EB: 62/231 (27%) vs. Control: 63/232 (27%) No difference (hazard ratio [HR] = 1.07; 95% CI, 0.87 to 1.33, P = .522) Progression-free survival: no difference (HR = 1.07; 95% CI, 0.89 to 1.30, P = .448). Transfusion- and severe anemia-free survival: significant ↑ compared with control (HR = 0.59; P = .0097). Median Hb: EB↑ Hb (11.7 g/dL at baseline to 13.3 g/dL at 24 weeks) vs. no change with control (11.5 v 11.4 g/dL). TEEs: EB->↑ TEEs cf. controls (13% v 6%; P = .012) with no difference in serious TEEs (4% v 3%). QoL: EB-> no significant improvement QoL in this study (in patients with a high baseline Hb	EB increased Hb in patients with initial Hb less than 12.9 g/dL. **No difference was detected in overall survival but design may have precluded detection**.

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				value)	
(16) Wright et al., 2007	Patients with non-small cell carcinoma of the lung not curable with therapy and baseline Hb<12.1g/dl. (n=70: 300 intended but study stopped early)	Multicenter RCT: EA, sc, q1w, 12 weeks vs. placebo	Change in Functional Assessment of Cancer Therapy Anemia scores from baseline to 12 weeks; QOL, survival	EA decreased median survival (63 vs. 129 days, HR, 1.84, p=0.04), but EA appeared to ↑ Hb. Numbers too small to assess effect on QOL.	EA's association with **decreased survival** led to early termination of study.
(74) Aapro et al., 2006 UK	Cancer patients (56% hematological cancers and 44% solid tumors) (1,413)	Meta-analysis of 9 RCTs EB: median initial dose 30,000IU/wk	Survival, disease progression, TEE and TEE-mortality	Survival (0-6mos) for EB same as control (0.31 vs. 0.32 deaths/pt-year) Mortality risk: no difference (RR 0.97, 95% CI: 0.69, 1.36; P = 0.87) Risk of rapidly progressive disease significantly reduced for EB (RR 0.78, 95% CI: 0.62, 0.99; P = 0.042). TEE: slightly increased risk for EB (5.9% vs 4.2% of patients) TEE-related mortality: no difference	Epoetin beta provided a slight beneficial effect on tumour progression and did not impact on early survival or thromboembolic-related mortality
Other AEs					
(8) Han et al., 2008	Patients w/ limited disease small-cell lung cancer (LD-SCLC) receiving two 28-day cycles cisplatin (30mg/m(2)) days 1 and 8 and irinotecan at a dose of 60 mg/m(2) (Days 1, 8, and 15) followed by two 21-day cycles of cisplatin at a dose of 60 mg/m(2) (Day 1) and etoposide at a dose of 100 mg/m(2) (Days 1-3) with concurrent twice-daily thoracic radiotherapy for a total of 45 days (n=76, but 15 of 36 amifostine pts did not get treatment)	Phase II RCT: amifostine (500mg) vs. epo-alpha (10,000IU sc 3x/wk)	Anemia and adverse events	Amifostine~↑febrile neutropenia (p=0.003); grade 2-3 nausea (p=0.03); grade 4 leukopenia (p=0.05); Grade 3 esophagitis in 30% of amifostine pts. vs. 9% of epo patients (P = .059). Epo associated with less grade 2-3 anemia (P = .031) and lower decreases in Hgb during therapy (P = .016). Median survival times for both treatment arms were comparable (22.6 months in the amifostine arm vs 25.6 months in the epoetin-alpha arm; P = .447)	Epo was more effective than amifostene in preventing severe anemia in LD-SCLC pts undergoing chemo-hyperfractionated radiotherapy
(2) ALTERNATIVE DOSING STRATEGIES					

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
(6)Pedrazzoli et al., 2008	Patients with lung, gynecologic, breast, and colorectal cancers and ≥12 weeks planned chemotherapy (n=176 pts, 33 institutions); Hemoglobin ≤11 g/L and no absolute or functional iron deficiency.	RCT (?) of sodium ferric gluconate 125 mg/wk for the first 6 weeks (n = 73) or no iron (n = 76) in patients taking DA (150 ug subcutaneously once weekly for 12 weeks)	Percentage of patients achieving hematopoietic response (hemoglobin ≥12 g/dL or ≥2 g/dL increase), safety	Intention-to-treat analysis: Hematopoetic response: DA+Fe: 76.7% (95%CI, 65.4% to 85.8%) DA-Fe: 61.8% (95%CI, 50.0% to 72.7%) (P = .0495). Among patients fulfilling eligibility criteria and having received at least four DA administrations: hematopoietic responses in the DA+Fe: 92.5% (95% CI, 81.8% to 97.9%) (n = 53) DA-Fe: 70% (95% CI, 55.4% to ≥82.1%) (n = 50)(P = .0033). Hb ↑ during treatment showed a time profile favoring DA/Fe with statistically significant effect from week 5 on. No difference in safety profile.	Fe reduces treatment failure of DA and improves effectiveness of DA
(13) Bastit et al., 2008	Patients with nonmyeloid malignancies and hemoglobin (Hb) less than 11 g/dL (n=396)	Multicenter, open-label, phase III RCT DA 500 ug with (n = 200) or without (n = 196) IV Fe Q3W for 16 weeks	Hematopoietic response (proportion of patients achieving Hb ≥12 g/dL or Hb increase of ≥ 2 g/dL from baseline) and # transfusions	Hematopoietic response rate: IV iron group: 86% Standard practice group 73% (difference of 13% [95% CI, 3% to 23%]; P = .011). Transfusions (week 5 to the end of the treatment period): IV iron group: 9% Standard practice group: 20% (difference of -11% [95% CI, -18% to -3%]; P = .005). Both treatments were well tolerated with no notable differences in adverse events. Serious adverse events related to iron occurred in 3% of patients in the IV iron group: mostly gastrointestinal	Addition of IV Fe to DA in patients with chemotherapy-induced anemia was well tolerated, improved hematopoietic response rate, and decreased transfusion rate compared with DA alone
(58) Steensma et al., 2006	Patients with cancer and anemia (n=365)	RCT comparing EA 40,000U sc q3w followed by 1) standard weekly EA (40K) or 2) 120,000U EA (120K) sc	Requirement for transfusion, Hb increment; AE (TEE or death)	Requirement for transfusions during the study did not differ: 23% in 40K arm vs. 18% in 120K arm (P = 0.22) Req. for transfusion during the maintenance phase also did not	After three weekly doses of 40K U EA, a dose of 120K U can be administered safely once every 3

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
		q3w for 18 add'l weeks		differ: 13% in 40K arm v 15% in 120K arm (P = .58). Hb: 40K grp more likely than 120K grp to have a ≥ 2 or ≥3 g/dL Hb increment, to have a drug dose held because of high Hb, and had higher mean end-of-study Hb levels. AE, including TEE and overall survival, were similar. Global QOL: 40K arm higher at baseline but 120K grp improved more so equal at end of study.	weeks without increasing transfusion needs or sacrificing QOL. The Hb increment is somewhat greater with continued weekly EA. Lack of blinding as a result of different treatment schedules may have confounded results.
(70) Glaspy et al., 2006	Patients≥18yoa w/ a nonmyeloid malignancy (most commeon were lung, breast, GI) with ≥8wks planned chemotherapy, and anemia (Hb≤11g/dl) (1,220, 1209 of whom received ≥1 dose of a study drug)	RCT cf. DA 200ug q2w vs. EA 40,000U q1w up to 16 wks, with identical dose adjustment rules	Incidence of RBC transfusion; Definition of non-inferiority was that upper 95% CI limit of observed difference in transfusions between groups was <11.5%, based on treatment effect observed in placebo controlled EA studies	Transfusion incidence from week 5 to the end of the treatment phase (the primary end point) was 21% in the DA group and 16% in the EA group; noninferiority was concluded because the upper 95% CI limit of the difference between groups (10.8%) was below the prespecified noninferiority margin. Sensitivity analyses using alternate statistical methods and analysis sets yielded similar results. HB, QOL, and AEs did not differ between therapies.	Study shows comparable efficacy of DA Q2W and EA QW. Less frequent dosing offers potential benefits for patients, caregivers and health care providers.
(3) ALTERNATIVE THRESHOLDS FOR INITIATING TREATMENT					
(56) Straus et al., 2006	Patients with non-Hodgkin lymphoma, Hodgkin lymphoma, chronic lymphocytic leukemia, or multiple myeloma and baseline hemoglobin of 10-12 g/dL who were scheduled for ≥ 4 months of myelosuppressive chemotherapy (n=269 randomized)	RCT: Patients randomized to receive ≤16 weeks of EA at a dose of 40,000 U q1w immediately (early) or to wait and only receive EA if hemoglobin decreased to ≤9 g/dL (late). (Any patients with a hemoglobin level ≥12 g/dL after 3 chemotherapy cycles	1°: Mean change in Functional Assessment of Cancer Therapy-Anemia (FACT-An) total 2°: Hb, AEs	Mean total FACT-An increased 3.84 (95% CI, 0.21-7.46) in early patients and decreased 4.37 (95% CI, -7.99 to -0.74) in late patients (P = .003). Early patients had significantly (P< .05) higher mean scores for total FACT-General; FACT-General physical and functional well-being subscales, total anemia scale, and fatigue subscale; and daily activity, energy, and important activity Linear Analog Scale Assessment scales, as well as reduced bedrest days and restricted activity days. The mean Hb	Treating mild anemia immediately with EA during chemotherapy for hematologic malignancy significantly improved QOL, productivity, and Hb compared with delaying treatment until the hemoglobin level decreases to < 9.0 g/dL.

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
		were not randomized		increased 1.2 g/dL (95% CI, 0.98-1.46) in early patients but decreased 0.2 g/dL (95% CI, -0.32-0.12) in late patients (P<0.0001). AEs were similar between groups (with fatigue being the most prevalent); clinically relevant thromboembolic events were more common in early patients	
(66) Lyman et al., 2006	Systematic review of 11 studies of patients with chemotherapy induced anemia (abstract indicated that only a subset of these studies compared early and late intervention and did not indicate n)	11 RCTs purporting to assess clinical benefit of early erythropoetic intervention	Proportion of pts w/ Hb≥10 g/dl, transfusion incidence,	Erythropoietic treatment decreased transfusion incidence cf. placebo (RRR 0.50, 95% CI 0.43, 0.59; 7 studies, P< 0.0001) and the proportion of patients with hemoglobin <10 g/dL(0.40, 95% CI, 0.19, 0.83; 4 studies, P = 0.147). Findings from both prospective studies and planned subset analyses in which early and late intervention were compared also indicated a reduction in the RR of transfusions (0.55, 95% CI, 0.42, 0.73; 5 studies, P<0.0001] and Hb <10 g/dL (0.44, 95% CI, 0.33, 0.57; 2 studies, P<0.0001] after early intervention	these findings suggest that optimal clinical benefit from erythropoietic treatment of chemotherapy-induced anemia may be achieved through early intervention
PATIENT CHARACTERISTICS USEFUL FOR SELECTING PATIENTS OR PREDICTING RESPONSES					
(2) Smith et al., 2008	Patients with active cancer and anemia (how defined?), not receiving or planning to receive cytotoxic chemotherapy or myelosuppressive radiotherapy (n not reported in abstract)	Phase III multi-center RCT comparing Darbepo alpha (DA) to placebo: 6.75 ug/kg every 4 weeks (Q4W) for up to 16 weeks	Need for transfusion in wks 5-17; adverse events; survival (over 2-year followup)	DA assoc with non-statistically significant ↓ in # transfusions; DA assoc. with stat. sign. ↑ in cardiovascular and thromboembolic events, deaths in first 16 wks. Sign.↓ long-term survival (p=0.22) Survival effect varied by sex, tumor type, geographic region and disappeared w/sensitivity analysis*	Study does not support use of DA in this subset of cancer patients w/ anemia

*Include in response to question 4 regarding patient characteristics

Notes: Fe: iron; Hb hemoglobin; iv: intravenous; Q3W: every 3 weeks; sc: subcutaneous;

CER 6 - Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics

Conclusions From CER Executive Summary	Has there been new evidence that may change this conclusion?	References
Key Question 1: What are the leading off-label uses of atypical antipsychotics in the literature?		
The most common off-label uses of atypical antipsychotics found in the literature were treatment of depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, Tourette's syndrome, autism, and agitation in dementia. In October 2006, risperidone was approved for use in autism.	There are several new RCTs of atypicals for anorexia nervousa and bulimia. Court (2008) published a systematic review in Eating Disorders which included four RCTs.	RCTs: Mondraty, 2005, Australas Psychiatry; Bissada, 2008, Am J Psychiatry; Spettique, 2008, BMC Pediatrics
Key Question 2: What does the evidence show regarding the effectiveness of atypical antipsychotics for off-label indications, such as depression? How do atypical antipsychotic medications compare with other drugs for treating off-label indications?		
There is a small but statistically significant benefit for risperidone and aripiprazole on agitation and psychosis outcomes in dementia patients. The clinical benefits must be balanced against side effects and potential harms.	a) CATIE-AD found that olanzapine and risperidone improved NPI total score and BPRS (Brief Psychiatric Rating Scale) hostile suspiciousness factor. There were no significant differences between antipsychotics and placebo on cognition, function, care needs, or quality of life, except for worsened functioning with olanzapine. b) New RCT shows quetiapine 200 mg associated with significant improvements in PANNS-EC, CGI-C compared to placebo c) New meta-analysis shows effect sizes of atypical antipsychotics for behavioral problems in dementia are medium, and there are no statistically or clinically significant differences between them and placebo. d) Head to head RCT shows quetiapine and risperidone equally effective and well tolerated.	a) Sultzer, 2008, Am J Psychiatry b) Zhong, 2007, Curr Alzheimer Res c) Yury, 2007, Psychother Psychosom d) Rainer, 2007, Eur Psychiatry e) Carson , 2006, JAGS f) Mintzer, 2007, Am J Geri Psych g) Stein, 2008, Am J Geri Psych h) Naber, 2007, Psychopharmacology

Conclusions From CER Executive Summary	Has there been new evidence that may change this conclusion?	References
	e) New systematic review on dementia symptoms show olanzapine and risperidone effective compared with placebo. Short-term AEs similar to placebo. Risperidone had advantage over haldol in EPS. Evidence for other atypicals too limited to assess. f) New RCT found aripiprazole 10 mg/day was efficacious and safe for psychosis associated with AD, significantly improving psychotic symptoms, agitation, and clinical global impression. g) In another RCT in nursing home residents with AD and psychosis, aripiprazole did not confer specific benefits for the treatment of psychotic symptoms; but psychological and behavioral symptoms, including agitation, anxiety, and depression, were improved with aripiprazole, with a low risk of AEs. h) An RCT in elderly patients with organic brain disease (N= 15) showed no difference between risperidone and placebo, as measured by PANSS items.	
For SRI-resistant patients with major depressive disorder, combination therapy with an atypical antipsychotic plus an SRI antidepressant is not more effective than an SRI alone at 8 weeks.	a) Aripiprazole approved by FDA for adjunctive tx in unipolar, non-psychotic depression after two RCTs (Marcus, 2008, J Clinc Psychopharmacol; Berman, 2007, J Clin Psychiatry) b) RCT of risperidone augmentation showed higher odds of remitting (OR = 3.33) than placebo at 4 weeks. c) New RCT shows olanzapine/ fluoxetine combo effective at 8 weeks. d) Meta-analysis of 10 clinical trials finds patients on adjunct atypicals significantly more likely to experience remission or clinical response than those on adjunct placebo. No studies on aripiprazole or	a) Philip, 2008, J Psychiatric Practice b) Keitner, 2008, J Psychiatr Res c) Thase, 2007, J Clin Psychiatry d) Papakostas, 2007, J Clin Psychiatry e) Gharabawi, 2007, Ann Intern Med

Conclusions From CER Executive Summary	Has there been new evidence that may change this conclusion?	References
	ziprasidone were included. e) RCT of risperidone augmentation show significant reduction in depression symptoms, substantial increase in remission and response, compared to augmentation with placebo at 6 weeks.	
In patients with major depressive disorder with psychotic features, olanzapine and olanzapine plus fluoxetine were compared with placebo for 8 weeks in 2 trials. There was a benefit for olanzapine alone.	New Evidence: None	
For bipolar depression, olanzapine and quetiapine were superior to placebo in one study for each drug, but data are conflicting in two other studies that compared atypical antipsychotics to conventional treatment.	a) Two new RCTs found aripriprazole not significantly more effective in bipolar depression than placebo at 8 weeks.	a) Thase, 2008, J Clin Psychopharmacol
We identified 12 trials of risperidone, olanzapine, and quetiapine used as augmentation therapy in patients w/ OCD who were resistant to standard treatment (nine trials were sufficiently similar clinically to pool). Atypical antipsychotics have a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy for OCD patients who fail to adequately respond to SRI therapy. There were too few studies of olanzapine augmentation to permit separate pooling for this drug.	a) A retrospective comparative study showed ziprasidone was less effective than quetiapine in refractory OCD. b) Head-to-head RCT showed both risperidone and olanzapine effective, no significant differences between the two drugs.	a) Savas, 2008, Clin Drug Investig b) Maina, 2008, Eur Neuropsychopharmacol

Conclusions From CER Executive Summary	Has there been new evidence that may change this conclusion?	References
We found four trials of risperidone and two trials of olanzapine of at least 6 weeks duration in patients with PTSD. There were three trials enrolling men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. There were three trials of olanzapine or risperidone as monotherapy for women with PTSD; the evidence was inconclusive regarding efficacy.	A new meta-analysis (Pae, 2008) analyzed data from seven RCTs involving a total of 192 PTSD patients (102 randomized to AAs and 90 randomized to placebo). The results show that AAs may have a beneficial effect in the treatment of PTSD, as indicated by the changes from baseline in Clinician Administered PTSD Scale total scores [standardized mean difference (SMD)=-0.45, 95% confidence interval (CI) (-0.75, -0.14), P=0.004]. In addition, the overall SMD of the mean changes in the three Clinician Administered PTSD Scale subscores was statistically significant (P=0.007) between AAs and placebo groups, favoring AAs over placebo (SMD=-0.27, 95% CI=-0.47, -0.07). In particular, the symptom of 'intrusion' was mainly responsible for this significance. Clinical significance of the results, however, should be carefully interpreted and translated into clinical practice, given that the quality and availability of currently existing RCTs included in the analysis.	Pae, 2008, In Clin Psychopharm
We identified five trials of atypical antipsychotic medications as treatment for borderline personality disorder & one trial as treatment for schizotypal personality disorder. Three RCTs each w/ no more than 60 subjects provide evidence that olanzapine is more effective than placebo & may be more effective than fluoxetine in treating borderline personality disorder. The benefit of adding olanzapine to dialectical therapy for borderline personality disorder was small.	An RCT of ziprasidone failed to show benefit in BPD.	Pascual, 2008, J Clin Psychiatry

Conclusions From CER Executive Summary	Has there been new evidence that may change this conclusion?	References
Risperidone was more effective than placebo for the treatment of schizotypal personality disorder in one small trial.	New Evidence: None	
Aripiprazole was more effective than placebo for the treatment of borderline personality in one small trial.	18-month f/u of the original included aripiprazole trial shows significant improvement at 18 months.	Nickel, 2007
We found four trials of risperidone and one of ziprasidone for treatment of Tourette's syndrome. Risperidone was more effective than placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three remaining trials. The one available study of ziprasidone showed variable effectiveness compared to placebo.	New Evidence: None	
Two trials support the superiority of risperidone over placebo in improving serious behavioral problems in children with autism.	Another trial showed that (non-autistic) children who respond to initial treatment with risperidone would benefit from continuous long-term treatment.	Reyes, 2006
Key Question 3: What subset of the population would potentially benefit from off-label uses?		
Other than specific populations listed in the finding for Key Question 2, there was insufficient information to answer this question. Therefore, it is included as a topic for future research.	New Evidence: None	

Conclusions From CER Executive Summary	Has there been new evidence that may change this conclusion?	References
Key Question 4: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics?		
Olanzapine patients are more likely to report weight gain than those taking placebo, other atypical antipsychotics, or conventional antipsychotics.	New Evidence: None	
In a recently published meta-analysis death occurred in 3.5 percent of dementia patients randomized to receive atypical antipsychotics vs. 2.3 percent of patients randomized to receive placebo. The difference in risk for death was small but statistically significant. Sensitivity analyses did not show evidence for differential risks for individual atypical antipsychotics. In another recently published meta-analysis of six trials of olanzapine in dementia patients, differences in mortality between olanzapine and risperidone were not statistically significant, nor were differences between olanzapine and conventional antipsychotics.	a) A new meta-analysis of six RCTs of risperidone regarding mortality in elderly dementia patients showed 4.0% mortality with risperidone versus 3.1% with placebo (relative risk 1.21, 95% CI 0.71-2.06) during tx or within 30 days or tx discontinuation. b) Study assessed short-term mortality in a population-based cohort of elderly people in British Columbia who were prescribed conventional or atypical antipsychotic medications. Within the first 180 days of use, 1822 patients (14.1%) in the conventional drug group died, compared with 2337 (9.6%) in the atypical drug group (mortality ratio 1.47, 95% CI 1.39-1.56). Multivariable adjustment resulted in a 180-day mortality ratio of 1.32 (1.23-1.42).	a) Haupt, 2006, J Clin Psychopharmacol b) Schneeweiss, 2007, Cmaj
In our pooled analysis of three RCTs of elderly patients with dementia, risperidone was associated with increased odds of cerebrovascular accident compared to placebo. This risk was equivalent to 1 additional stroke for every 31 patients treated in this patient population (i.e.,	a) Retrospective cohort study with N >40,000 used a logistic regression model to show that relative to those who received no antipsychotics, community dwelling elderly newly dispensed an atypical were 3.2 times more likely, and those who received a conventional antipsychotic were 3.8 more likely, to develop any serious event during the first 30 days.	a) Rochon, 2008, Arch Intern Med; Gill, 2007, Ann Intern Med b) Kales, 2007, Am J Psychiatry c) Hollis, 2007, Am J Geriatric Psychiatry

Conclusions From CER Executive Summary	Has there been new evidence that may change this conclusion?	References
number needed to harm of 31). The manufacturers of risperidone pooled four RCTs and found that cerebrovascular adverse events were twice as common in dementia patients treated with risperidone as in the placebo patients. In a separate industry-sponsored analysis of five RCTs of olanzapine in elderly dementia patients, the incidence of cerebrovascular adverse events was three times higher in olanzapine patients than in placebo patients.	b) Retrospective cohort study of VA data on patients age 65+ (N = 10,615) who began outpatient treatment with psyc meds following a dementia diagnosis showed that those taking antipsychotics had significantly higher mortality rates (22.6% to 29.1%) than patients taking non-antipsychotic meds (14.6%). Adjusted mortality risks for atypicals were similar to those for conventional antipsychotics. The proportions of patients taking antipsychotics who died from cerbrovascular, cardiovascular, or infectious causes were not higher than rates for those taking other psyc meds. c) Death rates for incident (N=16,634) and prevalent (N=9,831) users of various antipsychotics, carbamazepine, and sodium valproate age 65+ were compared. Haloperidol was consistently associated with increased risk of death compared with olanzapine (RR for incident users 2.26, 95% CI 2.08 – 2.47). Risperidone (RR 1.23, 95% CI: 1.07 – 1.40) was also associated with increased risk of death compared to olanzapine in incident users.	
We pooled three aripiprazole trials and four risperidone trials that reported extrapyramidal side effects (EPS) in elderly dementia patients. Both drugs were associated with an increase in EPS.	New Evidence: None	
Ziprasidone was associated with an increase in EPS when compared to placebo in a pooled analysis of adults with depression, PTSD, or personality disorders.	New Evidence: None	

Conclusions From CER Executive Summary	Has there been new evidence that may change this conclusion?	References
Risperidone was associated with increased weight gain compared to placebo in our pooled analyses of three trials in children/adolescents. Odds were also higher for gastrointestinal problems, increased salivation, fatigue, EPS, and sedation among these young risperidone patients.	New Evidence: None	
Compared to placebo, all atypicals were associated with sedation in multiple pooled analyses for all psychiatric conditions studied.	New Evidence: None	
Key Question 5: What are the appropriate dose and time limit for off-label indications?		
There was insufficient information to answer this question. Therefore, it is included as a topic for future research	New Evidence: None	

Are there new data that could inform the key questions that might not be addressed in the conclusions?

Glucose / Diabetes: Sacher (2008, Neuropsychopharmacology) reports a small RCT where olanzapine but not ziprasidone lead to a decrease in whole body insulin sensitivity in response to a hyperinsulinemic euglycemic challenge in healthy adults.

Bayesian data-mining of FDA adverse events reporting system (DuMouchel, 2008, Ann Clin Psychiatry) showed consistent and substantial differences between atypicals in reporting ratios re glycemic effects, especially life-threatening ones. Low association: ziprasidone, aripriprazole, and risperidone; medium association: quetiapine, and strong association: olanzapine.

A VA retrospective cohort analysis (Duncan, 2007) showed that in patients without a random plasma glucose of >=160 mg/dl before medication exposure (n=1394), treatment with olanzapine, risperidone, or a typical antipsychotic was associated with an incidence of new diabetes-level hyperglycemia of 78.7 cases per 1,000 individuals exposed per year. Olanzapine was associated with a greater rate of developing at least one fasting glucose measurement of >=200 than risperidone (OR = 2.14).

In a systematic review of 17 pharmacoepidemiologic studies (Ramaswamy, 2006, Ann Clin Psychiatry) olanzapine, but not risperidone, was associated with significantly increased risk of new-onset diabetes. Of nine studies comparing relative risk of diabetes with olanzapine and risperidone, six demonstrated significantly greater risk with olanzapine.

A retrospective study of schizophrenia patients at Mass General (Henderson, 2007, J Clin Psychiatry) showed that the incidence of diabetes presenting as diabetic ketoacidosis was higher than in the general hospital population and differed across drugs (olanzapine, 0.8%, risperidone, 0.2%, no incidence with ziprasidone or quetiapine).

A retrospective analysis of diabetes risk in elderly patients with dementia in seven olanzapine clinical trails (Micca, 2006, Am J Geriatr Psychiatry) showed that risk of diabetes was not significantly associated with antipsyc treatment.

Pituitary tumors: Sarfman (2006) analyzed the FDA AERS and found that risperidone had the highest adjusted reporting rations for hyperprolactinemia, galactorrhea, and pituitary tumor among the antipsychotics, and one of the highest scores for all drugs in the database.

Cholesterol: Using MediCal data, Olfson (2006) estimated the relative risk of developing hyperlipidemia after treatment with antipsychotics compared to no antipsychotic treatment. 12,133 incident cases of hyperlipidemia were matched to 72,140 control subjects. Compared with no antipsyc meds, tx with risperidone (OR 1.56, 95% CI 1.43 – 1.64), quetiapine (OR 1.52, 95% CI 1.40 – 1.65), olanzapine (OR 1.56, 95%CI 1.47 – 1.67) and ziprasidone (OR 1.40, CI 1.19 – 1.65) were associated with increased risk of hyperlipidemia, as were conventional antipsychotics (OR 1.26, 95% CI 1.14 – 1.39).

Muscle toxicity: Waring (2006) reviewed case notes from 64 consecutive patients admitted after olanzapine overdose. Serum creatine kinase was > 5 times the upper limit of normal in 17% of patients, and there was a dose-dependent relationship. No patients developed renal failure.

New drug: Paliperidone-ER, first atypical with extended release formulation approved by FDA for schizophrenia (Lautneschlager, 2008; Yang, 2007; Owen, 2007; Howland, 2007).

CER 7 - Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression

Treatment of Major Depressive Disorder (KQ 1): For adults with MDD, dysthymia, or subsyndromal depressive disorders, do commonly used medications for depression differ in efficacy or effectiveness in treating depressive symptoms? If a patient has responded to one agent in the past, is that agent better than current alternatives at treating depressive symptoms?

Original Findings	New findings
Efficacy and effectiveness.	
38 percent of patients did not respond during 6 to 12 weeks of treatment with second-generation antidepressants; 54 percent did not achieve remission. The evidence is insufficient to determine factors that can reliably predict response or nonresponse in individual patients.	A pooled analysis of 9 RCTs, comparing duloxetine with placebo for 8-9 weeks, found duloxetine produced significantly greater baseline-to-endpoint mean change than placebo in HAMD17 total score, Maier and retardation subscales, and the Clinical Global Impressions-Severity of Illness scale in mild (HAMD17: < or =19; n=682), moderate (HAMD17: between 19 and 25, n=1099), or severe (HAMD17: > or =25; n=446) groups. Effective sizes were largest in the most severely depressed patients. (Shelton, Andorn et al. 2007) An analysis of 62 RCTs of patients with depressive disorder, comparing paroxetine vs. placebo or other antidepressants (amisulpride, amitriptyline, bupropion, clomipramine, doxepin, fluvoxamine, fluoxetine, imipramine, lofepramine, mianserin, mirtazapine, moclobemide, maprotiline, nefazodone, nortriptyline, sertraline, tianeptine, venlafaxine), found paroxetine yielded consistently and significantly better remission (rate difference (RD): 10%, 95% CI 6 to 14), clinical response (RD: 17%, 95% CI 7 to 27), and symptom reduction (effect size: 0.2, 95% CI 0.1 to 0.3) than placebo. No consistent and significant difference was observed between paroxetine and other antidepressants. (Katzman, Tricco et al. 2007)
Seventy-two head-to-head comparisons (i.e., comparisons between medications conducted within trials) provided data on 35 of the potential comparisons between the 12 second-generation antidepressants addressed in this report. Five trials directly compared any non-SSRI second-generation antidepressant with any other non-SSRI second-generation antidepressant; of these, only one comparison was evaluated in more than one trial. Many efficacy trials were not powered to detect statistically or clinically significant differences, leading to inconclusive results. Direct evidence from head-to-head trials was considered sufficient to conduct meta-analyses for four drug-drug comparisons. Differences in efficacy reflected in some of these meta-analyses are of modest magnitude and clinical implications remain to be determined.	2 direct comparison studies with escitalopram vs. venlafaxine XR, and indirect comparison, using 10 placebo-controlled studies, found escitalopram was non-inferior to venlafaxine XR (indirect comparison: mean -0.02, 95% CI: -0.16 to infinity; direct comparison: mean: 0.23, 95% CI: -0.01 to infinity). The results were consistent after controlling age, gender repartition and severity at baseline. (Eckert and Falissard 2006) A prospective, 24-week open label study of 170 patients with major depressive disorder, comparing venlafaxine vs. paroxetine, found venlafaxine was comparable with paroxetine on response rate and remission, whereas paroxetine produced significantly higher remission rates at weeks 4, 8, 16, 20, 24 when remission was defined as HRSD =5. Conclusion: Venlafaxine treatment was similar to paroxetine according to the typical efficacy measures. However, the authors feel that paroxetine might be superior to venlafaxine if the stricter remission criterion is

	used. (Wu, Chen et al. 2007) Pairwise comparisons of paroxetine and venlafaxine, mirtazapine, mianserin, or fluoxetine yielded inconsistent results across efficacy outcomes, using 62 RCTs of patients with depressive disorder. (Katzman, Tricco et al. 2007)
Citalopram vs. escitalopram (five studies; 1,545 patients): Patients on escitalopram had an additional treatment effect of a 1.25-point reduction (95-percent confidence interval [CI], 0.10-2.39) on the Montgomery-Asberg Depression Rating Scale (MADRS) compared with patients on citalopram. The relative risk (RR) of response was statistically significantly greater for escitalopram than for citalopram (RR: 1.14; 95-percent CI, 1.04-1.26). The number needed to treat (NNT) to gain one additional responder at week 8 with escitalopram was 14 (95-percent CI, 7-111). Both drugs are produced by the same manufacturer, which funded all available studies.	2 placebo-controlled trials and a head-to-head superiority study show escitalopram was numerically better than citalopram in reducing Montgomery-Asberg Depression Rating Scale (MADRS). Meta-analysis of 5 clinical trials (3 placebo-controlled trials, 1 head-to-head superiority study, and 1 long-term non-inferiority study) showed statistically significant differences in favor of escitalopram in terms of reducing MADRS and increasing response. (LanÃ§on, Verpillat et al. 2007)
Fluoxetine vs. paroxetine (seven studies; 950 patients): The study did not find any statistically significant differences in effect sizes on the Hamilton Depression Rating Scale (HAM-D) or response rates between fluoxetine and paroxetine. Fluoxetine had an additional reduction of 0.55 (95-percent CI, –1.4-0.36; *P* = 0.23) points on HAM-D compared with paroxetine; paroxetine led to a higher rate of responders than fluoxetine (RR 1.09; 95-percent CI, 0.99-1.21).	An analysis of 12 RCTs of patients with depressive disorder, comparing paroxetine and fluoxetine, found inconsistent results across efficacy outcomes. (Katzman, Tricco et al. 2007)
Fluoxetine vs. sertraline (four studies; 940 patients): Patients on sertraline had an additional, statistically nonsignificant treatment effect of a 0.75-point reduction (95-percent CI, –0.45-1.95) on the Hamilton Rating Scale for Depression (HAM-D) scale compared with patients on fluoxetine. The relative risk of response was statistically significantly greater for sertraline than for fluoxetine (RR: 1.11; 95-percent CI, 1.01-1.21). The NNT to gain one additional responder at 6 to 12 weeks with sertraline was 14 (95-percent CI, 8-22).	No new evidence
Fluoxetine vs. venlafaxine (eight studies; 1,814 patients): Patients on venlafaxine had an additional, statistically nonsignificant treatment effect of a 1.31-point reduction (95-percent CI, 0.10-2.39) on the HAM-D scale compared with patients on fluoxetine. The relative risk of response was statistically significantly greater for venlafaxine than for fluoxetine (RR: 1.12; 95 percent CI, 1.01-1.24). The NNT to gain one additional responder at 6 to 12 weeks with venlafaxine was 12 (95-percent CI, 7-50). All studies were funded by the makers of venlafaxine.	A direct comparison of venlafaxine vs. fluoxetine among patients with major depressive disorder, followed up for 1 year, found no significant difference in time to rehospitalization.(Lin, Lin et al. 2008) A meta-analysis of 34 RCTs, comparing venlafaxine to fluoxetine, found venlafaxine is statistically superior to fluoxetine. (Nemeroff, Entsuah et al. 2008)
Most trials were efficacy trials conducted in carefully selected populations under carefully controlled conditions. Only three trials met criteria for being an effectiveness trial, which is intended to have greater generalizability to typical	No new evidence

practice. Of these trials, two were conducted in French primary care settings and one in primary care clinics in the United States. Findings were generally consistent with efficacy trials and did not reflect any substantial differences in comparative effectiveness in adults.	
Findings from indirect comparisons (i.e., comparisons of medications conducted across placebo-controlled trials rather than within a single trial) yielded no statistically significant differences in response rates. The precision of some of these estimates was low, leading to inconclusive results with wide confidence intervals. Nevertheless, point estimates of treatment effects from these analyses were consistent with those from direct evidence trials in indicating no or minimal differences in efficacy among available comparisons.	Indirect comparison with escitalopram vs. venlafaxine XR, using 10 placebo-controlled studies, and two direct comparison studies found escitalopram was non-inferior to venlafaxine XR (indirect comparison: mean -0.02, 95% CI -0.16 to infinity; direct comparison: mean: 0.23, 95% CI: -0.01 to infinity). The results were consistent after controlling age, gender repartition and severity at baseline. (Eckert and Falissard 2006)
Overall, the strength of the evidence was moderate for both comparative efficacy and comparative effectiveness.	
Although second-generation antidepressants appear similar in average efficacy and effectiveness, the studies were not designed to test variation among individuals in their responses to individual drugs. The second-generation antidepressants cannot be considered identical drugs. Evidence of moderate strength supports some differences among individual drugs with respect to onset of action and some measures (e.g., sexual functioning) that could affect health-related quality of life. These are statistically significant but of modest magnitude; potential benefits might be offset by specific adverse events. Nonetheless, some of these differences may influence the choice of a medication for specific patients.	A meta-analysis of 34 RCTs, comparing venlafaxine and SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram), found venlafaxine had higher ITT remission rate than the SSRIs as a group (the overall difference is 5.9%, 95% CI 0.038 to 0.081; $p<0.001$). The number needed to treat (NNT) to benefit is 17 (95% CI 12-26). The difference vs. fluoxetine was significant (6.6%, 95% CI 0.030 to 0.095); smaller difference vs. paroxetine, sertraline, and citalopram were not significant. Venlafaxine therapy is statistically superior to SSRI as a class, but only to fluoxetine individually. The clinical significance of the modest advantage seems limited to the broad grouping of major depressive disorder. (Nemeroff, Entsuah et al. 2008)
Quality of life. Quality of life or functional capacity was infrequently assessed, usually as a secondary outcome. Eighteen studies (4,050 patients), mostly of fair quality, indicated no statistical differences in health-related quality of life. The strength of evidence is moderate.	No new evidence
Speed of response. Seven studies, all of fair quality and funded by the maker of mirtazapine, reported that mirtazapine had a significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline. The NNT to yield one additional responder after 1 or 2 weeks of treatment is 7 (95-percent CI, 5-12); after 4 weeks of treatment, however, most response rates were similar. Again, this treatment effect was consistent across all studies, but whether this difference can be extrapolated to other second-generation antidepressants remains unclear. The strength of evidence is moderate.	No new evidence
Response to a second agent. The Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial is the only well-done study looking at the question of response to a second agent among those failing initial therapy. Results show that about one in four of the 727 people who participated in the switch responded to sym-bupropion sustained release (SR), sertraline, and venlafaxine extended release	A review of 5 randomized comparative studies (3 RCTs and 2 randomized open label studies) and 9 non-randomized non-comparative studies (2 switch studies, 5 open label switch studies, 1 post-hoc analysis, and 1 open case study) of >5,000 patients with treatment resistant depression shows venlafaxine is associated with modest rates of response and remission in patients who have failed previous SSRI

(XR).	treatment. However, the findings from the comparative studies do not uniformly find venlafaxine to be superior. The author supports the use of venlafaxine as a common switch agent following initial antidepressant failure. (Dunner 2007)
Treatment of Dysthymia	
Efficacy and effectiveness. No head-to-head trial compared different medications in a population with dysthymia. In placebo-controlled trials, significant differences in population characteristics make the evidence insufficient to identify differences between treatments. One good-quality and four fair-quality placebo-controlled trials provide mixed evidence on the general efficacy and effectiveness of fluoxetine, paroxetine, and sertraline for the treatment of dysthymia. A fair-quality effectiveness study provides mixed evidence on the effectiveness of paroxetine compared to placebo. A subgroup of patients older than 60 years showed a significantly greater improvement than those on placebo; a subgroup of patients younger than 60 years did not show any difference in effectiveness between paroxetine and placebo. The strength of evidence is low.	No new evidence
Treatment of Subsyndromal Depression	
Efficacy and effectiveness. The only head-to-head evidence for treating patients with subsyndromal depression came from a nonrandomized, open-label trial comparing citalopram with sertraline. This study did not detect any differences in efficacy. Findings from two placebo-controlled trials (both fair quality) were insufficient to draw any conclusions about the comparative efficacy and effectiveness of second-generation antidepressants for the treatment of subsyndromal depression. The strength of evidence is low.	No new evidence

Maintenance of Response or Remission (KQ 2a): For adults with a depressive syndrome, do antidepressants differ in their efficacy or effectiveness for maintaining response or remission (i.e., preventing relapse or recurrence)?

Original Findings	New findings
Efficacy and effectiveness. Three head-to-head RCTs suggest that no substantial differences exist between fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine for maintaining response or remission (i.e., preventing relapse or recurrence of MDD). The strength of the evidence is moderate. Twenty-one placebo-controlled trials support the general efficacy and effectiveness of most second-generation antidepressants for preventing relapse or recurrence. No evidence exists for duloxetine. The overall strength of this evidence is moderate.	A review of 5 placebo-controlled acute-phase studies found most of the relapse rate during new-generation antidepressant continuation treatment may be due to relapse in patients who were not true drug responders. (Zimmerman and Thongy 2007) A meta-analysis of 1833 outpatients with major depressive disorder found the HAMD-sub-1-sub-7 remission rate was 40.3% for duloxetine, 38.3% for 2 SSRIs (paroxetine or fluoxetine), and 28.4% for placebo. Active treatments were superior to placebo. The difference between duloxetine and SSRIs was not statistically significant. Duloxetine therapy was significant more effective than therapy with the 2 SSRIs for patients with more severe depression, with remission rates of 35.9% vs. 28.6% (P=0.046). (Thase, Pritchett et al. 2007) An update of the orginal report, using four head-to-head trials and 23 placebo-controlled trials from 1980-2007, did not find statistically difference in relapse or recurrence prevention between duloxetine and paroxetine, fluoxetine and sertraline, and trazodone and venlafaxine. Compared with placebo, the class of second-generation antidepressants had a relatively large effect size that persists over time. The number of patients needed to treat is 5 (95% CI: 4-6). (Hansen, Gaynes et al. 2008)

Treatment of Treatment-Resistant Depression Syndrome or Relapse or Recurrence (KQ 2b): For adults receiving antidepressant treatment for a depressive syndrome that either has not responded (acute phase) or has relapsed (continuation phase) or recurred (maintenance phase), do alternative antidepressants differ in their efficacy or effectiveness?

Original Findings	New findings
Efficacy and effectiveness. One head-to-head efficacy study and two effectiveness studies provide conflicting evidence on differences among second-generation antidepressants in treatment-resistant depression. The efficacy study (fair quality) suggests that venlafaxine is modestly more effective than paroxetine. A good-quality effectiveness study suggests that no substantial differences exist among bupropion SR, sertraline, and venlafaxine XR, but a fair-quality effectiveness study suggests that venlafaxine is modestly more effective than citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline. Given the conflicting results, the overall strength of the evidence is moderate.	A review of 5 randomized comparative studies (3 RCTs and 2 randomized open label studies) and 9 non-randomized non-comparative studies (2 switch studies, 5 open label switch studies, 1 post-hoc analysis, and 1 open case study) of >5,000 patients with treatment resistant depression supports the use of venlafaxine as a common switch agent following initial antidepressant failure. (Dunner 2007) An 8-week double-blind, placebo controlled trial of elderly patients with recurrent major depressive disorder comparing duloxetine vs. placebo, found duloxetine significantly improved cognition, depression and some pain measures. Hamilton depression scale response (37.3% vs. 18.6%) and remission (27.4% vs. 14.7%) rates at endpoint were significantly higher for duloxetine than placebo. (Raskin, Wiltse et al. 2007)
Although several comparative studies included patients who had relapsed or who were experiencing a recurrent depressive episode, no study *specifically* compared one second-generation antidepressant with another as a second-step treatment in such patients.	

Treatment of Depression in Patients With Accompanying Symptom Clusters (KQ 3a): Do medications differ in their efficacy and effectiveness in treating the depressive episode?

Original Findings	New findings
Anxiety. Evidence from six head-to-head trials and one placebo-controlled trial (all fair quality) suggests that antidepressant medications do not differ substantially in antidepressive efficacy for patients with MDD and anxiety symptoms. The trials found no substantial differences in efficacy between fluoxetine, paroxetine, and sertraline; sertraline and bupropion; and sertraline and venlafaxine. One trial found statistically significant superiority of venlafaxine over fluoxetine. The strength of evidence is moderate.	A prospective cohort study of 6,719 adult patients with depressive syndrome and associated with anxiety symptoms, treated with venlafaxine XR for 24 weeks, found venlafaxine XR was associated with significant decrease in the scores in the HAM depression rating and HAM-A anxiety rating. (Roca Benassar and Baca Baldomero 2006)
Insomnia. Three head-to-head trials that identified a specific insomnia group (all fair quality) provide limited evidence regarding comparative efficacy of medications for treating depression in patients with accompanying insomnia. One trial found statistically significant superiority for escitalopram over citalopram. The strength of evidence is low.	No new evidence
Melancholia. Two head-to-head trials (both fair quality), one poor-quality head-to-head trial, and one fair-quality placebo-controlled study provide limited evidence on the comparative effects of medication for treating depression in patients with melancholia. In one, depression response rates for sertraline were superior to those for fluoxetine; in another, depression scores improved more for venlafaxine than for fluoxetine. The strength of evidence is low.	No new evidence
Pain. One fair-quality trial that required baseline pain for inclusion found no difference in efficacy for duloxetine compared with placebo for treating depression in patients with pain of at least mild intensity. The strength of evidence is low.	No new evidence
Psychomotor changes. One fair-quality head-to-head trial reported no statistically significant difference between fluoxetine and sertraline for treating depression in patients with psychomotor retardation. The same study found that sertraline was more efficacious than fluoxetine for treating depression in patients with psychomotor agitation. The strength of evidence is low.	No new evidence
Somatization. No relevant study.	

Treatment of Symptom Clusters in Patients with Accompanying Depression (KQ 3b): Do medications differ in their efficacy and effectiveness in treating the accompanying symptoms?

Original Findings	New findings
Anxiety. Ten head-to-head trials and two placebo-controlled trials (all fair quality) provide evidence that antidepressant medications do not differ substantially in efficacy for treatment of anxiety associated with MDD. Trials found no substantial differences in efficacy between fluoxetine, paroxetine, and sertraline; sertraline and bupropion; sertraline and venlafaxine; citalopram and mirtazapine; and paroxetine and nefazodone. One trial found that venlafaxine was statistically significantly superior to fluoxetine. The strength of evidence is moderate.	No new evidence
Insomnia. Six head-to-head trials (all fair quality) provide limited evidence about	An analysis of 10 double blind head-to-head trials of patients with major

comparative effects of antidepressants on insomnia in patients with depression. The strength of evidence is low.	depressive disorder found bupropion and the SSRIs appear to be equally effective in treating insomnia in depression. (Papakostas, Kornstein et al. 2007)
Melancholia. No relevant study.	No new evidence
Pain. Two head-to-head trials (one of fair and the other of poor quality) and three placebo-controlled trials (all fair quality) provide limited evidence about effects of antidepressants on pain symptoms in depressed patients. Two trials found no substantial difference in efficacy between duloxetine and paroxetine. The strength of evidence is low.	A pooled analysis of 9 RCTs, comparing duloxetine with placebo for 8-9 weeks, found mildly (HAMD17: < or =19; n=682) and severely (HAMD17: > or =25; n=446) depressed patients with duloxetine exhibited significant reduction in visual analog scale overall pain severity. (Shelton, Andorn et al. 2007) An 8-week double-blind, placebo controlled trial of elderly patients with recurrent major depressive disorder, comparing duloxetine vs. placebo, found duloxetine significantly improved Visual Analogue Scale scores for back pain and time in pain while awake vs. placebo. (Raskin, Wiltse et al. 2007)
Psychomotor changes. No relevant study.	A meta-analysis of 44 placebo-controlled trials of patients with Parkinson's disease (PD) and depression found a modestly positive and significant effect size result with SSRIs on motor function (d=0.34, p<0.05). (Frisina 2005)
Somatization. One open-label effectiveness trial found no statistically significant difference among three SSRIs for treating somatization in patients with depression. The strength of evidence is low.	No new evidence

Differences in Harms (Adverse Events) (KQ 4): For adults with a depressive syndrome, do commonly used antidepressants differ in safety, adverse events, or adherence?

Original Findings	**New findings**
General tolerability	
Adverse events profiles. Constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence were commonly and consistently reported adverse events. On average, 61 percent of patients in efficacy trials experienced at least one adverse event. Nausea and vomiting were found to be the most common reasons for discontinuation in efficacy studies. Overall, second-generation antidepressants have similar adverse events profiles, and the strength of evidence is high.	An update of the orginal report, using four head-to-head trials and 23 placebo-controlled trials from 1980-2007, found the most common adverse event due to treatment of second generation antidepressants (including duloxetine, paroxetine, fluoxetine, sertraline, trazodone and venlafaxine) in continuation- and maintenance-phase studies was headache, followed by nausea (weighted mean incidence=15.5% and 7.4%, respectively). Compared with the incidence of adverse events in acute-phase studies, the relative incidence during long-term treatment was slightly lower. (Hansen, Gaynes et al. 2008) In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, among 2,876 patients with major depression, ratings of side effect frequency, intensity, and burden, as well as the number of serious adverse events, were significantly greater in the anxious depression group than those with nonanxious depression. (Fava, Rush et al. 2008) A randomized study of 727 patients with nonpsychotic major depressive disorder and taking any of sustained-release bupropion hydrochloride, sertraline hydrochloride, or extended release venlafaxine hydrochloride, intolerance was less

	likely for Hispanic participants, more likely for those with previous suicide attempts or intolerance to citalopram. (Rush, Wisniewski et al. 2008) A clinical trial of 35 adult cancer outpatients with depression, during chemotherapy, found sertraline was well tolerated. No severe adverse effects were observed. (Torta, Siri et al. 2008) A retrospective cohort study of elderly patients prescribed SSRIs found the risk of poisoning during SSRI use was higher than nonuse. The adjusted hazard ratio (95% CI) of poisoning was higher during SSRI use vs nonuse (1.16 [1.07 to 1.25]) and varied between SSRI agents from 0.93 (0.74 to 1.16) for fluoxetine to 1.45 (1.23 to 1.71) for fluvoxamine. (Rahme, Dasgupta et al. 2008) Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), found nausea was the only AE with an incidence greater than or equal to 10% and 5 percentage points greater than with placebo during short-term treatment. In general, AEs of escitalopram were mild to moderate in severity. (Baldwin, Reines et al. 2007) A meta-analysis of 7 double-blind placebo controlled trials of patients with MDD who received duloxetine found the most common treatment-emergent adverse events due to duloxetine in African-American and Caucasian patients included nausea, headache, constipation, dizziness and insomnia. The rate of occurrence of these events did not differ significantly between these two groups. (Bailey, Mallinckrodt et al. 2006)
Venlafaxine was associated with an approximately 10-percent (95-percent CI, 4-17 percent) higher incidence of nausea and vomiting than SSRIs as a class. In addition, pooled discontinuation rates because of adverse events in efficacy trials are statistically significantly higher for venlafaxine than for SSRIs (RR: 1.50; 95-percent CI, 1.21-1.84). The strength of evidence is high.	A meta-analysis of 34 RCTs, comparing venlafaxine and SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram), found attrition rates due to adverse events were higher with venlafaxine than with SSRI therapy, 11% and 9%, respectively (p=0.0011). (Nemeroff, Entsuah et al. 2008)
In most studies, sertraline led to higher rates of diarrhea than comparator drugs (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine). The incidence was 8-percent (95-percent CI, 3-11 percent) higher than with comparator drugs. Whether this finding can be extrapolated to comparisons of sertraline with other second-generation antidepressants remains unclear. The strength of evidence is moderate.	No new evidence
Mirtazapine led to higher weight gains than comparator drugs (fluoxetine, paroxetine, venlafaxine, and trazodone). Mean weight gains compared to pretreatment ranged from 0.8 kg to 3.0 kg after 6 to 8 weeks of treatment.	No new evidence

Paroxetine had higher weight gains than fluoxetine and sertraline. The strength of evidence is moderate.	
Trazodone was associated with an approximately 16-percent (3-percent less to 36 percent higher) higher incidence of somnolence than comparator drugs (bupropion, fluoxetine, mirtazapine, paroxetine, venlafaxine). Whether this finding can be extrapolated to comparisons of trazodone with other second-generation antidepressants remains unclear. The strength of evidence is moderate.	No new evidence
Discontinuation syndromes (e.g., headache, dizziness, nausea) occurred in 0 to 86 percent of patients. Paroxetine and venlafaxine had the highest incidence of this problem, and fluoxetine the lowest incidence. The strength of evidence is moderate.	A review of 385 patients taking paroxetine found 41 patients experienced the discontinuation syndrome. The occurrence of the discontinuation syndrome did not correlate with gender, maintenance dosage of paroxetine, or duration of treatment with the drug. The discontinuation syndrome occurred significantly more frequently in those patients in whom paroxetine was abruptly discontinued. (Himei and Okamura 2006) Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), found, compared with paroxetine, escitalopram resulted in significantly fewer discontinuation symptoms (average increase in Discontinuation Emergent Signs and Symptoms Scale of 1.6 vs. 3.9, $p<0.01$). (Baldwin, Reines et al. 2007)
Discontinuation rates. Overall discontinuation rates did not differ significantly between SSRIs as a class and bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine. In the case of venlafaxine compared with SSRIs, higher discontinuation rates because of adverse events (11.5 percent vs. 8.5 percent) appear to be balanced by lower discontinuation rates because of lack of efficacy (3.5 percent vs. 4.4 percent). The strength of evidence is high.	An analysis of the Medical Expenditure Panel Survey for 1996-2001 found 42.4% of patients discontinued antidepressant therapy during the first 30 days. 27.6% of the patients continued antidepressant treatment for more than 90 days. Antidepressant discontinuation during the first 30 days were more common among Hispanics (53.8%) than non-Hispanics (43.7%), patients with few than 12 years of education than those with 12 or more years of education. (Olfson, Marcus et al. 2006) A prospective cohort study of 6,719 adult patients with depressive syndrome and associated with anxiety symptoms, treated with venlafaxine XR for 24 weeks, found 81.8% of patients completed 24 weeks of treatment. (Roca Benassar and Baca Baldomero 2006) An analysis of 62 RCTs found controlled-release paroxetine had significantly fewer dropouts due to adverse events than immediate-release paroxetine (RD: 5%, 95% CI 0.1 to 11). No other difference found between paroxetine and other antidepressants (amisulpride, amitriptyline, bupropion, clomipramine, doxepin, fluvoxamine, fluoxetine, imipramine, lofepramine, mianserin, mirtazapine, moclobemide, maprotiline, nefazodone, nortriptyline, sertraline, tianeptine, venlafaxine). (Katzman, Tricco et al. 2007) Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), the 8 week withdrawal

	rate due to AEs was higher with escitalopram than with placebo (7.3% vs 2.8%, p<0.001) but lower than with paroxetine (6.6% vs 9.0%; p<0.01) or venlafaxine (6.1% vs 13.2%, p<0.01). (Baldwin, Reines et al. 2007) A meta-analysis of 7 double-blind placebo controlled trials of patients with MDD who received duloxetine found no significant difference in discontinuation rates due to adverse events between African-American and Caucasian patients. (Bailey, Mallinckrodt et al. 2006)
Severe adverse events.	
Sexual dysfunction. Bupropion is associated with a lower incidence of sexual dysfunction than fluoxetine, paroxetine, and sertaline. The NNT to gain one additional person with high overall satisfaction of sexual functioning is 6 (95-percent CI, 4-9). In head-to-head trials, paroxetine consistently had higher rates of sexual dysfunction than comparators (fluoxetine, fluvoxamine, nefazodone, and sertraline; 16 percent vs. 6 percent). Underreporting of absolute rates of sexual dysfunction, however, is likely in these studies. Whether these findings can be extrapolated to comparisons of bupropion and paroxetine with other second-generation antidepressants is unclear. The strength of evidence is moderate.	Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), found AEs related to sexual dysfunction were similarly frequent with escitalopram and citalopram, but were higher with paroxetine. (Baldwin, Reines et al. 2007)
Other severe adverse events. The existing evidence on the comparative risk for rare but severe adverse events, such as suicidality, seizures, cardiovascular events (i.e., elevated systolic and diastolic blood pressure and elevated pulse/heart rate), hyponatremia, hepatotoxicity, and serotonin syndrome, is insufficient to draw firm conclusions. The strength of evidence is low. Clinicians should keep in mind the risk of such harms during any course of treatment with a second-generation antidepressant.	A matched case-control study with Medicaid beneficiaries did not find antidepressant drugs are statistically associated with suicide attempts (OR: 1.10 95% CI 0.86-1.39) or suicide deaths (OR 0.90, 95% CI: 0.52-1.55) in adults. However, in children and adolescents, antidepressant drugs were significantly associated with suicide attempts (OR, 1.52, 95% 1.12-2.07) and suicide deaths (OR, 15.62; 95% CI, 1.65-infinity). (Olfson, Marcus et al. 2006) A comparison of before and during 12 weeks of antidepressant treatment in 437 elderly patients with major depression found 7.8% with emergent suicidality, 12.6% with persistent suicidality, and 15.6% with resolved suicidality. Rates of emergent suicidality didn't differ significantly between paroxetine-and nortriptyline-treated patients. (Szanto, Mulsant et al. 2007) A observational cohort study in Denmark found patients who continued treatment with antidepressants had a decreased rate of suicide compared to those who purchased antidepressant once (rate ratio: 0.31, 95% CI: 0.26-0.36). The rate of suicide decreased consistently with the number of prescriptions. (Sondergard, Lopez et al. 2007) A retrospective cohort study with 219,099 UK patients found venlafaxine was associated with an increased risk of attempted suicide, compared to citalopram, fluoxetine and dothiepin. For completed suicides, unadjusted and adjusted hazard ratio for venlafaxine compared with citalopram were 2.44 (95% 1.12 to 5.31) and 1.70 (95% CI 0.76-3.80), for venlafaxine compared with fluoxetine were 2.85

	(95% CI 1.37 to 5.94) and 1.63 (95% CI 0.74 to 3.59). (Rubino, Roskell et al. 2007) A retrospective cohort study of elderly patients prescribed SSRIs found the risk of suicide death was not higher during periods of SSRI use vs. nonuse. The adjusted risk of suicide death was not higher during SSRI use vs. nonuse (hazard ratio (95% CI)): any SSRI=0.64 (0.38 to1.07), paroxetine=0.71 (0.37 to 1.35), citalopram=1.16 (0.59 to 2.25), and sertraline=0.38 (0.16 to 0.93). (Rahme, Dasgupta et al. 2008) An evaluation of 12 placebo controlled trials of MDD patients, comparing duloxetine vs. placebo didn't find significant difference in the incidence of suicide-related events with duloxetine vs. placebo. (Acharya, Rosen et al. 2006) Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), did not find significant differences between escitalopram and placebo in incidence of suicidal behavior, measured by self-harm and suicidal thoughts. The incidence of cardiovascular events with escitalopram was similar to that with placebo. (Baldwin, Reines et al. 2007) An open-label study of 62 patients aged 60+ with major depressive disorder, treated with venlafaxine XR for 12 weeks, found 24% (95% CI 7.3% to 40.7%) of initially normotensive participants and 54% (95% CI 34.3% to 74%) of those with preexisting hypertension experienced an increase in blood pressure. 29% (95% CI 14.6% to 43.4%) developed orthostatic hypotension. 2 experienced a clinically significant increase in QTc interval. 1 participant reported new-onset mild dizziness, 4 reported new-onset tachycardia or palpitation. Overall, 17 unique participants (28.8%, 95% CI 17.3% to 40.4%) experienced a new-onset cardiovascular problem. Systematic monitoring of cardiovascular parameters during treatment with venlafaxine-XR should be strongly recommended, especially in the elderly. (Johnson, Whyte et al. 2006)
Adherence	
Efficacy studies do not indicate any substantial differences in adherence among second-generation antidepressants. The strength of evidence is moderate. One observational study indicated that extended-release formulations might have a better adherence rate than immediate-release medications. This finding, however, is likely attributable more to differences in dosing regimens than to differences in efficacy and harms. To what extent findings from highly controlled efficacy trials can be extrapolated to "real-world" settings remains uncertain. The evidence is insufficient to reach any conclusions about differences in adherence in effectiveness studies. The strength of evidence is low.	An analysis of US nationally representative prescription database found adherence to bupropion therapy was better with the once daily bupropion XL than with the twice-daily bupropion SR formulation. (Stang, Young et al. 2007)

Efficacy, Effectiveness, and Harms for Selected Populations (KQ 5): How do the efficacy, effectiveness, or harms of treatment with antidepressants for a depressive syndrome differ for the elderly, other demographic population and patients with medical comorbidities?

Original Findings	New findings
Age. Twelve head-to-head trials (one an effectiveness study), nine placebo-controlled trials, one retrospective cohort study, and one set of meta-analyses suggest that no major differences in efficacy and effectiveness exist among second-generation antidepressants in elderly or very elderly populations. The strength of the evidence is moderate. Harms such as hyponatremia and weight loss may differ in elderly or very elderly patients on active treatment vs. placebo, but the evidence on these two adverse events is limited to one small RCT and one observational study (both fair quality). The strength of the evidence is low.	An analysis of 10 double blind head-to-head trials of patients with major depressive disorder found no age-related difference in efficacy between bupropion and the SSRIs. (Papakostas, Kornstein et al. 2007) Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), found the risk of AEs due to escitalopram was no higher in special patient populations, such as the elderly or those with hepatic dysfunction. (Baldwin, Reines et al. 2007) An open-label study of 62 patients aged 60+ with major depressive disorder, treated with venlafaxine XR for 12 weeks, found 24% (95% CI 7.3% to 40.7%) of initially normotensive participants and 54% (95% CI 34.3% to 74%) of those with preexisting hypertension experienced an increase in blood pressure. 29% (95% CI 14.6% to 43.4%) developed orthostatic hypotension. 2 experienced a clinically significant increase in QTc interval. 1 participant reported new-onset mild dizziness, 4 reported new-onset tachycardia or palpitation. Overall, 17 unique participants (28.8%, 95% CI 17.3% to 40.4%) experienced a new-onset cardiovascular problem. Systematic monitoring of cardiovascular parameters during treatment with venlafaxine-XR should be strongly recommended, especially in the elderly. (Johnson, Whyte et al. 2006)
Sex. Indirect evidence from one fair-quality pooled analysis of head-to-head RCTs suggests that efficacy among second-generation antidepressants does not differ between men and women. This conclusion is supported by observational evidence. One fair-quality observational study indicated that harms, specifically the rates of sexual dysfunction, might differ between men and women. The strength of the evidence is low.	An analysis of 10 double blind head-to-head trials of patients with major depressive disorder found greater improvement in efficacy in anxious/somatic symptoms of depression among women during SSRIs treatment than men. (Papakostas, Kornstein et al. 2007)
Race or ethnicity. One poor-quality RCT suggests that the efficacy of second-generation antidepressants does not differ for patients in different race or ethnic groups. This study, however, may not have been powered to detect a difference. The strength of the evidence is low.	An analysis of the Medical Expenditure Panel Survey for 1996-2001 found antidepressant discontinuation during the first 30 days were more common among Hispanics (53.8%) than non-Hispanics (43.7%). (Olfson, Marcus et al. 2006) A randomized study of 727 patients with nonpsychotic major depressive disorder and taking any of sustained-release bupropion hydrochloride, sertraline hydrochloride, or extended release venlafaxine hydrochloride, remission was more likely among those who were white. Intolerance was less likely for Hispanic participants. (Rush, Wisniewski et al. 2008)

	An analysis of STAR*D patients with nonpsychotic major depressive disorder, treated with citalopram up to 14 weeks, found Black, and to a lesser extent Hispanic patients, had a poorer response to citalopram than white patients. After adjusting for baseline differences, the remission rates seemed to be more similar on the HRSD, but remained worse for blacks on the QIDS-SR. (Lesser, Castro et al. 2007) A meta-analysis of 7 double-blind placebo controlled trials of patients with MDD who received duloxetine found no significant difference in duloxetine's treatment effect between African-American and Caucasian patients. Discontinuation rates due to adverse events did not differ significantly between African-Americans and Caucasians. No adverse event led to discontinuation in more than one African-American patient. The rate of occurrence of AEs did not differ significantly between two groups. (Bailey, Mallinckrodt et al. 2006)
Comorbidities. The evidence for various comorbidities (e.g., HIV/AIDS, alcohol abuse, Alzheimer's disease or other dementia, breast cancer, cardiovascular disease, stroke, and substance abuse) is limited to one head-to head study, a small number of placebo-controlled trials, and one systematic review. They provide limited evidence on the comparative efficacy of second-generation antidepressants in subgroups with different coexisting conditions. The strength of the evidence is low.	A clinical trial of 35 adult cancer outpatients with depression, during chemotherapy, found sertraline could significantly decrease mean depression scores, analyzed by HADS and MADRS scales, HADS anxiety scores. No severe adverse effects were observed. (Torta, Siri et al. 2008) A meta-analysis of 44 placebo-controlled trials of patients with Parkinson's disease (PD) and depression found SSRIs produced a robust antidepressant effect on moderately depressed PD patients ($d=0.44$, $p< 0.05$). A modestly positive and significant effect size result was observed with SSRIs on motor function ($d=0.34$, $p<0.05$), and there were no significant side effects ($d=-0.002$, $p=0.50$). These results show that SSRIs can be used to treat depression without the fear of worsening PD. (Frisina 2005) Analyses of RCTs, comparing escitalopram with placebo or other antidepressants (citalopram, fluoxetine, paroxetine, sertraline, venlafaxine), found the risk of AEs due to escitalopram was no higher in special patient populations, such as the elderly or those with hepatic dysfunction. (Baldwin, Reines et al. 2007)

CER 9 - Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease

Summary statement: Since the publication of this report and its primary peer-reviewed publication (Bravata et al. Ann Intern Med. 2007), no new studies have been published that either significantly changed the summary results of this review or changed the strength of evidence for any of the key questions it addressed.

Key Questions and Outcomes	Summary, Conclusions, and Comments	Has there been any new evidence that may change this conclusion?	References
Procedural survival	- Reported by 23 randomized controlled trials (RCTs) - Procedural survival was slightly, but not significantly higher in PCI patients (PCI-CABG survival difference 0.1%; 95 percent Confidence Interval (CI): -0.3 to 0.6%). - Procedural survival in RCTs was higher than that reported by large administrative databases and clinical registries.	A new report from the NY State Registry showed no difference in procedural mortality. (Data from this registry were already included in the evidence report.) A meta-analysis of 4 of the included RCTs of multi-vessel disease found no difference in survival between the procedures.	Hannan et al. Takagi et al.
Freedom from procedural stroke	- Reported by 14 RCTs - Freedom from procedural strokes was significantly more common after PCI (PCI-CABG difference in freedom from procedural stroke 0.6% CI: 0.2 to 1.0%; p=0.01).	New Evidence: None	
Freedom from procedural myocardial infarction	- Reported by 20 RCTs - Definition of MI varied across trials; results were heterogeneous - Freedom from procedural MI was slightly, but not significantly lower after CABG	New Evidence: None	
Survival	- Overall survival in RCTs was slightly higher after CABG than after PCI between one and five years of follow-up, but the absolute PCI-CABG survival difference was small at each time point (less than 1%) and not statistically significant. - Five year survival was significantly higher after CABG in balloon-era trials (PCI-CABG survival difference -2.1%, CI: -4.1 to -0.1%). However, in stent-era trials, five year survival was not significantly different (PCI-CABG	-A 6-yr follow up study of the SoS trial was published. We combined these results with the 5 year data from other RCTs in an editorial accompanying the publication of the SoS report. Overall, it did not significantly change our results. See Figure 1 below from that editorial. -A new report from the NY State Registry confirmed slightly improved survival with CABG at 18 months compared with PCI. (Data from this registry were already included in the evidence report and the new report was not significantly different from the prior one.) -A meta-analysis of 4 of the included RCTs of multi-vessel disease found no difference in survival between the procedures.	Booth et al. Hlatky & Bravata. Hannan et al.

Key Questions and Outcomes	Summary, Conclusions, and Comments	Has there been any new evidence that may change this conclusion?	References
	survival difference 1.1%, CI: -1.4 to +3.7%). - There was no significant difference in the PCI-CABG survival difference according to extent of disease.		Takagi et al.
Freedom from angina	- Reported by 12 RCTs at 1-year and 7 RCTs at 3- and 5-years - Freedom from angina was significantly greater after CABG (PCI-CABG difference in freedom from angina ranges from -5% to -8%; p value <0.0001 at 1-, 3-, and 5-years).	New Evidence: None	
Freedom from repeat revascularization	- Reported by 11 RCTs at 1-year and 9 RCTs at 5-years - Patients assigned to PCI required 24% more repeat procedures than patients assigned to CABG at 1-year (p <0.0001), and 33% more at 5 years (p<0.0001).	A new report from the NY State Registry also confirmed a higher revascularization rate among stent recipients than CABG patients. (Data from this registry were already included in the evidence report.) A meta-analysis of 4 of the included RCTs of multi-vessel disease found increased repeat revascularization after CABG than after PCI.	Hannan et al. Takagi et al.
Freedom from myocardial infarction	- 10 RCTs reported follow-up data - There was no difference in freedom from MI between PCI and CABG.	New Evidence: None	
Quality of life	- Reported by 11 RCTs using a variety of different measures. - Quality of life scores improved significantly more after CABG than after PCI between one and three years. - Quality of life scores were correlated with the presence and severity of angina.	- Data available from an additional RCT: MASSII. Similar to what was found before, the CABG group had greater improvements in SF36 measured QOL than the PCI group.	Favarato et al.

Key Questions and Outcomes	Summary, Conclusions, and Comments	Has there been any new evidence that may change this conclusion?	References
Cost	- Reported by 10 RCTs, using a variety of methods. - 9 RCTs found significantly lower initial costs for PCI than for CABG, but this difference narrowed substantially over subsequent follow-up.	A cost-effectiveness analysis of minimally invasive internal thoracic artery bypass vs PCI-stenting for LAD lesions found that stenting was the dominant strategy in the first two years; however CABG became more cost-effective over time as the revascularization rate for PCI increased.	Rao et al.
Survival	- 11 trials (including 77% of all randomized patients) reported 5 or more years of follow-up. - The PCI-CABG survival difference in these 11 trials did not change significantly between one and five years - Four trials with longer follow-up showed no major changes in the PCI-CABG survival difference between five and seven to eight years of follow-up.	See the comment about the SoS trial above and Figure 1.	
Freedom from angina	- The initial significant advantage of CABG over PCI in freedom from angina grew progressively smaller between one year and five years of follow-up.	New Evidence: None	
Age	- Outcomes by age reported by 3 studies - There were more procedural complications in the older patients, especially stroke. - Patients aged 65 years and older had lower overall survival - The RCTs enrolled very few patients over 75 years of age, limiting conclusions about the comparative effectiveness of PCI and CABG in this population.	New Evidence: None (Please see Comment 1 below.)	
Gender	- Outcomes by gender reported by 3 studies. - Women had lower overall survival, but the survival difference between PCI and CABG was similar to that in men -Women had lower quality of life at baseline, but improved to a similar degree with CABG and PCI.	New Evidence: None	
Race	- Outcomes by race reported by only one study - African-American patients had a lower	New Evidence: None	

Key Questions and Outcomes	Summary, Conclusions, and Comments	Has there been any new evidence that may change this conclusion?	References
	survival regardless of PCI or CABG treatment.		
Diabetes	- Survival at 1 and 5 years in patients with diabetes was reported by 6 RCTs. - The BARI trial found significantly better survival for patients with diabetes assigned to CABG (five-year survival of 80% vs 65%). - None of the other five reports found a significant difference in survival between patients with and without diabetes. -The pooled data from all trials showed no significant difference in survival after PCI vs after CABG (PCI-CABG survival difference -0.8%, CI: -8.3 to +6.6%)	New Evidence: None (Please see Comment 1 below.)	
Obesity	- Obesity did not consistently alter the comparative effectiveness of PCI and CABG.	New Evidence: None	
Other comorbidities	- There was no evidence suggesting that hypertension, tobacco use, renal dysfunction and vascular disease increased risk differently among PCI and CABG recipients.	New Evidence: None	
Extent of disease	- There was no significant difference by extent of disease among patients assigned to PCI or CABG - In clinical registries, patients with extensive disease had improved survival with CABG, whereas patients with minimal disease had improved survival with PCI (interaction test was highly significant).	A new report from the NY State Registry was similar to what was seen in other prior registries—namely that patients with more extensive disease had improved survival with CABG. (Data from this registry were already included in the evidence report.)	Hannan et al.
Left ventricular function	- Few patients with poor left ventricular function were enrolled in RCTs - There was no evidence that the PCI-CABG survival difference was modified by the degree of left ventricular dysfunction	New Evidence: None	

Key Questions and Outcomes	Summary, Conclusions, and Comments	Has there been any new evidence that may change this conclusion?	References
Use of stents	- 10 trials used bare metal stents, 11 used balloon angioplasty, and only the Seoul trial used drug-eluting stents. - Survival at five years was significantly better after CABG in balloon-era trials, but there was no difference in survival in stent-era trials.	New Evidence: None	
Use of minimally invasive techniques	New Evidence: None		
Use of mammary arteries	New Evidence: None		
Clinical presentation	New Evidence: None		
Adjunctive therapies	New Evidence: None		
Process characteristics	New Evidence: None		
Prior revascularization	New Evidence: None		

Comments:

1. The authors at the Stanford-UCSF Evidence-based Practice Center are currently preparing an addendum to the report of individual level patient data from the RCTs of the multi-vessel disease. We have already run this analysis but are expecting data from a final large RCT in the next few weeks and will redo our analyses. This will represent the most important update of the evidence report as it has the ability to address Key questions 2a-c and we have found two striking differences from the synthesis of the trial level data (namely, for diabetes and age). We hope to have the results ready for publication in the next few months.

2. There have been a couple registry reports (which would not have met our inclusion criteria because they are too small (e.g., Javaid et al. Circulation 2007; 116[suppl I]:I-200-I-206) or do not adequately account for key covariates. However, none of these would have changed either our results or our overall confidence rating.

Figure 1.

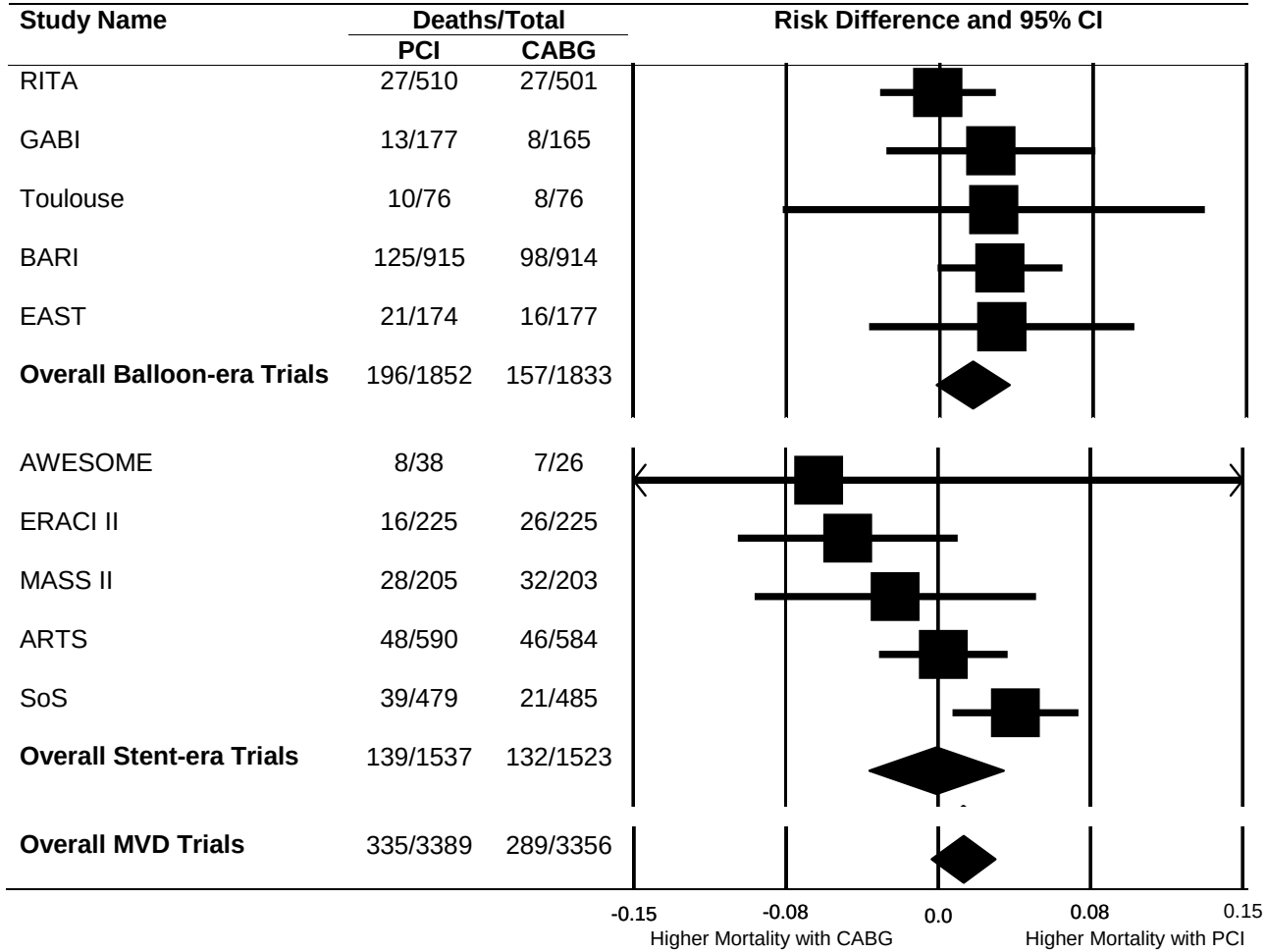

Figure 1. The difference at five years in the risk of death between PCI assigned and CABG assigned patients with multivessel disease in randomized trials. The reported numbers of deaths and patients randomized are listed on the left for each trial, for all balloon-era trials, for all stent-era trials, and for all trials. The risk difference and 95% confidence limits are plotted on the right. Homogeneity statistics for the overall effect from all trials: I^2=21.8; Q=11.5, p=0.24.

CER 10 - Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension

Summary: The original evidence report was a synthesis of data from 69 reports of 61 studies that directly compared the long-term benefits and harms of ACEI vs ARBs. The authors initially considered an analysis of indirect comparisons but ultimately found too much heterogeneity of comparison arms to be able to synthesize these data. Since the publication of this report, there have been several publications of single arm studies but little additional comparative evidence. Specifically, no new studies have been published that either significantly changed the summary results of this review or changed the strength of evidence for any of the key questions it addressed.

Key Questions and Outcomes	ength of Evidence	Summary, Conclusions, and Comments	Has there been any new evidence that may change this conclusion?	References
Key Question 1. For adult patients with essential hypertension, how do ACEIs and ARBs differ in the following health outcomes:				
a. Blood pressure control	igh	ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. This conclusion is based on evidence from 50 studies (47 RCTs, 1 nonrandomized controlled clinical trial, 1 retrospective cohort study, and 1 case-control study) in which 13,532 patients receiving an ACEI or an ARB were followed for periods from 12 weeks to 5 years (median 16.5 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols.	New Evidence: None	

b. Mortality and major cardiovascular events	oderate	Due to insufficient numbers of deaths or major cardiovascular events in the included studies, it was not possible to discern any differential effect of ACEIs vs. ARBs for these critical outcomes. In 9 studies that reported mortality, MI, or clinical stroke as outcomes among 3,356 subjects, 16 deaths and 13 strokes were reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup.	Hackam et al. performed a case-control study of the association of ACE inhibitors and aortic rupture in patients with AAA. They enrolled 15,326 patients admitted with AAA and found that patients on ACEIs had lower risk of rupture than patients on ARBs but this was not a statistically significant finding (OR 1.24; 0.71-2.18). Two reviews published in the same issue of Circulation 2006 (vol 114) evaluated the association of ARBs and MI (see Hall and Strauss). Only one of these included any direct ACEI vs ARB comparison evidence (namely from the CHARM-Added trial). The evidence from this would neither change the conclusion or the quality rating for the risk of MI in this report.	Hackam et al.[i] Hall and Strauss[ii]
c. Quality of life	ow	No differences were found in measures of general quality of life; this is based on 4 studies, 2 of which did not provide quantitative data.	New Evidence: None	

d. Rate of use of a single antihypertensive	igh	There was no statistically evident difference in the rate of treatment success based on use of a single antihypertensive for ARBs compared to ACEIs. The trend toward less frequent addition of a second agent to an ARB was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients, and by RCTs with very loosely defined protocols for medication titration and switching.	New Evidence: None	
e. Risk factor reduction and other intermediate outcomes	loderate (lipid levels, markers f carbohydrate etabolism/ abetes ntrol, rogression of renal disea se) Low rogression to type 2 diabetes d LV ass/function)	There were no consistent differential effects of ACEIs vs. ARBs on several potentially important clinical outcomes, including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, measures of LV mass or function, and progression of renal disease (either based on creatinine, GFR, or proteinuria). Relatively few studies assessed these outcomes over the long term.	The original evidence report was a synthesis of data from 69 reports of 61 studies that directly compared the long-term benefits and harms of ACEI vs ARBs. The authors initially considered an analysis of indirect comparisons but did not include these in the evidence report because of heterogeneity in the treatment and study designs. Elliott and Meyer performed a network meta-analysis (which facilitates the inclusion of both direct and indirect comparison trials) to evaluate the incident diabetes in 22 clinical trials of antihypertensive drugs. They found that ARBs and ACE inhibitors are the antihypertensive agents least associated with incident hypertension but did not find a robust difference between the two. Given the novelty of this method, this would not change the conclusion or level of confidence.	Elliott and Meyer[iii]

Key Question 2. For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety, adverse events, tolerability, persistence, and adherence?	igh (cough, ithdrawals ue to adverse vents) to loderate ersistence/ dherence) to Low ngioedema)	ACEIs have been consistently shown to be associated with greater risk of cough than ARBs: pooled odds ratio (Peto) = 0.32. For RCTs, this translates to a difference in rates of cough of 6.7 percent (NNT = 15); however, for cohort studies with lower rates of cough, this translates to a difference of 1.1 percent (NNT = 87). This is generally consistent with evidence reviewed regarding withdrawals due to adverse events, in which the NNT is on the order of 27—that is, 1 more withdrawal per 27 patients treated with an ACEI vs. an ARB. There was no evidence of differences in rates of other commonly reported specific adverse events. Angioedema was reported only in patients treated with ACEIs; however, because angioedema was rarely explicitly reported in the included studies, it was not possible to estimate its frequency in this population. ACEIs and ARBs have similar rates of adherence based on pill counts; this result may not be applicable outside the clinical trial setting. Rates of continuation with therapy appear to be somewhat better with ARBs than with ACEIs; however, due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify.	New Evidence: None	

Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?	ery low	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs and ARBs for any particular patient subgroup.	New Evidence: None	

References:
[1] Hackam, D. G., D. Thiruchelvam and D. A. Redelmeier (2006). "Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study." Lancet **368**(9536): 659-65.
[1] Hall, A. S. and M. H. Strauss (2007). "More about the "ARB MI paradox"." Heart **93**(9): 1011-4.
[1] Elliott, W. J. and P. M. Meyer (2007). "Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis." Lancet **369**(9557): 201-7.

CER 12 - Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
1. COMPARATIVE BENEFITS IN FRACTURE REDUCTION					
a. BISPHOSPHONATES					
Alendronate					
(65) Jamal, 2007, FIT, ? (Included in LBD final version)	Menopausal women (6458 for total study; 581 w/*severely reduced renal function* (GFR <45ml/min)	RCT of **Alendronate** vs. placebo	Clinical, vertebral frx, AEs	Alendronate reduced the risk of clinical fractures to a similar degree in those with (OR: 0.78; 95% CI: 0.51-1.21) and without reduced renal function (OR: 0.80; 95% CI; 0.70-0.93; p for interaction = 0.89). Alendronate reduced the risk of spine fractures to a similar degree in those with (OR: 0.72; 95% CI: 0.31-1.7) and without reduced renal function (OR: 0.50; 95% CI: 0.32-0.76; p for interaction = 0.44). No diffs in AEs by renal function.	
(115) Black, 2006, FIT	Postmenopausal women with a mean of 5 years **prior alendronate treatment** (1099)	RCT 5, 10 mg/d **Alendronate** or placebo X 5 yrs	Frx incidence as exploratory outcome measure ***to assess persistence of effx***	5-year cumulative risk nonvertebral frx (RR 1.00, 0.76-1.32) did not differ between continuers and discontinuers; Continuers had significant ↓clinical vertebral frx	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				(2.4% vs/ 5.3% for placebo; RR 0.45, 0.24-0.85) but NO difference in morphometric vertebral frx (11.3% for placebo and 9.8% for alendronate; RR, 0.86; 95% CI, 0.60-1.22)	
(146) Hochberg, 2005, multicenter, FIT	Postmenopausal women with OP, 55-80 yoa (3658)	RCT of **alendronate,** 5mg/d x 2 yrs followed by 10mg for 1-2.5 add'l years	Clinical frx	↓ Relative risk for hip, clinical spine, and wrist fractures: constant across age groups, without evidence of a decline at older ages. ALE ↓ risk of clinical fracture by 53% at the hip (RR = 0.47; 95% CI = 0.27-0.81; p≤ 0.01), 45% at the spine (RR = 0.55; 95% CI = 0.37-0.83; p < 0.01), and 31% at the wrist (RR = 0.69; 95% CI = 0.50-0.98; p = 0.038). In addition, alendronate produced a significant risk reduction of 40% (RR = 0.60; 95% CI = 0.47-0.77; p≤ 0.01) for the composite event of clinical hip, spine, and wrist fractures. Effectiveness was somewhat greater in women with T≤-2.5 cf. T≤-2.0.	Absolute risk reduction increased with age because of ↑ risk with age: absolute risk reduction for the composite event (hip, spine, and wrist fractures together) for alendronate treatment versus placebo was 65, 80, 111, and 161 women with fractures per 10,000 Person-yrs for the 55 to ≤ 65, 65 to ≤ 70, 70 to ≤ 75, and 75-85 year age groups, respectively;
(116) Bauer, 2006, FIT	Postmenopausal women 55-80 years, femoral neck T-score≤-1.6 (6,186); with (T≤2.5 or prevalent vertebral frx)(3,495) or without (T≥2.5 or no prevalent vertebral frx)(2,689) OP	RCT **Alendronate** 5-10mg/d vs. placebo, mean FU 3.2 yrs	Risk of incident vertebral and non-vertebral frx in ALN vs. placebo ***stratified by baseline BM marker levels***	492 nonvertebral and 294 morphometric vertebral fractures. ALN-induced↓ in non-vertebral fracture cf placebo was a fn of PINP: (p = 0.03 for trend). E.g., among osteoporotic women in the lowest tertile of pretreatment PINP (≤41.6 ng/ml), ALN vs PBO relative hazard for nonvertebral fracture=0.88 (95% CI: 0.65, 1.21) compared with a relative hazard of 0.54 (95% CI: 0.39, 0.74) among those in the highest tertile of PINP, ≥56.8 ng/ml). Results similar among women without baseline OP. Similar (but non-sign) trends observed with baseline levels of BSALP.	Findings suggest bisphosphonate treatment may be more effective in women with elevated bone turnover

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				Conversely, vertebral frx treatment efficacy among OP women did not differ significantly according to pretreatment marker levels. Vertebral frx treatment efficacy among non-OP women was related to baseline BSALP (p = 0.05 for trend).	
Clodronate					
(55) McCloskey, 2007, UK	Community-dwelling women (≥ 75 yoa) (5,596 Intention to treat)	3-year RCT of oral **clodronate** (800 mg/d) vs. placebo	Fracture incidence and AE	114 new hip frx during the 3-year treatment phase: 56 (2.0%) women in the clodronate group and 58 (2.1%) women in the placebo group (HR, 1.02; 95% CI, 0.71-1.47). Clodronate decreased the incidence of any clinical fracture by 20% (264 women [9.5%] versus 337 [12.1%] in the placebo group; HR, 0.80; 95% CI, 0.68-0.94). Clodronate also decreased the incidence of OP-associated nonhip fractures by 29% (5.2% versus 7.4%; HR, 0.71; 95% CI, 0.57-0.87). AE not significant.	Effect of CLO independent of baseline BMD but NNT less w/OP
Ibandronate					
(32) Cranney, 2008, 8 trials	Postmenopausal women	Pooled analysis of 8 randomized trials of **ibandronate** to compare higher vs. lower doses: Expressed as annual cumulative exposure (ACE) ≥10.8mg (monthly, quarterly, or bimonthly dosing) vs. ACE=5.5 mg	Non-vertebral frx	Dose-response trend with increasing ACE doses (7.2-12 mg). (HR 0.62 [95% CI 0.396-0.974, p=0.038 for the latter) Significant reduction for ≥10.8mg vs. 7.2 and 10.8 vs. 5.5 mg (38%).	
(110) Cooper, 2006, BONE, North American and Europe	Postmenopausal women with osteoporosis at relatively low risk for frx (2,946)	RCT of 2.5 mg/d vs. intermittent regimen (20mg every other day plus dose-free intervals for 12 doses/3 mos) **ibandronate** (IB) vs. placebo	Vertebral, non-vertebral frx, AE profile	Daily, intermittent IB ->↓vertebral frx risk(p≤0.0006); incidences non-vertebral frx similar in all groups except higher risk women (femoral neck T-score≤-3)(p=0.012) Safety profile similar for both regimens and placebo	(study underpowered to identify changes in non-vertebral frx risk)

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
Risedronate					
(1) Watts, 2008, risedronate, VERT-NA, US	Postmenopausal women (759)	3 years on 5 mg **Risedronate+Ca+D**, discontinued risedronate 1 year cf placebo+CA+D	New vertebral fractures after 1 yr (***persistence of effx***)	46% lower incidence of new vertebral fractures in risedronate discontinuers vs placebo (RR 0.54 [95% CI, 0.34, 0.86, p=0.009])	
(5) Siris, 2008, risedronate, posthoc analysis of 4 trials (BMD Multinational, BMD NA, VERT Multinational, VERT NA)	Postmenopausal women with osteopenia and no fractures (620) Sensitivity analysis excluded women with osteopenia at femoral neck (FN) but w/BMD T-score <-2.5SD at lumbar spine (LS)	Post hoc analysis of 4 trials: 1.5-3 yrs 5mg/d **risedronate**	Fragility fractures	73% decreased risk of fragility frx over 3 years vs. placebo (2.2% vs. 6.9%, p=0.023); similar in sensitivity analysis	
(29) Delmas, 2008, US?	Postmenopausal women with OP (1292)	Randomized, double-blind, multi-center study: 150 mg **risedronate**, **once-a-month** oral dose (and daily placebo) vs. 5 mg/d, 2 years	Fractures and AE	Frx data not reported in abstract, but two regimens determined not to be different in efficacy. AE rates, AEs that led to withdrawal (9.5% daily vs. 8.6% monthly), and upper GI AEs were similar.	
(30) Delmas, 2008	Postmenopausal women w/ OP (1229)	Randomized, double-blind study of 75,g **risedronate** on 2 consecutive days/month (2CMD) vs. 5 mg/d	Fractures, AEs	New vertebral fracture rate=1% in both groups. Both treatments were well-tolerated and safe.	
(121) Watts, 2005, 3 trials	Postmenopausal women receiving risedronate (2.5 or 5mg/d up to 3 yrs) (3979)	Meta-analysis of women taking **risedronate**	Incidence of non-vertebral frx ***stratified by changes in LS and FN BMD***	Nonvertebral frx incidence in risedronate-trx pts was not predicted by change in BMD. Changes in LS and FN BMD explained only 12% (2%-21%, p=0.014) and 7% 2%-13%, p=0.005), respectively of risedronate's nonvertebral frx efficacy.	
(136) Palomba, 2005, multicenter	Postmenopausal OP women with inflammatory bowel disease (IBD) in remission (90)	RCT of **risedronate** (35mg/wk), 12 mos	Lumbar and thoracic spinal fractures	Risedronate signif ↓frx incidence (12.5 vs. 34.1%, p<0.05) throughout study. RR new vertebral frx after 1 yr=0.36 (0.14-0.85)	
Zoledronic acid					
(58, 59 one article?)	No description of pts.	Double blind RCT of IV	Rate of frx and mortality	Risk of any new clinical fracture ↓	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
Lyles, 2007	except all w/in 90 days of surgical repair of hip frx, mean age 74.5 y (2127)	ZOL (5mg) + vit D + CA vs. placebo + vit D + CA, med. FU 1.9 yrs	after hip frx	35% in ZOL vs. placebo (8.6% vs. 13.9% , P=0.001); New clinical vertebral fracture: 1.7% vs. 3.8% (P=0.02); new nonvertebral fracture rate: 7.6% vs. 10.7% (P=0.03). AEs: 101 of 1054 ZOL patients (9.6%) and 141 of placebo 1057 patients (13.3%) died, (28% ↓ in deaths from any cause in the ZOL group (P=0.01)). The most frequent AEs in ZOL patients were pyrexia, myalgia, and bone and musculoskeletal pain. No cases of osteonecrosis of the jaw were reported, and no AEs on frx healing noted. The rates of renal and cardiovascular AEs, including atrial fibrillation and stroke, were similar in the two groups	
(81) Black, 2007, US	Postmenopausal women with OP, mean age 73 y, (3889)	***Annual 15-minute infusion of zoledronic acid*** (5mg) vs. placebo at baseline, 12 mos, 24 mos, followed through 36 mos.	New vertebral frx (primary) in pts not taking concomitant meds; hip frx in all pts; safety (secondary), AEs	ZOL-> 70% ↓ in morphometric vertebral frx over 3 years cf placebo (3.3% vs. 10.9%, RR 0.30, 95% CI, 0.24-0.38); ZOL-> 41% ↓ risk hip frx (1.4% vs. 2.5%, HR 0.59, 95% CI, 0.42-0.83). ZOL-> ↓ Non-vertebral frx(25%), clinical (33%), clinical vertebral frx (77%) (p<0.001) AEs, including change in renal fn, similar in two study grps except Atrial fib↑ in ZOL grp (50 vs. 20, p<0.001)	
Comparison of Bisphosphonates					
(54) McClung, 2007	Postmenopausal women with LBD previously treated with ALN ≥ 1yr (225)	Single dose **zoledronic acid** (ZOL) 5g vs. oral **ALN** 70 mg/wk	AEs (and bone markers)	Overall AE rate comparable betw grps (ZOL 86.7% vs. ALN 80.4%): Headache more common w/ZOL than ALN	Patients preferred ZOL 1x/yr over ALN
(42) Silverman, 2007	Postmenopausal women (≥65 yoa) (12,215 risedronate; 21,615 alendronate)	Retrospective record abstraction: **Risedronate, alendronate**, once-a-	Incidence of hip, nonvertebral fractures in the year following treatment initiation	507 nonvertebral fractures and 109 hip fractures. Incidence of nonvertebral fractures in the risedronate cohort (2.0%) was 18%	Consistent across a number of sensitivity analyses (not specified in abstract)

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
		week		lower (95% CI 2% - 32%) than in the alendronate cohort (2.3%). Incidence of hip fractures in the risedronate cohort (0.4%) was 43% lower (95% CI 13% - 63%) than in the alendronate cohort (0.6%)	
(93) Nguyen, 2006, meta-analysis	Postmenopausal women with low BMD or osteoporosis (18,667) followed 1-4 years	Meta-analysis of 12 RCTs of women taking **etidronate**, **alendronate**, **risedronate**, **clodronate.**	Incidence of hip frx	42% ↓ risk of hip frx (RR 0.58, 95% credible interval 0.42-0.8); absolute rate reduction 52 frx/10,000 women for 3 years of treatment. Probability bisphosphonates better than placebo at reducing risk by at least 30% was 0.90.	Bayesian analysis
(56) Mamdani, 2007 (Canada)	Bisphosphonate-naïve women with prior Hx of frx (≥66 yoa) (20,587)	Administrative data used to cf users of 1st vs. 2nd generation bisphosphonates **etidronate**+Ca(19,127) vs. **Alendronate** or **risedronate** (1,460)	Hospital admissions for first(?) frx	292 admissions over >23,000 person-years of follow-up; frx risk the same for each group: adjusted rate ratio=1.0; 95% CI 0.6, 1.6)	Abstract was ambiguous re: frx hx of participants
b. SELECTIVE ESTROGEN RECEPTOR MODULATORS					
Raloxifene					
(27) Ensrud, 2008, RUTH, US?	Postmenopausal women ≥55 yoa w/CHD or at high risk for CHD, but not selected based on osteoporosis or frx risk	Random assignment to 60 mg/d raloxifene or placebo, median 5.6 yrs follow-up	Non-vertebral and clinical vertebral frx	Non-vertebral frx: no difference between raloxifene and placebo (incl hip/femur, wrist) Vertebral frx: raloxifene ↓ frx risk (64 vs. 97; HR, 0.65, 0.47-0.89) ***Effx consistent across frx risk categories, incl age, smoking status, physical activity, prior Hx, Fx Hx hip frx, DM, previous use of HRT, thyroid hormone use, statin use, weight loss, BMI, frx-specific summary risk score***	
(85) Seeman, 2007, meta-analysis	Postmenopausal women w/ OP(?) (n not included)	RCT, **Raloxifene** 60 mg/d, 120/150mg/d	Vertebral frx data from prospectively scheduled spinal radiographs	Intention to treat analysis: RLX 60: OR 0.60 (0.49-0.74) RLX 120/150: 0.51 (0.41, 0.64)	Assessmentof consistency of effx. No signif. heterogeneity; 3 prevention studies, 2 arms of MORE, and 3

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
					add'l treatment studies
(117) Barrett-Connor, 2006,	Postmenopausal women with CHD or multiple risk factors for CHD, (mean age 67.5 years) (10,101)	RCT 60mg raloxifene/d vs. placebo, median FU 5.6 years	Effects on CHD, BC vs. clinical vertebral frx	Raloxifene had no effect on risk for primary coronary events and reduced risk of invasive BC. No significant difference in rates of death from any cause or total stroke, but ↑risk fatal stroke (59 vs. 39, HR 1.49, 1.00-2.24; absolute risk increase 0.7/1000 woman-years) and VT (103 vs. 71; HR 1.44, 1.06-1.95, absolute risk increase 1.2/1000 woman-years). Risk clinical vertebral frx↓ 964 vs. 97; HR 0.65; 0.47-0.89; absolute risk reduction 1.3/1000)	
(126) Siris, 2005 , MORE/ CORE	Women enrolled in a 4-year study assessing the efficacy of raloxifene (RAL) for preventing OP followed 4 add'l years to assess effx on BC risk and frx risk (4011)	Women who had been taking 60 or 120mg RAL/d were continued on 60mg/d and followed 4 add'l years; substudy assessed risk among women who were≥80% compliant and did not take other bone agents	New non-vertebral frx	Risk of at least one new nonvertebral frx *did not differ* between placebo and trx grps. (22.9 vs. 22.8%); same with risk of at least one new frx at one of six sites (17.5%). In women with prevalent vertebral frx, no overall effect on nonvertebral frx risk but a decreased risk at six major nonvertebral sites (HR 0.78, 0.63-0.96).	No findings reported in abstract for compliant subset; abstract reported limitations for assessing frx risk
Comparison of Bazedoxifene w/ raloxifene					
(6) Silverman , 2008, **bazedoxifene (B)**	Healthy postmenopausal women (55-85 yoa) with osteoporosis (6,847 intent-to-treat)	3-year, Randomized, double-blind, placebo and active controlled: 20, 40 mg/d B vs. 60 mg/d raloxifene vs. placebo	Incidence of new vertebral and non-vertebral fracture and AE	Incidence of new vertebral frx signif lower in 20 mg B (2.3%), 40 mg (2.5%), raloxifene (2.3%) cf. placebo; RR reduction 42%, 37%, 42%, resp. Incidence of non-vertebral frx: no difference; In subset of women at higher risk (lower T score or prior fractures), 20 mg B showed 50% and 44% RR non-vertebral frx cf. placebo (p=0.02) and raloxifene (p=0.05) Incidence vasodilatation, leg cramps, VT higher with B and raloxifene cf. placebo	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
D. PARATHYROID HORMONE (TERIPARATIDE)					
(67) Greenspan, 2007, 168 centers in 9 countries	Postmenopausal women with LBD at hip or lumbar spine (2532)	RCT of 100 mug recombinant human PTH (subcut) + Ca (700mg/d) and Vit D_3 (400u/d) vs. placebo+ Ca (700mg/d) and Vit D_3 (400u/d) daily; Duration???	New or worsened vertebral frx (primary outcome); safety (secondary outcome)	67.2% of those who received at least one dose completed study(?) PTH decreased frx risk but magnitude of redux changed with sensitivity analysis including assumptions about frx incidence in pts who did not complete study. Assuming no frx: RR 0.42 (95% CI, 0.24 to 0.72, p=0.001); Assuming same frx incidence as completers: 0.60 (0.36-1.00, p=0.05); Assuming frx incidence of placebo grp: 0.62 (0.37-1.04, p=0.07). PTH increased risk for hypercalciuria (24%, 20-27%) , hypercalcemia (23%, 21-26%), nausea (14%, 11-16%)	
(52) Miller, 2007 FPT	Postmenopausal women w/ osteoporosis and renal impairment (n not specified in abstract)	RCT of daily subcutaneous injections of **teriparatide** 20 or 40 mcg/day vs. placebo	Fracture risk and AE by GFR (as index of renal function)	Teriparatide-mediated vertebral and nonvertebral fracture risk reductions were similar and did not differ significantly between patients with normal or impaired renal function (treatment-by-subgroup interactions p>0.05?). The incidences of treatment-emergent and renal-related AEs were consistent across treatment assignment in the normal, mildly impaired, and moderately impaired renal function subgroups. Teriparatide-induced changes in mean GFR were unaffected by baseline renal function (treatment-by-renal function interaction p>0.05 for normal, mildly impaired, or moderately impaired subgroups).	
(134) Prince, 2005, FPT followup	Former FPT participants (20, 40ug teriparatide(TP) /d vs. placebo, 4 yrs) allowed to continue on or begin TP	Observation study of followup; approx 60% received some TP during followup (FU).	Non-vertebral fragility frx	HR for frx in each TP group rel to placebo were significant for the 50-month period that included treatment and FU ($p \leq 0.03$). During FU, HR	Results support sustained effect of TP in reducing risk of nonvertebral fragility frx up to 30 mos after

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
	(1262)			differed signif between 40ug (and combined) grps and placebo but not 20ug vs placebo; no difference between 20 and 40. Frx incidence in former placebo and treatment groups diverged in FU (p=0.0009)	discontinuation
G. AND H. CALCIUM/VITAMIN D					
(41) Tang, 2007 Meta-analysis	Individuals 50 and over with osteoporosis(?) 17 trials (52,625)	Calcium alone or combined with vitamin D	Fractures of all types	Treatment associated with a 12% risk reduction in fractures of all types (risk ratio 0.88, 95% CI 0.83-0.95; p=0.0004); The fracture risk reduction was significantly greater (24%) in trials in which the compliance rate was high (p<0.0001). Treatment effect for calcium ≥ 1200 mg > for Ca <1200 mg (0.80 vs. 0.94; p=0.006), and TE for vitamin D ≥ 800 IU > for D<800 IU (0.84 vs. 0.87; p=0.03)	
(57) Lyons, 2007, Wales UK	Individuals in 314 residential care homes (2,624 women, 816 men)	Double blind RCT of vitamin D supplementation (100,000 IU D2)	Incidence of first frx (intention to treat)	205 first fractures occurred in the intervention group during a total of 2,846 person years of follow-up (7 fractures per 100 people per year of follow-up) vs. 218 first fractures in the control group over 2,860 person years of follow-up. HR 0.95 (95% confidence interval 0.79-1.15) not statistically significant	
(102) Jackson, 2006, WHI	Postmenopausal women enrolled in WHI, 50-79 yoa (36,282)	RCT 1000mg/d elemental **Ca** ($CaCO_3$)+400IU **Vit D_3**/d vs. placebo; avge FU 7 yrs	Hip and spinal frx, AEs	HR hip frx=0.88 (0.72-1.08) HR spinal frx=0.900.90 (0.74 to 1.10), and HR total fractures=0.96 (0.91 to 1.02). (no signif diff) Risk of renal calculi increased with calcium plus vitamin D (HR, 1.17; 1.02 to 1.34). Excluding data from non-adherent women->HR for hip fracture of 0.71 (0.52 to 0.97).	Intention-to-treat analysis; Effects did not vary significantly according to prerandomization serum vitamin D levels
I. EXERCISE					
(96) Lock, 2006, US	Individuals at high risk	Meta-analysis of 6 RCTs	Risk of spinal, hip frx	Exercise assoc with nonsignificant ↓	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
	for osteoporosis (>1,656)	on **exercise** (3), multifactorial interventions (2), and sunlight (1)		risk of spinal frx 9RR 0.52, 95% CI 0.17-1.60); multifactorial interventions assoc with borderline significant ↓ hip frx (RR 0.37, 0.13-1.03); Exposure to sunlight assoc with a non-significantly lower risk of hip fracture (RR=0.17, 95% CI=0.02 to 1.35). No indications of AE.	
(J) Comparisons of Bisphosphonates w/ SERMS					
(118) Adami, 2006, ICARO, Italy	Postmenopausal women treated w/ALN, RIS, or raloxifene≥1 year w/ compliance≥50%	Observational multicenter study cf. **ALN, RIS, raloxifene**	Risk factors for an "inadequate clinical response" (ICR)to drug therapy, defined as the occurrence of new vertebral or nonvertebral fragility frx in patients prescribed, for at least 1 year, alendronate, risedronate, or raloxifene, with compliance≥50%	220/880 pts treated w/ antiresorptives for median of 2 years were ICR (25%). ICRs had more pretrx frx and longer trx (2.8 vs. 1.8 yrs). Adjusting for confounders, significant determinants of ICR were poorer compliance and less frequent use of Ca and Vit D.	Major determinants of poor response in clinical setting cf. RCTs identified
(38) Adami, 2008	Postmenopausal women with severe osteoporosis (862), 10.7% with inadequate clinical treatment response (ICR, i.e., fracture during treatment of at least 1 year duration)	**Alendronate, risedronate, raloxifene**, doses not specified in abstract	Fracture risk during treatment	BMI, follow-up duration, # prevalent vertebral fractures, treatment modality , proportion of patients taking calcium and vitamin D supplements, and compliance with treatment did not differ between ICR and non-ICR groups; ICR patients were significantly older and had ↑# vertebral deformities	
(48) Recker, 2007	Postmenopausal women with no low bone mass, no prior fractures, and no prior OP treatment, mean age 66 (1423)	RCT of **Raloxifene** (RLX, 60 mg/d) vs. **alendronate** (ALN, 10 mg/d) 5 years (stopped prematurely due to low enrollment)	≥1 new vertebral or non-vertebral fracture; AE, discontinuation due to AE	After 312±254 days, 22 women in the ALN grp and 20 in the RLX grp had new vertebral or non-vertebral frx; 4 in the ALN group and none in the RLX group had moderate/severe vertebral fractures, a pre-specified endpoint (P=0.04)(insufficient power to cf); # w/ ≥ 1 AE similar in each group, and discontinuation due to AE similar; Need for colonoscopy,	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				diarrhea, and nausea were more common in ALN group (each p<0.05); 1 case BC and one VTE in each grp;	
Comparison of Parathyroid Hormone with Bisphosphonates					
(45) Saag, 2007	Men and women with osteoporosis, 22-89 yoa who had received GC>3 months (428)	18-month double-blind RCT cf. **teriparatide** (20ug/d) vs. **alendronate** (10mg/d)	New vertebral and non-vertebral fracture incidence an AE as secondary outcomes	Teriparatide resulted in fewer new vertebral fractures than alendronate (0.6% vs. 6.1%, P=0.004); incidence of nonvertebral fractures was similar in the two groups (5.6% vs. 3.7%, P=0.36); no AE info in abstract	
(40) Vestergard, 2007 Meta-analysis	Not specified in abstract	RCTs of PTH alone or in combination with antiresorptives	Vertebral and non-vertebral frx risk, AE	PTH alone or in combination with antiresorptive drugs reduced vertebral [relative risk (RR)=0.36, 95% confidence interval (CI): 0.28-0.47, p<0.01] and non-vertebral (RR=0.62, 95% CI: 0.48-0.82, p<0.01) fracture risk; No significant effect of study duration on fracture risk; major adverse events were hypercalcaemia, nausea and discomfort at the injection sites	
STRONTIUM RANELATE					
(7) Seeman, 2008, **strontium ranelate,** SOTI, TROPOS, Italy	Postmenopausal women with LS and/or FN osteopenia (1431)	Pooled data from two 3-yr randomized trials of 2g/d Sr or placebo	Risk of new vertebral fractures	LS osteopenia: 41%↓ risk vertebral frx (RR 0.59, 0.43-0.82) in women with no prevalent frx; 59%↓ (RR = 0.41; 95% CI, 0.17-0.99) in the 447 patients with no prevalent fractures, and 38%↓ (RR = 0.62; 95% CI, 0.44-0.88) in the 719 patients with prevalent fractures. Osteopenia at both sites: 52%↓ frx risk (RR = 0.48; 95% CI, 0.24-0.96)	Abstract conclusion alluded to safety but no AE data
(87) Roux, 2006, multi-national	Postmenopausal women, avge age 74 y (5082)	2 pooled RCTs: strontium ranelate 2g/d vs. placebo, 3-year FU	Vertebral frx, risk of first vertebral frx, non-vertebral frx	Sr->↓risk vertebral (RR 0.60, 0.53-0.69, p<0.001) and non-vertebral (RR 0.85, 0.74-0.99, p = 0.03) frx Women < 70 yoa: 37%↓Vertebral frx (p=0.003); Women 70-80 yoa: 42% (p< 0.001); Women≥80 years: 32%	Cox model for cf and RR

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				(p = 0.013). RR of vertebral fracture was 0.28 (0.07-0.99) in osteopenic and 0.61 (0.53-0.70) in osteoporotic women; Risk of experiencing 1st vertebral frx (n=2605) ↓ by 48% (p<0.001). Risk of experiencing 2nd vertebral frx (1100) ↓ by 45% (p< 0.001). Risk of experiencing >2 vertebral frx (1365) ↓ by 33% (p< 0.001;). BMD, Fx Hx OP, baseline BMI, and addiction to smoking were not determinants of efficacy	
(119) Adami, 2006, TROPOS, Italy	Postmenopausal women w/ OP (5091)	Double-blind RCT of strontium ranelate (2g/d orally) over 3 years	Incidence of non-vertebral and other major (hip, wrist, pelvis, sacrum, ribs, sternum, clavicle, humerus) frx	16%↓ risk non-vertebral frx (p=0.04) 19%↓ risk other major frx (p=0.031) 36%↓ risk hip frx in women ≥74 yoa who were treated with Sr ranelate (n=982) AE incidence comparable between grps	
KQ2. FRACTURE REDUCTION FOR VARIOUS RISK GROUPS					
(65) Jamal, 2007, FIT, ?	Menopausal women (6458 for total study; 581 w/*severely reduced renal function* (GFR <45ml/min)	RCT of **Alendronate** vs. placebo	Clinical, vertebral frx, AEs	Alendronate reduced the risk of clinical fractures to a similar degree in those with (OR: 0.78; 95% CI: 0.51-1.21) and without reduced renal function (OR: 0.80; 95% CI; 0.70-0.93; p for interaction = 0.89). Alendronate reduced the risk of spine fractures to a similar degree in those with (OR: 0.72; 95% CI: 0.31-1.7) and without reduced renal function (OR: 0.50; 95% CI: 0.32-0.76; p for interaction = 0.44). No diffs in AEs by renal function.	
(146) Hochberg, 2005, multicenter, FIT	Postmenopausal women with OP, 55-80 yoa (3658)	RCT of **alendronate,** 5mg/d x 2 yrs followed by 10mg for 1-2.5 add'l years	Clinical frx	↓ Relative risk for hip, clinical spine, and wrist fractures: constant across age groups, without evidence of a decline at older ages. ALE ↓ risk of clinical fracture by 53% at the hip (RR = 0.47; 95% CI = 0.27-0.81; p≤ 0.01), 45% at the spine (RR = 0.55;	Absolute risk reduction increased with **age** because of ↑ risk with age: absolute risk reduction for the composite event (hip,

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				95% CI = 0.37-0.83; p < 0.01), and 31% at the wrist (RR = 0.69; 95% CI = 0.50-0.98; p = 0.038). In addition, alendronate produced a significant risk reduction of 40% (RR = 0.60; 95% CI = 0.47-0.77; p≤ 0.01) for the composite event of clinical hip, spine, and wrist fractures. Effectiveness was somewhat greater in women with T≤-2.5 cf. T≤-2.0.	spine, and wrist fractures together) for alendronate treatment versus placebo was 65, 80, 111, and 161 women with fractures per 10,000 Person-yrs for the 55 to ≤ 65, 65 to ≤ 70, 70 to ≤ 75, and 75-85 year age groups, respectively;
(116) Bauer, 2006, FIT	Postmenopausal women 55-80 years, femoral neck T-score≤-1.6 (6,186); with (T≤2.5 or prevalent vertebral frx)(3,495) or without (T≥2.5 or no prevalent vertebral frx)(2,689) OP	RCT **Alendronate** 5-10mg/d vs. placebo, mean FU 3.2 yrs	Risk of incident vertebral and non-vertebral frx in ALN vs. placebo ***stratified by baseline BM marker levels***	492 nonvertebral and 294 morphometric vertebral fractures. ALN-induced↓ in non-vertebral fracture cf placebo was a fn of PINP: (p = 0.03 for trend). E.g., among osteoporotic women in the lowest tertile of pretreatment PINP (≤41.6 ng/ml), ALN vs PBO relative hazard for nonvertebral fracture=0.88 (95% CI: 0.65, 1.21) compared with a relative hazard of 0.54 (95% CI: 0.39, 0.74) among those in the highest tertile of PINP, ≥56.8 ng/ml). Results similar among women without baseline OP. Similar (but non-sign) trends observed with baseline levels of BSALP. Conversely, vertebral frx treatment efficacy among OP women did not differ significantly according to pretreatment marker levels. Vertebral frx treatment efficacy among non-OP women was related to baseline BSALP (p = 0.05 for trend).	Findings suggest bisphosphonate treatment may be more effective in women with elevated bone turnover
(110) Cooper, 2006, BONE, North American and Europe	Postmenopausal women with osteoporosis at relatively low risk for frx (2,946)	RCT of 2.5 mg/d vs. intermittent regimen (20mg every other day plus dose-free intervals for 12 doses/3 mos)	Vertebral, non-vertebral frx in women with higher vs. lower BMD, AE profile	Daily, intermittent IB ->↓vertebral frx risk(p≤0.0006); incidences non-vertebral frx similar in all groups except higher risk women (femoral neck T-score≤-3)(p=0.012)	(study underpowered to identify changes in non-vertebral frx risk)

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
		ibandronate (IB) vs. placebo		Safety profile similar for both regimens and placebo	
(121) Watts, 2005, 3 trials	Postmenopausal women receiving risedronate (2.5 or 5mg/d up to 3 yrs) (3979)	Meta-analysis of women taking **risedronate**	Incidence of non-vertebral frx ***stratified by changes in LS and FN BMD***	Nonvertebral frx incidence in risedronate-trx pts was not predicted by change in BMD. Changes in LS and FN BMD explained only 12% (2%-21%, p=0.014) and 7% 2%-13%, p=0.005), respectively of risedronate's nonvertebral frx efficacy.	
(27) Ensrud, 2008, RUTH, US?	Postmenopausal women ≥55 yoa w/CHD or at high risk for CHD, but not selected based on osteoporosis or frx risk	Random assignment to 60 mg/d **raloxifene** or placebo, median 5.6 yrs follow-up	Non-vertebral and clinical vertebral frx	Non-vertebral frx: no difference between raloxifene and placebo (incl hip/femur, wrist) Vertebral frx: raloxifene ↓ frx risk (64 vs. 97; HR, 0.65, 0.47-0.89) ***Effx consistent across frx risk categories, incl age, smoking status, physical activity, prior Hx, Fx Hx hip frx, DM, previous use of HRT, thyroid hormone use, statin use, weight loss, BMI, frx-specific summary risk score***	
(126) Siris, 2005 , MORE/ CORE	Women enrolled in a 4-year study assessing the efficacy of raloxifene (RAL) for preventing OP followed 4 add'l years to assess effx on BC risk and frx risk (4011)	Women who had been taking 60 or 120mg RAL/d were continued on 60mg/d and followed 4 add'l years; substudy assessed risk among women who were≥80% compliant and did not take other bone agents	New non-vertebral frx	Risk of at least one new nonvertebral frx *did not differ* between placebo and trx grps. (22.9 vs. 22.8%); same with risk of at least one new frx at one of six sites (17.5%). In ***women with prevalent vertebral frx***, no overall effect on nonvertebral frx risk but a decreased risk at six major nonvertebral sites (HR 0.78, 0.63-0.96).	No findings reported in abstract for compliant subset; abstract reported limitations for assessing frx risk
(52) Miller, 2007 FPT	Postmenopausal women w/ osteoporosis and renal impairment (n not specified in abstract)	RCT of daily subcutaneous injections of **teriparatide** 20 or 40 mcg/day vs. placebo	Fracture risk and AE by GFR (as index of renal function)	Teriparatide-mediated vertebral and nonvertebral fracture risk reductions were similar and did not differ significantly between patients with normal or impaired renal function (treatment-by-subgroup interactions p>0.05?). The incidences of treatment-emergent and renal-related	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				AEs were consistent across treatment assignment in the normal, mildly impaired, and moderately impaired renal function subgroups. Teriparatide-induced changes in mean GFR were unaffected by baseline renal function (treatment-by-renal function interaction p>0.05 for normal, mildly impaired, or moderately impaired subgroups).	
(102) Jackson, 2006, WHI	Postmenopausal women enrolled in WHI, 50-79 yoa (36,282)	RCT 1000mg/d elemental **Ca** ($CaCO_3$)+400IU **Vit D_3**/d vs. placebo; avge FU 7 yrs	Hip and spinal frx, AEs	HR hip frx=0.88 (0.72-1.08) HR spinal frx=0.900.90 (0.74 to 1.10), and HR total fractures=0.96 (0.91 to 1.02). (no signif diff) Risk of renal calculi increased with calcium plus vitamin D (HR, 1.17; 1.02 to 1.34). Excluding data from non-adherent women->HR for hip fracture of 0.71 (0.52 to 0.97).	Intention-to-treat analysis; Effects did not vary significantly according to prerandomization serum vitamin D levels
(38) Adami, 2008	Postmenopausal women with severe osteoporosis (862), 10.7% with inadequate clinical treatment response (ICR, i.e., fracture during treatment of at least 1 year duration)	**Alendronate, risedronate, raloxifene**, doses not specified in abstract	Fracture risk during treatment	BMI, follow-up duration, # prevalent vertebral fractures, treatment modality , proportion of patients taking calcium and vitamin D supplements, and compliance with treatment did not differ between ICR and non-ICR groups; ICR patients were significantly older and had ↑# vertebral deformities	
KQ3. ADHERENCE AND PERSISTENCE EFFECTS					
(115) Black, 2006, FIT	Postmenopausal women with a mean of 5 years **prior alendronate treatment** (1099)	RCT 5, 10 mg/d **Alendronate** or placebo X 5 yrs	Frx incidence as exploratory outcome measure ***to assess persistence of effx***	5-year cumulative risk nonvertebral frx (RR 1.00, 0.76-1.32) did not differ between continuers and discontinuers; Continuers had significant ↓clinical vertebral frx (2.4% vs/ 5.3% for placebo; RR 0.45, 0.24-0.85) but NO difference in morphometric vertebral frx (11.3%	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				for placebo and 9.8% for alendronate; RR, 0.86; 95% CI, 0.60-1.22)	
(1) Watts, 2008, risedronate, VERT-NA, US	Postmenopausal women (759)	3 years on 5 mg **Risedronate+Ca+D**, discontinued risedronate 1 year cf placebo+CA+D	New vertebral fractures after 1 yr (***persistence of effx***)	46% lower incidence of new vertebral fractures in risedronate discontinuers vs placebo (RR 0.54 [95% CI, 0.34, 0.86, p=0.009])	
(126) Siris, 2005 , MORE/ CORE	Women enrolled in a 4-year study assessing the efficacy of raloxifene (RAL) for preventing OP followed 4 add'l years to assess effx on BC risk and frx risk (4011)	Women who had been taking 60 or 120mg RAL/d were continued on 60mg/d and followed 4 add'l years; substudy assessed ***risk among women who were≥80% compliant*** and did not take other bone agents	New non-vertebral frx	Risk of at least one new nonvertebral frx *did not differ* between placebo and trx grps. (22.9 vs. 22.8%); same with risk of at least one new frx at one of six sites (17.5%). In women with prevalent vertebral frx, no overall effect on nonvertebral frx risk but a decreased risk at six major nonvertebral sites (HR 0.78, 0.63-0.96).	No findings reported in abstract for ***compliant subset***; abstract reported limitations for assessing frx risk
(134) Prince, 2005, FPT followup	Former FPT participants (20, 40ug teriparatide(TP) /d vs. placebo, 4 yrs) allowed to continue on or begin TP (1262)	Observation study of followup; approx 60% received some TP during followup (FU).	Non-vertebral fragility frx	HR for frx in each TP group rel to placebo were significant for the 50-month period that included treatment and FU (p≤0.03). During FU, HR differed signif between 40ug (and combined) grps and placebo but not 20ug vs placebo; no difference between 20 and 40. Frx incidence in former placebo and treatment groups diverged in FU (p=0.0009)	Results support ***sustained effect of TP in reducing risk of nonvertebral fragility frx up to 30 mos after discontinuation***
(118) Adami, 2006, ICARO, Italy	Postmenopausal women treated w/ALN, RIS, or raloxifene≥1 year w/ compliance≥50%	Observational multicenter study cf. **ALN, RIS, raloxifene**	Risk factors for an "inadequate clinical response" (ICR)to drug therapy, defined as the occurrence of new vertebral or nonvertebral fragility frx in patients prescribed, for at least 1 year, alendronate, risedronate, or raloxifene, with compliance≥50%	220/880 pts treated w/ antiresorptives for median of 2 years were ICR (25%). ICRs had more pretrx frx and longer trx (2.8 vs. 1.8 yrs). Adjusting for confounders, significant determinants of ICR were poorer **compliance** and less frequent use of Ca and Vit D.	Major determinants of poor response in clinical setting cf. RCTs identified
(38) Adami, 2008	Postmenopausal women with severe osteoporosis	**Alendronate, risedronate, raloxifene**,	Fracture risk during treatment	BMI, follow-up duration, # prevalent vertebral fractures, treatment	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
	(862), 10.7% with inadequate clinical treatment response (ICR, i.e., fracture during treatment of at least 1 year duration)	doses not specified in abstract		modality , proportion of patients taking calcium and vitamin D supplements, and compliance with treatment did not differ between ICR and non-ICR groups; ICR patients were significantly older and had ↑# vertebral deformities	
KQ4. ADVERSE EFFECTS					
(65) Jamal, 2007, FIT, ?	Menopausal women (6458 for total study; 581 w/*severely reduced renal function* (GFR <45ml/min)	RCT of **Alendronate** vs. placebo	Clinical, vertebral frx, AEs	Alendronate reduced the risk of clinical fractures to a similar degree in those with (OR: 0.78; 95% CI: 0.51-1.21) and without reduced renal function (OR: 0.80; 95% CI; 0.70-0.93; p for interaction = 0.89). Alendronate reduced the risk of spine fractures to a similar degree in those with (OR: 0.72; 95% CI: 0.31-1.7) and without reduced renal function (OR: 0.50; 95% CI: 0.32-0.76; p for interaction = 0.44). No diffs in AEs by renal function.	
(55) McCloskey, 2007, UK	Community-dwelling women (≥ 75 yoa) (5,596 Intention to treat)	3-year RCT of oral **clodronate** (800 mg/d) vs. placebo	Fracture incidence and AE	114 new hip frx during the 3-year treatment phase: 56 (2.0%) women in the clodronate group and 58 (2.1%) women in the placebo group (HR, 1.02; 95% CI, 0.71-1.47). Clodronate decreased the incidence of any clinical fracture by 20% (264 women [9.5%] versus 337 [12.1%] in the placebo group; HR, 0.80; 95% CI, 0.68-0.94). Clodronate also decreased the incidence of OP-associated nonhip fractures by 29% (5.2% versus 7.4%; HR, 0.71; 95% CI, 0.57-0.87). AE not significant.	Effect of CLO independent of baseline BMD but NNT less w/OP
(110) Cooper, 2006, BONE, North American and Europe	Postmenopausal women with osteoporosis at relatively low risk for frx (2,946)	RCT of 2.5 mg/d vs. intermittent regimen (20mg every other day plus dose-free intervals	Vertebral, non-vertebral frx in women with higher vs. lower BMD, AE profile	Daily, intermittent IB ->↓vertebral frx risk($p \leq 0.0006$); incidences non-vertebral frx similar in all groups except higher risk women (femoral	(study underpowered to identify changes in non-vertebral frx risk)

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
		for 12 doses/3 mos) **ibandronate** (IB) vs. placebo		neck T-score≤-3)(p=0.012) Safety profile similar for both regimens and placebo	
(29) Delmas, 2008, US?	Postmenopausal women with OP (1292)	Randomized, double-blind, multi-center study: 150 mg **risedronate**, **once-a-month** oral dose (and daily placebo) vs. 5 mg/d, 2 years	Fractures and AE	Frx data not reported in abstract, but two regimens determined not to be different in efficacy. AE rates, AEs that led to withdrawal (9.5% daily vs. 8.6% monthly), and upper GI AEs were similar.	
(30) Delmas, 2008	Postmenopausal women w/ OP (1229)	Randomized, double-blind study of 75,g **risedronate** on 2 consecutive days/month (2CMD) vs. 5 mg/d	Fractures, AEs	New vertebral fracture rate=1% in both groups. Both treatments were well-tolerated and safe.	
(58, 59 one article?) Lyles, 2007 HORIZON (#3581 – included in final version of LBD)	No description of pts. except all w/in 90 days of surgical repair of hip frx, mean age 74.5 y (2127)	Double blind RCT of IV **ZOL** (5mg once a year) + vit D + CA vs. placebo + vit D + CA, med. FU 1.9 yrs	Rate of frx and ***mortality*** after hip frx, other AEs	Risk of any new clinical fracture ↓ 35% in ZOL vs. placebo (8.6% vs. 13.9% , P=0.001); New clinical vertebral fracture: 1.7% vs. 3.8% (P=0.02); new nonvertebral fracture rate: 7.6% vs. 10.7% (P=0.03). AEs: 101 of 1054 ZOL patients (9.6%) and 141 of placebo 1057 patients (13.3%) died, (28% ↓ in deaths from any cause in the ZOL group (P=0.01)). The most frequent AEs in ZOL patients were pyrexia, myalgia, and bone and musculoskeletal pain. No cases of osteonecrosis of the jaw were reported, and no AEs on frx healing noted. The rates of renal and cardiovascular AEs, including atrial fibrillation and stroke, were similar in the two groups. No cases of osteonecrosis of the jaw were reported.	
(81) Black, 2007, US HORIZON (#3578 – included in final LBD)	Postmenopausal women with OP, mean age 73 y, (3889)	***Annual 15-minute infusion of zoledronic acid*** (5mg) vs. placebo at baseline, 12 mos, 24 mos, followed through	New vertebral frx (primary) in pts not taking concomitant meds; hip frx in all pts; safety (secondary), AEs	ZOL-> 70% ↓ in morphometric vertebral frx over 3 years cf placebo (3.3% vs. 10.9%, RR 0.30, 95% CI, 0.24-0.38); ZOL-> 41% ↓ risk hip frx (1.4% vs.	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
		36 mos.		2.5%, HR 0.59, 95% CI, 0.42-0.83). ZOL-> ↓ Non-vertebral frx(25%), clinical (33%), clinical vertebral frx (77%) (p<0.001) AEs, including change in renal fn, similar in two study grps except serious Atrial fib↑ in ZOL grp (50 vs. 20, p<0.001) but most were more than 30 days after infusion when ZOL would have dispersed. No cases of osteonecrosis of the jaw reported. Possible ONJ reported 1 case each in control and treated.	
Cummings, 2007* FIT (#3577 – included in final LBD)	Editorial/review of FIT participants	Alendronate treatment	Incidence of atrial fibrillation	Increase in serious AF but not total AF in women who took alendronate	*Cummings SR, Schwartz AV, Black DM; Alendronate and Atrial Fibrillation; NEJM 356(18):1895-6; 2007
(117) Barrett-Connor, 2006,	Postmenopausal women with CHD or multiple risk factors for CHD, (mean age 67.5 years) (10,101)	RCT 60mg **raloxifene**/d vs. placebo, median FU 5.6 years	Effects on CHD, BC vs. clinical vertebral frx	Raloxifene had no effect on risk for primary coronary events and reduced risk of invasive BC. No significant difference in rates of death from any cause or total stroke, but ↑risk fatal stroke (59 vs. 39, HR 1.49, 1.00-2.24; absolute risk increase 0.7/1000 woman-years) and VT (103 vs. 71; HR 1.44, 1.06-1.95, absolute risk increase 1.2/1000 woman-years). Risk clinical vertebral frx↓ 964 vs. 97; HR 0.65; 0.47-0.89; absolute risk reduction 1.3/1000)	
(6) Silverman , 2008, **bazedoxifene (B)**	Healthy postmenopausal women (55-85 yoa) with osteoporosis (6,847 intent-to-treat)	3-year, Randomized, double-blind, placebo and active controlled: 20, 40 mg/d B vs. 60 mg/d raloxifene vs. placebo	Incidence of new vertebral and non-vertebral fracture and AE	Incidence of new vertebral frx signif lower in 20 mg B (2.3%), 40 mg (2.5%), raloxifene (2.3%) cf. placebo; RR reduction 42%, 37%, 42%, resp. Incidence of non-vertebral frx: no difference; In subset of women at higher risk (lower T score or prior	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
				fractures), 20 mg B showed 50% and 44% RR non-vertebral frx cf. placebo (p=0.02) and raloxifene (p=0.05) ***Incidence vasodilatation, leg cramps, VT higher with B and raloxifene cf. placebo***	
(67) Greenspan, 2007, 168 centers in 9 countries	Postmenopausal women with LBD at hip or lumbar spine (2532)	RCT of 100 mug recombinant human PTH (subcut) + Ca (700mg/d) and Vit D_3 (400u/d) vs. placebo+ Ca (700mg/d) and Vit D_3 (400u/d) daily; Duration???	New or worsened vertebral frx (primary outcome); safety (secondary outcome)	67.2% of those who received at least one dose completed study(?) PTH decreased frx risk but magnitude of redux changed with sensitivity analysis including assumptions about frx incidence in pts who did not complete study. Assuming no frx: RR 0.42 (95% CI, 0.24 to 0.72, p=0.001); Assuming same frx incidence as completers: 0.60 (0.36-1.00, p=0.05); Assuming frx incidence of placebo grp: 0.62 (0.37-1.04, p=0.07). PTH increased risk for hypercalciuria (24%, 20-27%) , hypercalcemia (23%, 21-26%), nausea (14%, 11-16%)	
(52) Miller, 2007 FPT	Postmenopausal women w/ osteoporosis and renal impairment (n not specified in abstract)	RCT of daily subcutaneous injections of **teriparatide** 20 or 40 mcg/day vs. placebo	Fracture risk and AE by GFR (as index of renal function)	Teriparatide-mediated vertebral and nonvertebral fracture risk reductions were similar and did not differ significantly between patients with normal or impaired renal function (treatment-by-subgroup interactions p>0.05?). The incidences of treatment-emergent and renal-related AEs were consistent across treatment assignment in the normal, mildly impaired, and moderately impaired renal function subgroups. Teriparatide-induced changes in mean GFR were unaffected by baseline renal function (treatment-by-renal function interaction p>0.05 for normal, mildly impaired, or moderately impaired subgroups).	

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
(102) Jackson, 2006, WHI	Postmenopausal women enrolled in WHI, 50-79 yoa (36,282)	RCT 1000mg/d elemental **Ca** ($CaCO_3$)+400IU **Vit D_3**/d vs. placebo; avge FU 7 yrs	Hip and spinal frx, AEs	HR hip frx=0.88 (0.72-1.08) HR spinal frx=0.900.90 (0.74 to 1.10), and HR total fractures=0.96 (0.91 to 1.02). (no signif diff) Risk of renal calculi increased with calcium plus vitamin D (HR, 1.17; 1.02 to 1.34). Excluding data from non-adherent women->HR for hip fracture of 0.71 (0.52 to 0.97).	Intention-to-treat analysis; Effects did not vary significantly according to prerandomization serum vitamin D levels
(48) Recker, 2007	Postmenopausal women with no low bone mass, no prior fractures, and no prior OP treatment, mean age 66 (1423)	RCT of **Raloxifene** (RLX, 60 mg/d) vs. **alendronate** (ALN, 10 mg/d) 5 years (stopped prematurely due to low enrollment)	≥1 new vertebral or non-vertebral fracture; AE, discontinuation due to AE	After 312±254 days, 22 women in the ALN grp and 20 in the RLX grp had new vertebral or non-vertebral frx; 4 in the ALN group and none in the RLX group had moderate/severe vertebral fractures, a pre-specified endpoint (P=0.04)(insufficient power to cf); # w/ ≥ 1 AE similar in each group, and discontinuation due to AE similar; Need for colonoscopy, diarrhea, and nausea were more common in ALN group (each p<0.05); 1 case BC and one VTE in each grp;	
(40) Vestergard, 2007 Meta-analysis	Not specified in abstract	RCTs of PTH alone or in combination with antiresorptives	Vertebral and non-vertebral frx risk, AE	PTH alone or in combination with antiresorptive drugs reduced vertebral [relative risk (RR)=0.36, 95% confidence interval (CI): 0.28-0.47, p<0.01] and non-vertebral (RR=0.62, 95% CI: 0.48-0.82, p<0.01) fracture risk; No significant effect of study duration on fracture risk; major adverse events were hypercalcaemia, nausea and discomfort at the injection sites	
Sorensen, 2008 Denmark (not identified in search)	13,586 female patients with atrial fibrillation and flutter and 68 054 population controls	Population based case-control study	Adjusted relative risk of AF among users of bisphosphonates (or use of bisphosphonates	435 cases (3.2%) and 1958 population controls(2.9%) were current users of bisphosphonates for osteoporosis. Etidronate and	Conclusion No evidence was found that use of bisphosphonates

Author, year, agent, trial name, country	Inclusions/Exclusion Criteria, Sample#	Study design, intervention	Outcomes Assessed	Findings	Quality/Notes
BMJ. 2008 April 12; 336(7648): 813–816. HT Sørensen, Christensen S, Mehnert F, Pedersen L, Chapurlat RD, Cummings SR, Baron JA Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study			among AF patients and controls?)	alendronate were used with almost the same frequency among cases and controls. The adjusted relative risk of current use of bisphosphonates compared with non-use was 0.95 (95% confidence interval 0.84 to 1.07). New users had a relative risk of 0.75 (95% confidence interval 0.49 to 1.16), broadly similar to the estimate for continuing users (relative risk 0.96, 95% confidence interval 0.85 to 1.09). The relative risk estimates were independent of number of prescriptions and the position of the atrial fibrillation and flutter diagnosis in the discharge record, and were similar for inpatients and outpatients.	increases the risk of atrial fibrillation and flutter
Majumdar SR 2008 (editorial/review) Oral Bisphosphonates and AF; BMJ 336(7648): 784-785					Evidence does not support a role for bisphosphonates in causing AF
Heckbert SR, Li G, Cummings SR, Smith NK, Psaty BM, 2008 **Use of Alendronate and Risk of Incident Atrial Fibrillation in Women** *Arch Intern Med. 2008;168(8):826-831*	Women with a Hx of AF in Group Health (727) and controls (1057)	population-based case-control study	Ever having used alendronate	More AF case patients than controls had ever used alendronate (6.5% [n=47] vs 4.1% [n=40]; *P*=.03). Compared with never use of any bisphosphonate, ever use of alendronate was associated with a higher risk of incident AF (odds ratio, 1.86; 95% confidence interval, 1.09-3.15) after adjustment for the matching variables, a diagnosis of osteoporosis, and a history of cardiovascular disease	Ever use of alendronate was associated with an increased risk of incident AF in clinical practice

AE: adverse events; AF: atrial fibrillation; ALN: alendronate; BONE: Oral iBandronate Osteoporosis vertebral fracture trial in North American and Europe; DM: diabetes mellitus; FN: femoral neck; Fx: family; FIT: Fracture Intervention Trial; FPT: Fracture Prevention Trial; FU: follow-up; HRT: hormone replacement therapy; Hx: history; LS: lumbar spine; PINP: N-terminal propeptide of type 1 collagen; VT venous thromboembolism

CER 13 - Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer

Original Findings	New findings
Comparative Efficacy and Safety	
No one therapy can be considered the preferred treatment for localized prostate cancer patient must make trade offs between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decision-making. Patient satisfaction with therapy is high and associated with several clinically relevant outcome measures.	**Author/Year:** Wong, 2006 **Study Objective:** Compare treatment with observation in men with low or intermediate risk prostate cancer **Study Design:** Observational Cohort using SEER data (SEER: Surveillance, Epidemiology and End Results) **Sample Size:** 44,630 (32, 022 Receiving treatment, 12,607 in the observation group) **Findings:** At 12 years of follow up, active treatment was associated with significantly better survival (adjusted hazard ratio of 0.69, 95% CI 0.66-0.72). Adjusted hazard ratio for specific treatment, were: radical prostatectomy 0.50 (91% CI 0.47- 0.53). Radiation 0.81 (95% CI 0.78-0.85). **Author/Year:** Sandra, 2008 **Study Objective:** Identify determinants of health-related quality of life after primary treatment of prostate cancer **Study Design:** Prospective observational cohort at 6 University-affiliated hospitals **Sample Size:** 1201 patients with previously untreated T1 or T2 prostate cancer who elected primary surgery **Findings:** Each primary therapy had distinct differences in health related quality of life. Prostatectomy had substantial effects on sexual and urinary incontinence symptoms while radiotherapy and brachytherapy had effects on bowel or rectal symptoms and urinary irritation with the use of hormonal therapy further effecting sexual symptoms and vitality.
The addition of neoadjuvant hormonal therapy to RP did not improve survival or cancer recurrence rates, defined by PSA recurrence, but increased AEs.	**Author/Year:** Albertson, 2007 **Study Objective:** Compare treatment with surgery or radiation to observation in men less than 75 years old with clinically localized prostate cancer **Study Design:** Observational Cohort using Connecticut tumor registry data. **Sample Size:** 1,618 (for receiving surgery, 702 for receiving external beam radiation, and 114 in the observation group **Findings:** At 13 years of follow up, prostate cancer mortality was 2.2-3.8 times higher in patients receiving external beam radiation than patients receiving surgery. **Author/Year:** Sandra, 2008 **Study Objective:** Identify determinants of health-related quality of life after primary treatment of prostate cancer **Study Design:** Prospective observational cohort at 6 University-affiliated hospitals **Sample Size:** 1201 patients with previously untreated T1 or T2 prostate cancer

	who elected primary surgery **Findings:** Each primary therapy had distinct differences in health related quality of life. Prostatectomy had substantial effects on sexual and urinary incontinence symptoms while radiotherapy and brachytherapy had effects on bowel or rectal symptoms and urinary irritation with the use of hormonal therapy further effecting sexual symptoms and vitality.
ADT combined with EBRT (ADT + EBRT) may decrease overall and disease-specific mortality but increase AEs compared with EBRT alone in high-risk patients defined by PSA levels and Gleason histologic score. One RCT found that conformal EBRT combined with 6 months of ADT reduced all-cause mortality, disease-specific mortality, and PSA failure compared with conformal EBRT alone after a median followup of 4.5 years. There were significant increases in gynecomastia and impotence in the ADT + EBRT group compared with EBRT alone.	**Author/Year:** D'Amico 2007 **Study Objective:** Compare androgen depravation therapy and radiation therapy to radiation therapy alone in men with localized prostate cancer. **Study Design:** RCT **Sample Size:** 206 **Findings:** At a median of 7.6 years of follow up, men receiving radiation therapy alone had a significant increase in overall mortality (hazard ratio = 1.8, 95% CI 1.1, 2.9) compared to men receiving radiation therapy plus androgen deprivation therapy. The effect was most pronounced in men with no or minimal comorbidities

Attachment III: Search Strategies by topic

CER 1 – GERD – 2008 UPDATE
SEARCH METHODOLOGY

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2005–2008

SEARCH STRATEGY:
gastroesophageal reflux OR gastro-esophageal reflux OR gastro-oesophageal reflux OR gastrooesophageal reflux OR esophagitis OR oesophagitis OR gerd OR gord OR bile reflux OR heartburn OR acid reflux OR dyspep*
AND
Search "JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Gastroenterology"[Journal:__jrid3841] OR "Am J Gastroenterol"[Journal:__jrid426] OR "Clin Gastroenterol Hepatol"[Journal:__jrid31839] OR "Gut"[Journal:__jrid3923] OR "Aliment Pharmacol Ther"[Journal:__jrid1160]
AND
randomized controlled trials[mh] OR randomized controlled trial* OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt]

TOTAL NUMBER OF ITEMS RETRIEVED: 302

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane DARE – No date limit allowed

SEARCH STRATEGY:
gastroesophageal reflux OR gastro-esophageal reflux OR gastro-oesophageal reflux OR gastrooesophageal reflux OR esophagitis OR oesophagitis OR gerd OR gord OR bile reflux OR heartburn OR acid reflux OR dyspepsia OR dyspeptic OR dyspepsic {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 7

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Database of Systematic Reviews – All years

SEARCH STRATEGY:
gastroesophageal reflux OR gastro-esophageal reflux OR gastro-oesophageal reflux OR gastrooesophageal reflux OR esophagitis OR oesophagitis OR gerd OR gord OR bile reflux OR heartburn OR acid reflux OR dyspepsia OR dyspeptic OR dyspepsic {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 6

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Central (Controlled Trials Register) – 2005-2008

SEARCH STRATEGY:
gastroesophageal reflux OR gastro-esophageal reflux OR gastro-oesophageal reflux OR gastrooesophageal reflux OR esophagitis OR oesophagitis OR gerd OR gord OR bile reflux OR heartburn OR acid reflux OR dyspepsia OR dyspeptic OR dyspepsic {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 21

CER 2 – BREAST NEOPLASMS – 2008 UPDATE
SEARCH METHODOLOGY

SEARCH #1A:
DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2005–2008

LIMITERS:
English
Human

SEARCH STRATEGY:
breast neoplasms[mh] OR breast diseases[mh] OR breast cancer* OR breast neoplasm*[tiab] OR breast carcinoma* OR breast disease*
AND
diagnosis OR diagnose OR diagnostic OR di[sh] OR “gold standard” OR “ROC” OR “receiver operating characteristic” OR sensitivity and specificity[mh] OR likelihood OR “false positive” OR “false negative” OR “true positive” OR “true negative” OR “predictive value" OR accuracy OR gold standard OR ROC OR receiver operating characteristic OR false positive OR false negative OR true positive OR true negative OR predictive value
AND
(ultrasonography[sh] OR ultrasonography, mammary[mh] OR echogra* OR echomammogr* OR sonogr* OR sonomammogr* OR ultrasound OR ultrason*) OR noninvasive OR non-invasive OR magnetic resonance imaging[mh] OR “magnet strength” OR miraluma OR pulse sequence OR MR OR MRI OR magnet strength OR nuclear magnetic resonance OR NMR OR (FDG* OR fluorodeoxyglucose F 18[mh] OR PET[ti] OR organotechnetium compounds/du[mh] OR positron emission tomography OR sestamibi OR technetium Tc 99m Sestamibi/du[mh] OR tomography, emission-computed[mh] OR tetrofosmin OR gamma camera OR gammagraph* OR nuclear medicine OR radionuclide OR radionuclide imaging[sh] OR radiotracer* OR radiopharmaceuticals[mh] OR scintimammogr* OR spectrometry, gamma[mh] OR spectrometry, x-ray emission[mh] OR SPET OR SPECT
AND
artifact* OR artifact* OR attenuate* OR boundar* OR calibration[mh] OR data acquisition OR delineat* OR differentiate* OR dynamic range OR exam time OR field of view OR focal zone OR foreign bodies OR gain setting OR intraobserver[tiab] OR intra-observer[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR interpret* OR kappa OR observer bias OR observer variability OR observer variation[mh] OR reader*[tiab] OR reader concordance OR reverberat* OR shadow* OR speckle reduction OR visuali* OR Accredit* OR Clinical competence[mh] OR experience OR “learning curve” OR learning curve OR “review time” OR review time OR diagnostic errors[mh] OR discomfort* OR “effective dose” OR effective dose OR hazard* OR iatrogenic OR medical errors[mh] OR occupational exposure[mh] OR pain OR patient satisfaction[mh] OR radiation dosage[mh] OR radiation monitoring[mh] OR radiometry[mh] OR safe* OR scintillation counting[mh] OR whole body counting[mh] OR human error OR human factors OR operator error OR timing OR user error OR equipment design[mh:noexp] OR equipment failure[mh:noexp] OR equipment failure analysis[mh] OR equipment reuse[mh] OR equipment safety[mh] OR ambulatory OR facility OR “free-standing” OR “free standing” OR free-standing OR freestanding OR free standing OR mobile OR surgicenter* OR tertiary
NOT
letter[pt] OR editorial[pt] OR news[pt] OR comment[pt] OR case reports[pt] OR review[pt]

TOTAL NUMBER OF ITEMS RETRIEVED: 1042

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SEARCH #1B (In-process Records – No MESH Terms Assigned):
DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-2008

LIMITERS:
English

SEARCH STRATEGY:
breast cancer* OR breast neoplasm*[tiab] OR breast carcinoma* OR breast disease*
AND
diagnosis OR diagnose OR diagnostic OR di[sh] OR “gold standard” OR “ROC” OR “receiver operating characteristic” OR sensitivity and specificity[mh] OR likelihood OR “false positive” OR “false negative” OR “true positive” OR “true negative” OR “predictive value" OR accuracy OR gold standard OR ROC OR receiver operating characteristic OR false positive OR false negative OR true positive OR true negative OR predictive value
AND
(ultrasonography[sh] OR ultrasonography, mammary[mh] OR echogra* OR echomammogr* OR sonogr* OR sonomammogr* OR ultrasound OR ultrason*) OR noninvasive OR non-invasive OR magnetic resonance imaging[mh] OR “magnet strength” OR miraluma OR pulse sequence OR MR OR MRI OR magnet strength OR nuclear magnetic resonance OR NMR OR (FDG* OR fluorodeoxyglucose F 18[mh] OR PET[ti] OR organotechnetium compounds/du[mh] OR positron emission tomography OR sestamibi OR technetium Tc 99m Sestamibi/du[mh] OR tomography, emission-computed[mh] OR tetrofosmin OR gamma camera OR gammagraph* OR nuclear medicine OR radionuclide OR radionuclide imaging[sh] OR radiotracer* OR radiopharmaceuticals[mh] OR scintimammogr* OR spectrometry, gamma[mh] OR spectrometry, x-ray emission[mh] OR SPET OR SPECT
AND
artifact* OR artifact* OR attenuate* OR boundar* OR calibration[mh] OR data acquisition OR delineat* OR differentiate* OR dynamic range OR exam time OR field of view OR focal zone OR foreign bodies OR gain setting OR intraobserver[tiab] OR intra-observer[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR interpret* OR kappa OR observer bias OR observer variability OR observer variation[mh] OR reader*[tiab] OR reader concordance OR reverberat* OR shadow* OR speckle reduction OR visuali* OR Accredit* OR Clinical competence[mh] OR experience OR “learning curve” OR learning curve OR “review time” OR review time OR diagnostic errors[mh] OR discomfort* OR “effective dose” OR effective dose OR hazard* OR iatrogenic OR medical errors[mh] OR occupational exposure[mh] OR pain OR patient satisfaction[mh] OR radiation dosage[mh] OR radiation monitoring[mh] OR radiometry[mh] OR safe* OR scintillation counting[mh] OR whole body counting[mh] OR human error OR human factors OR operator error OR timing OR user error OR equipment design[mh:noexp] OR equipment failure[mh:noexp] OR equipment failure analysis[mh] OR equipment reuse[mh] OR equipment safety[mh] OR ambulatory OR facility OR “free-standing” OR “free standing” OR free-standing OR freestanding OR free standing OR mobile OR surgicenter* OR tertiary
AND
inprocess[sb] OR publisher[sb]

TOTAL NUMBER OF ITEMS RETRIEVED: 54

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SEARCH #1C:
DATABASES SEARCHED & TIME PERIOD COVERED:
Database Of Abstracts Of Reviews Of Effects (DARE) – No year limit allowed

Cochrane Database Of Systematic Reviews – 2005-2008
Cochrane Central Register Of Controlled Trials – 2005-2008

SEARCH STRATEGY:
(breast neoplasms or breast diseases or breast disease or breast cancer or breast carcinoma).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]
AND
(diagnosis or diagnose or diagnostic or gold standard or ROC or receiver operating characteristic or (sensitivity and specificity) or likelihood or false positive or false negative or true positive or true negative or predictive value).mp.

TOTAL NUMBER OF ITEMS RETRIEVED: 205
TOTAL NUMBER OF RELEVANT ITEMS IDENTIFIED: 81

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SEARCH #2 – LIMITED SEARCH:
DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed – 2005-2008

LIMITERS:
English

SEARCH STRATEGY:
breast neoplasms OR breast diseases[mh] OR breast cancer* OR breast neoplasm*[tiab] OR breast carcinoma* OR breast disease
AND
diagnosis OR diagnose OR diagnostic OR di[sh] OR “gold standard” OR “ROC” OR “receiver operating characteristic” OR sensitivity and specificity[mh] OR likelihood OR “false positive” OR “false negative” OR “true positive” OR “true negative” OR “predictive value" OR accuracy OR gold standard OR ROC OR receiver operating characteristic OR false positive OR false negative OR true positive OR true negative OR predictive value
AND
(ultrasonography[sh] OR ultrasonography, mammary[mh] OR echogra* OR echomammogr* OR sonogr* OR sonomammogr* OR ultrasound OR ultrason*) OR noninvasive OR non-invasive OR magnetic resonance imaging[mh] OR “magnet strength” OR miraluma OR pulse sequence OR MR OR MRI OR magnet strength OR nuclear magnetic resonance OR NMR OR (FDG* OR fluorodeoxyglucose F 18[mh] OR PET[ti] OR organotechnetium compounds/du[mh] OR positron emission tomography OR sestamibi OR technetium Tc 99m Sestamibi/du[mh] OR tomography, emission-computed[mh] OR tetrofosmin OR gamma camera OR gammagraph* OR nuclear medicine OR radionuclide OR radionuclide imaging[sh] OR radiotracer* OR radiopharmaceuticals[mh] OR scintimammogr* OR spectrometry, gamma[mh] OR spectrometry, x-ray emission[mh] OR SPET OR SPECT
AND
artifact* OR artifact* OR attenuate* OR boundar* OR calibration[mh] OR data acquisition OR delineat* OR differentiate* OR dynamic range OR exam time OR field of view OR focal zone OR foreign bodies OR gain setting OR intraobserver[tiab] OR intra-observer[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR interpret* OR kappa OR observer bias OR observer variability OR observer variation[mh] OR reader*[tiab] OR reader concordance OR reverberat* OR shadow* OR speckle reduction OR visuali* OR Accredit* OR Clinical competence[mh] OR experience OR “learning curve” OR learning curve OR “review time” OR review time OR diagnostic errors[mh] OR discomfort* OR “effective dose” OR effective dose OR hazard* OR iatrogenic OR medical errors[mh] OR occupational exposure[mh] OR pain OR patient satisfaction[mh] OR radiation dosage[mh] OR radiation

monitoring[mh] OR radiometry[mh] OR safe* OR scintillation counting[mh] OR whole body counting[mh] OR human error OR human factors OR operator error OR timing OR user error OR equipment design[mh:noexp] OR equipment failure[mh:noexp] OR equipment failure analysis[mh] OR equipment reuse[mh] OR equipment safety[mh] OR ambulatory OR facility OR “free-standing” OR “free standing” OR free-standing OR freestanding OR free standing OR mobile OR surgicenter* OR tertiary
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985]) OR "Lancet"[Journal:__jrid5470]) OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274]) OR "Ann Intern Med"[Journal:__jrid596]) OR "CA Cancer J Clin"[Journal:__jrid2683]) OR "Radiol Clin North Am"[Journal:__jrid6854]) OR "J Nucl Med"[Journal:__jrid5045]) OR "Eur J Nucl Med"[Journal:__jrid3620]) OR "Radiology"[Journal:__jrid6859]) OR "J Magn Reson Imaging"[Journal:__jrid2081]) OR "J Ultrasound Med"[Journal:__jrid5330]

TOTAL NUMBER OF ITEMS RETRIEVED: 297

CER 3 – EPOETIN UPDATE
SEARCH METHODOLOGY

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2005–2008

SEARCH STRATEGY:
erythropoietin OR epoetin* OR epo OR eprex OR neorecormon OR aranesp OR procrit OR darbepoetin OR erythropoietin[mh] OR erythropoietin, recombinant[mh] OR epoetin alfa[mh] OR epoetin beta[substance name] OR darbepoetin alfa[mh] OR darbepoetin alfa[substance name}
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR ("Ann Oncol"[Journal:__jrid1846] OR "Br J Cancer"[Journal:__jrid1765] OR "Br J Cancer Suppl"[Journal:__jrid1766] OR "J Clin Oncol"[Journal:__jrid5023] OR "Oncology"[Journal:__jrid6265] OR "Oncology (Williston Park)"[Journal:__jrid1783]) OR "Cancer"[Journal:__jrid2771]
AND
randomized controlled trials[mh] OR randomized controlled trial* OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt]
AND
randomized controlled trial* OR randomized controlled trials OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt]) OR (triple blind* OR triple-blind* OR single blind* OR single-blind* OR double blind* OR double-blind* OR treble blind* OR treble-blind* OR placebo)

TOTAL NUMBER OF ITEMS RETRIEVED: 94

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane DARE – No date limit allowed

SEARCH STRATEGY:
erythropoietin OR epoetin* OR epo OR eprex OR neorecormon OR aranesp OR procrit OR darbepoetin {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 3

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Database of Systematic Reviews – 2005-2008

SEARCH STRATEGY:
erythropoietin OR epoetin* OR epo OR eprex OR neorecormon OR aranesp OR procrit OR darbepoetin {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 1

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Central (Controlled Trials Register) – 2005-2008

SEARCH STRATEGY:
erythropoietin OR epoetin* OR epo OR eprex OR neorecormon OR aranesp OR procrit OR darbepoetin {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 13

CER 4 – OSTEOARTHRITIS/ANALGESICS – 2008 UPDATE
SEARCH METHODOLOGY

SEARCH #1A:
DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2005–2008

LIMITERS:
English
Human

SEARCH STRATEGY:
"osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields]
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Rheumatology"[Journal:__jrid7289] OR "Rheumatology (Oxford)"[Journal:__jrid21385] OR "J Pain"[Journal:__jrid31708] OR "Pain"[Journal:__jrid6347] OR "Br J Rheumatol"[Journal:__jrid1901] OR "J Rheumatol"[Journal:__jrid5243] OR "J Rheumatol Suppl"[Journal:__jrid5244] OR "Arthritis Rheum"[Journal:__jrid881]
AND
celecoxib or choline magnesium trisalicylate or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclofenamate sodium or mefenamic acid or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tolmetin or valdecoxib
AND
randomized controlled trial* OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt]

TOTAL NUMBER OF ITEMS RETRIEVED: 19

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SEARCH #1B:
DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2005–2008

LIMITERS:
English
Human

SEARCH STRATEGY:
"Arthritis, Rheumatoid"[Mesh]
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Rheumatology"[Journal:__jrid7289] OR "Rheumatology (Oxford)"[Journal:__jrid21385] OR "J Pain"[Journal:__jrid31708] OR "Pain"[Journal:__jrid6347] OR "Br J Rheumatol"[Journal:__jrid1901] OR "J Rheumatol"[Journal:__jrid5243] OR "J Rheumatol Suppl"[Journal:__jrid5244] OR "Arthritis Rheum"[Journal:__jrid881]

AND
celecoxib or choline magnesium trisalicylate or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclofenamate sodium or mefenamic acid or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tolmetin or valdecoxib
AND
randomized controlled trial* OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt]

TOTAL NUMBER OF ITEMS RETRIEVED: 8

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SEARCH #1C:
DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2005–2008

LIMITERS:
English
Human

SEARCH STRATEGY:
"osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields] OR "Arthritis, Rheumatoid"[Mesh]
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Rheumatology"[Journal:__jrid7289] OR "Rheumatology (Oxford)"[Journal:__jrid21385] OR "J Pain"[Journal:__jrid31708] OR "Pain"[Journal:__jrid6347] OR "Br J Rheumatol"[Journal:__jrid1901] OR "J Rheumatol"[Journal:__jrid5243] OR "J Rheumatol Suppl"[Journal:__jrid5244] OR "Arthritis Rheum"[Journal:__jrid881]
AND
aspirin OR acetaminophen
AND
randomized controlled trial* OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt]

TOTAL NUMBER OF ITEMS RETRIEVED: 18

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SEARCH #1D:
DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2005–2008

LIMITERS:
English
Human

SEARCH STRATEGY:
"osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields]

AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Rheumatology"[Journal:__jrid7289] OR "Rheumatology (Oxford)"[Journal:__jrid21385] OR "J Pain"[Journal:__jrid31708] OR "Pain"[Journal:__jrid6347] OR "Br J Rheumatol"[Journal:__jrid1901] OR "J Rheumatol"[Journal:__jrid5243] OR "J Rheumatol Suppl"[Journal:__jrid5244] OR "Arthritis Rheum"[Journal:__jrid881]
AND
topical AND (capsaicin OR diclofenac OR ibuprofen OR ketoprofen OR salicylate)
AND
randomized controlled trial* OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt]

TOTAL NUMBER OF ITEMS RETRIEVED: 4

CER 6 – ATYPICAL ANTIPSYCHOTICS – 2008 UPDATE
SEARCH METHODOLOGY

SEARCH #1A – SYSTEMATIC REVIEWS & OTHER EVIDENCE-BASED SOURCES:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

LIMITERS:
English

SEARCH STRATEGY:
Antipsychotic Agents[mh] OR Antipsychotic Agents[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone
AND
depression OR dementia OR obsessive compulsive disorder OR post traumatic stress disorder OR ptsd OR off label OR off-label
AND
systematic review*

TOTAL NUMBER OF ITEMS RETRIEVED: 18

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SEARCH #1B – SYSTEMATIC REVIEWS & OTHER EVIDENCE-BASED SOURCES:

DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane DARE

SEARCH STRATEGY:
Antipsychotic Agents OR ziprasidone OR Risperidone OR olanzapine OR quetiapine OR aripiprazole OR antipsychotic OR antipsychotics OR anti-psychotic OR anti-psychotics {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 32

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SEARCH #1C – SYSTEMATIC REVIEWS & OTHER EVIDENCE-BASED SOURCES:

DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Systematic Reviews Database

SEARCH STRATEGY:
Antipsychotic Agents OR ziprasidone OR Risperidone OR olanzapine OR quetiapine OR aripiprazole OR antipsychotic OR antipsychotics OR anti-psychotic OR anti-psychotics {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 16

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SEARCH #1D – SYSTEMATIC REVIEWS & OTHER EVIDENCE-BASED SOURCES:

DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Central (Controlled Trials Register) – 2006-2008

SEARCH STRATEGY:
Antipsychotic Agents OR ziprasidone OR Risperidone OR olanzapine OR quetiapine OR aripiprazole OR antipsychotic OR antipsychotics OR anti-psychotic OR anti-psychotics {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 88

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SEARCH #1E – SYSTEMATIC REVIEWS & OTHER EVIDENCE-BASED SOURCES:

DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane – All databases – 2006-2008 (No date limit allowed in DARE)

SEARCH STRATEGY:
(Antipsychotic Agents OR ziprasidone OR Risperidone OR olanzapine OR quetiapine OR aripiprazole OR antipsychotic OR antipsychotics OR anti-psychotic OR anti-psychotics).mp. **[mp=ti, ot, ab, sh, hw, kw, tx, ct] (Note – Related terms included)**
AND
(atypical or off label or non intended or non intentional).mp.

TOTAL NUMBER OF ITEMS RETRIEVED: 224

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SEARCH #2A – OFF-LABEL + SPECIFIC DRUGS + CONDITIONS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

LIMITERS:
English

SEARCH STRATEGY:
"atypical use" OR "off label" OR "non intended" OR "non intentional" OR atypical use OR off label OR non intended OR non intentional
AND
risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR risperidone[mh] OR olanzapine[Substance Name] OR quetiapine[Substance Name] OR aripiprazole[Substance Name] OR ziprasidone[Substance Name]
AND
"Personality Disorders"[mh] OR "Dementia"[mh] OR "Depression"[mh] OR "Depressive Disorder"[mh] OR "Obsessive-Compulsive Disorder"[mh] OR "Stress Disorders, Post-Traumatic"[mh] OR "Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*" OR ptsd OR severe geriatric agitation OR geriatric agitation OR Personality Disorders[mh] OR Dementia[mh] OR Depression[mh] OR depressive Disorder[mh] OR Obsessive-Compulsive Disorder[mh] OR Stress Disorders, Post-Traumatic[mh] OR Personality Disorder* OR Dementia OR Depression OR depressive Disorder OR depress* OR Obsessive Compulsive Disorder OR ocd OR Post-Traumatic Stress disorder* OR ptsd OR severe geriatric agitation OR geriatric agitation

TOTAL NUMBER OF ITEMS RETRIEVED: 190

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DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

SEARCH STRATEGY:
(kw: off w label) OR kw: off-label OR kw: offlabel OR (kw: atypical w use) OR (kw: non w intended w use) OR (kw: non w intentional w use) OR (kw: "not" w intended w use)
AND
kw: Risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone or de: Risperidone OR de: olanzapine OR de: quetiapine OR de: aripiprazole OR de: ziprasidone
AND
su= "personality disorders" OR su= "obsessive compulsive disorder" OR su= "obsessive compulsive personality disorder" OR su= "posttraumatic stress disorder" or su: dementia OR su: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation) OR (kw: personality w disorders) OR (kw: obsessive w compulsive w disorder) OR (kw: obsessive w compulsive w personality w disorder) OR (kw: posttraumatic w stress w disorder) OR kw: ptsd OR kw: ocd OR (kw: post w traumatic w stress) OR (kw: obsessive w compulsive) or kw: dementia OR kw: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation)

TOTAL NUMBER OF ITEMS RETRIEVED: 6

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SEARCH #2B – OFF-LABEL + SPECIFIC DRUGS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

LIMITERS:
English

SEARCH STRATEGY:
“atypical use” OR “off label” OR “non intended” OR “non intentional” OR atypical use OR off label OR non intended OR non intentional
AND
risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR risperidone[mh] OR olanzapine[Substance Name] OR quetiapine[Substance Name] OR aripiprazole[Substance Name] OR ziprasidone[Substance Name]

TOTAL NUMBER OF ITEMS RETRIEVED: 826

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DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

SEARCH STRATEGY:
(kw: off w label) OR kw: off-label OR kw: offlabel OR (kw: atypical w use) OR (kw: non w intended w use) OR (kw: non w intentional w use) OR (kw: "not" w intended w use)
kw: Risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone or de: Risperidone OR de: olanzapine OR de: quetiapine OR de: aripiprazole OR de: ziprasidone

TOTAL NUMBER OF ITEMS RETRIEVED: 12

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SEARCH #2C – OFF-LABEL + SPECIFIC CONDITIONS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

LIMITERS:
English

SEARCH STRATEGY:
"atypical use" OR "off label" OR "non intended" OR "non intentional" OR atypical use OR off label OR non intended OR non intentional
AND
"Personality Disorders"[mh] OR "Dementia"[mh] OR "Depression"[mh] OR "Depressive Disorder"[mh] OR "Obsessive-Compulsive Disorder"[mh] OR "Stress Disorders, Post-Traumatic"[mh] OR "Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*" OR ptsd OR severe geriatric agitation OR geriatric agitation OR Personality Disorders[mh] OR Dementia[mh] OR Depression[mh] OR depressive Disorder[mh] OR Obsessive-Compulsive Disorder[mh] OR Stress Disorders, Post-Traumatic[mh] OR Personality Disorder* OR Dementia OR Depression OR depressive Disorder OR depress* OR Obsessive Compulsive Disorder OR ocd OR Post-Traumatic Stress disorder* OR ptsd OR severe geriatric agitation OR geriatric agitation

TOTAL NUMBER OF ITEMS RETRIEVED: 719

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DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

SEARCH STRATEGY:
(kw: off w label) OR kw: off-label OR kw: offlabel OR (kw: atypical w use) OR (kw: non w intended w use) OR (kw: non w intentional w use) OR (kw: "not" w intended w use)
su= "personality disorders" OR su= "obsessive compulsive disorder" OR su= "obsessive compulsive personality disorder" OR su= "posttraumatic stress disorder" or su: dementia OR su: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation) OR (kw: personality w disorders) OR (kw: obsessive w compulsive w disorder) OR (kw: obsessive w compulsive w personality w disorder) OR (kw: posttraumatic w stress w disorder) OR kw: ptsd OR kw: ocd OR (kw: post w traumatic w stress) OR (kw: obsessive w compulsive) or kw: dementia OR kw: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation)

TOTAL NUMBER OF ITEMS RETRIEVED: 29

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SEARCH #2D – SPECIFIC DRUGS + CONDITIONS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

LIMITERS:
English

SEARCH STRATEGY:
risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR risperidone[mh] OR olanzapine[Substance Name] OR quetiapine[Substance Name] OR aripiprazole[Substance Name] OR ziprasidone[Substance Name]
AND
"Personality Disorders"[mh] OR "Dementia"[mh] OR "Depression"[mh] OR "Depressive Disorder"[mh] OR "Obsessive-Compulsive Disorder"[mh] OR "Stress Disorders, Post-Traumatic"[mh] OR "Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*" OR ptsd OR severe geriatric agitation OR geriatric agitation OR Personality Disorders[mh] OR Dementia[mh] OR Depression[mh] OR depressive Disorder[mh] OR Obsessive-Compulsive Disorder[mh] OR Stress Disorders, Post-Traumatic[mh] OR Personality Disorder* OR Dementia OR Depression OR depressive Disorder OR depress* OR Obsessive Compulsive Disorder OR ocd OR Post-Traumatic Stress disorder* OR ptsd OR severe geriatric agitation OR geriatric agitation

TOTAL NUMBER OF ITEMS RETRIEVED: 551

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DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

SEARCH STRATEGY:
kw: Risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone or de: Risperidone OR de: olanzapine OR de: quetiapine OR de: aripiprazole OR de: ziprasidone
AND
su= "personality disorders" OR su= "obsessive compulsive disorder" OR su= "obsessive compulsive personality disorder" OR su= "posttraumatic stress disorder" or su: dementia OR su: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation) OR (kw: personality w disorders) OR (kw: obsessive w compulsive w disorder) OR (kw: obsessive w compulsive w personality w disorder) OR (kw: posttraumatic w stress w disorder) OR kw: ptsd OR kw: ocd OR (kw: post w traumatic w stress) OR (kw: obsessive w compulsive) or kw: dementia OR kw: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation)

TOTAL NUMBER OF ITEMS RETRIEVED: 391

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SEARCH #2E – SPECIFIC DRUGS + CONDITIONS + CLINICAL TRIALS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

SEARCH STRATEGY:
kw: Risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone or de: Risperidone OR de: olanzapine OR de: quetiapine OR de: aripiprazole OR de: ziprasidone
AND
su= "personality disorders" OR su= "obsessive compulsive disorder" OR su= "obsessive compulsive personality disorder" OR su= "posttraumatic stress disorder" or su: dementia OR su: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation) OR (kw: personality w disorders) OR (kw: obsessive w compulsive w disorder) OR (kw: obsessive w compulsive w personality w disorder) OR (kw: posttraumatic w stress w disorder) OR kw: ptsd OR kw: ocd OR (kw: post w traumatic w stress) OR (kw: obsessive w compulsive) or kw: dementia OR kw: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation)
AND

de= "clinical trials" OR (kw: controlled w clinical w trial) OR (kw: controlled w clinical w trials) OR (kw: randomized w trial) OR (kw: randomized w trials) OR (kw: randomized w controlled w trial) OR (kw: randomized w controlled w trials) OR (kw: clinical w trial) OR (kw: clincal w trials)

TOTAL NUMBER OF ITEMS RETRIEVED: 53

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SEARCH #2F – SPECIFIC DRUGS + CONDITIONS + CLINICAL TRIALS + OFF-LABEL:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

SEARCH STRATEGY:
kw: Risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone or de: Risperidone OR de: olanzapine OR de: quetiapine OR de: aripiprazole OR de: ziprasidone
AND
su= "personality disorders" OR su= "obsessive compulsive disorder" OR su= "obsessive compulsive personality disorder" OR su= "posttraumatic stress disorder" or su: dementia OR su: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation) OR (kw: personality w disorders) OR (kw: obsessive w compulsive w disorder) OR (kw: obsessive w compulsive w personality w disorder) OR (kw: posttraumatic w stress w disorder) OR kw: ptsd OR kw: ocd OR (kw: post w traumatic w stress) OR (kw: obsessive w compulsive) or kw: dementia OR kw: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation)
AND
de= "clinical trials" OR (kw: controlled w clinical w trial) OR (kw: controlled w clinical w trials) OR (kw: randomized w trial) OR (kw: randomized w trials) OR (kw: randomized w controlled w trial) OR (kw: randomized w controlled w trials) OR (kw: clinical w trial) OR (kw: clincal w trials)
AND
(kw: off w label) OR kw: off-label OR kw: offlabel OR (kw: atypical w use) OR (kw: non w intended w use) OR (kw: non w intentional w use) OR (kw: "not" w intended w use)

TOTAL NUMBER OF ITEMS RETRIEVED: 1

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SEARCH #2G – OFF-LABEL + GENERAL ATYPICAL ANTIPSYCHOTICS TERMS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

SEARCH STRATEGY:
(kw: off w label) OR kw: off-label OR kw: offlabel OR (kw: atypical w use) OR (kw: non w intended w use) OR (kw: non w intentional w use) OR (kw: "not" w intended w use)
AND
((kw: atypical and (kw: antipsychotic* OR kw: anti-psychotic*))
NOT
(kw: Risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone or de: Risperidone OR de: olanzapine OR de: quetiapine OR de: aripiprazole OR de: ziprasidone)

TOTAL NUMBER OF ITEMS RETRIEVED: 10

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SEARCH #2H – GENERAL ATYPICAL ANTIPSYCHOTICS TERMS + CONDITIONS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

SEARCH STRATEGY:
kw: atypical and (kw: antipsychotic* OR kw: anti-psychotic*)
AND
su= "personality disorders" OR su= "obsessive compulsive disorder" OR su= "obsessive compulsive personality disorder" OR su= "posttraumatic stress disorder" or su: dementia OR su: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation) OR (kw: personality w disorders) OR (kw: obsessive w compulsive w disorder) OR (kw: obsessive w compulsive w personality w disorder) OR (kw: posttraumatic w stress w disorder) OR kw: ptsd OR kw: ocd OR (kw: post w traumatic w stress) OR (kw: obsessive w compulsive) or kw: dementia OR kw: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation)
NOT
kw: Risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone or de: Risperidone OR de: olanzapine OR de: quetiapine OR de: aripiprazole OR de: ziprasidone

TOTAL NUMBER OF ITEMS RETRIEVED: 112

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SEARCH #2I – GENERAL ATYPICAL ANTIPSYCHOTICS TERMS + CONDITIONS + CLINICAL TRIALS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

SEARCH STRATEGY:
kw: atypical and (kw: antipsychotic* OR kw: anti-psychotic*)
AND
su= "personality disorders" OR su= "obsessive compulsive disorder" OR su= "obsessive compulsive personality disorder" OR su= "posttraumatic stress disorder" or su: dementia OR su: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation) OR (kw: personality w disorders) OR (kw: obsessive w compulsive w disorder) OR (kw: obsessive w compulsive w personality w disorder) OR (kw: posttraumatic w stress w disorder) OR kw: ptsd OR kw: ocd OR (kw: post w traumatic w stress) OR (kw: obsessive w compulsive) or kw: dementia OR kw: depression OR (kw: severe w geriatric w agitation) OR (kw: geriatric w agitation)
AND
de= "clinical trials" OR (kw: controlled w clinical w trial) OR (kw: controlled w clinical w trials) OR (kw: randomized w trial) OR (kw: randomized w trials) OR (kw: randomized w controlled w trial) OR (kw: randomized w controlled w trials) OR (kw: clinical w trial) OR (kw: clincal w trials)

TOTAL NUMBER OF ITEMS RETRIEVED: 8

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SEARCH #3A – LIMITED SEARCH:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

LIMITERS:
English

Letter
Editorial
Comment

SEARCH STRATEGY:
annals of internal medicine OR british medical journal OR jama OR lancet OR new england journal of medicine OR archives of general psychiatry OR american journal of psychiatry
AND
Antipsychotic Agents[mh] OR Antipsychotic Agents[Pharmacological Action] OR Risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR Risperidone[mh] OR olanzapine[Substance Name] OR quetiapine[Substance Name] OR aripiprazole[Substance Name] OR ziprasidone[Substance Name]

OR

annals of internal medicine OR british medical journal OR jama OR lancet OR new england journal of medicine OR archives of general psychiatry OR american journal of psychiatry
AND
atypical use OR off label OR non intended OR non intentional
AND
Personality Disorders[mh] OR Dementia[mh] OR Depression[mh] OR depressive Disorder[mh] OR Obsessive-Compulsive Disorder[mh] OR Stress Disorders, Post-Traumatic[mh] OR Personality Disorder* OR Dementia OR Depression OR depressive Disorder OR depress* OR Obsessive Compulsive Disorder OR ocd OR Post-Traumatic Stress disorder* OR ptsd OR severe geriatric agitation OR geriatric agitation OR "Personality Disorders"[mh] OR "Dementia"[mh] OR "Depression"[mh] OR "Depressive Disorder"[mh] OR "Obsessive-Compulsive Disorder"[mh] OR "Stress Disorders, Post-Traumatic"[mh] OR "Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*" OR ptsd OR severe geriatric agitation OR geriatric agitation

TOTAL NUMBER OF ITEMS RETRIEVED: 104

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SEARCH #3B – LIMITED SEARCH (Revision – Includes all publication types):

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

LIMITERS:
English

SEARCH STRATEGY: (Note – Journals were searched using the PubMed Journals Database)
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Arch Gen Psychiatry"[Journal:__jrid744] OR american journal of psychiatry[ta]
AND
Antipsychotic Agents[mh] OR Antipsychotic Agents[Pharmacological Action] OR Risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR Risperidone[mh] OR olanzapine[Substance Name] OR quetiapine[Substance Name] OR aripiprazole[Substance Name] OR ziprasidone[Substance Name] OR antipsychotic* OR anti-psychotic*

OR

"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Arch Gen Psychiatry"[Journal:__jrid744] OR american journal of psychiatry[ta]
AND
atypical use OR off label OR non intended OR non intentional
AND
Personality Disorders[mh] OR Dementia[mh] OR Depression[mh] OR depressive Disorder[mh] OR Obsessive-Compulsive Disorder[mh] OR Stress Disorders, Post-Traumatic[mh] OR Personality Disorder* OR Dementia OR Depression OR depressive Disorder OR depress* OR Obsessive Compulsive Disorder OR ocd OR Post-Traumatic Stress disorder* OR ptsd OR severe geriatric agitation OR geriatric agitation OR "Personality Disorders"[mh] OR "Dementia"[mh] OR "Depression"[mh] OR "Depressive Disorder"[mh] OR "Obsessive-Compulsive Disorder"[mh] OR "Stress Disorders, Post-Traumatic"[mh] OR "Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*" OR ptsd OR severe geriatric agitation OR geriatric agitation

TOTAL NUMBER OF ITEMS RETRIEVED: 265

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SEARCH #3C – LIMITED SEARCH (Revision - Add RCT's):

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

LIMITERS:
English
Letter
Editorial
Comment
Randomized Controlled Trial

SEARCH STRATEGY: (Note – Journals were searched using the PubMed Journals Database)
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Arch Gen Psychiatry"[Journal:__jrid744] OR american journal of psychiatry[ta]
AND
Antipsychotic Agents[mh] OR Antipsychotic Agents[Pharmacological Action] OR Risperidone OR olanzapine OR quetiapine OR aripiprazole OR ziprasidone OR Risperidone[mh] OR olanzapine[Substance Name] OR quetiapine[Substance Name] OR aripiprazole[Substance Name] OR ziprasidone[Substance Name] OR antipsychotic* OR anti-psychotic*
AND
Personality Disorders[mh] OR Dementia[mh] OR Depression[mh] OR depressive Disorder[mh] OR Obsessive-Compulsive Disorder[mh] OR Stress Disorders, Post-Traumatic[mh] OR Personality Disorder* OR Dementia OR Depression OR depressive Disorder OR depress* OR Obsessive Compulsive Disorder OR ocd OR Post-Traumatic Stress disorder* OR ptsd OR severe geriatric agitation OR geriatric agitation OR "Personality Disorders"[mh] OR "Dementia"[mh] OR "Depression"[mh] OR "Depressive Disorder"[mh] OR "Obsessive-Compulsive Disorder"[mh] OR "Stress Disorders, Post-Traumatic"[mh] OR "Personality Disorder*" OR "Dementia" OR "Depression" OR "Depressive Disorder" OR depress* OR "Obsessive Compulsive Disorder" OR ocd OR "Post-Traumatic Stress disorder*" OR ptsd OR severe geriatric agitation OR geriatric agitation
AND

atypical use OR atypical[tiab] OR off label OR offlabel OR non intended OR non intentional OR non-intended OR non-intentional
AND
randomized controlled trial* OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR

TOTAL NUMBER OF ITEMS RETRIEVED: 265

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SEARCH #3D – LIMITED SEARCH:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

LIMITERS:
Letter
Editorial
Comment

SEARCH STRATEGY:
so: bmj OR (so: annals and so: internal and so: medicine) OR (so: british and so: medical and so: journal) OR so: jama OR so: lancet OR (so: new and so: england and so: journal and so: medicine) OR (so: archives and so: general and so: psychiatry) OR (so: american and so: journal and so: psychiatry)
AND
kw: risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone OR (kw: atypical and kw: antipsychotic*) OR (kw: atypical and kw: anti-psychotic*)

TOTAL NUMBER OF ITEMS RETRIEVED: 28

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SEARCH #3F – LIMITED SEARCH (Revision - Add RCT's):

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

LIMITERS:
Letter
Editorial
Comment
Randomized Controlled Trials

SEARCH STRATEGY:
so: bmj OR (so: annals and so: internal and so: medicine) OR (so: british and so: medical and so: journal) OR so: jama OR so: lancet OR (so: new and so: england and so: journal and so: medicine) OR (so: archives and so: general and so: psychiatry) OR (so: american and so: journal and so: psychiatry)
AND
kw: risperidone OR kw: olanzapine OR kw: quetiapine OR kw: aripiprazole OR kw: ziprasidone OR (kw: atypical and kw: antipsychotic*) OR (kw: atypical and kw: anti-psychotic*)
AND

(kw: Personality and kw: Disorder*) OR kw: Dementia OR kw: Depress* OR kw: Obsessive-Compulsive OR (kw: obsessive and kw: compulsive) OR kw: ocd OR (kw: post and kw: traumatic and kw: stress) OR kw: ptsd OR (kw: geriatric and kw: agitat*)
AND
kw: atypical OR (kw: off and kw: label) OR kw: offlabel OR (kw: non and kw: intended) OR kw: non-intended OR (kw: non and kw: intentional) OR kw: non-intentional
AND
(kw: randomized and kw: controlled and kw: trial*) OR kw: rct* OR (kw: random and kw: allocation) OR kw: randomi* OR (kw: double and kw: blind) OR kw: double-blind OR (kw: single and kw: blind) OR kw: single-blind OR kw: letter* OR kw: editorial* OR kw: comment*

TOTAL NUMBER OF ITEMS RETRIEVED: 130

CER 7 - ANTIDEPRESSIVE AGENTS – 2008 UPDATE
SEARCH METHODOLOGY

SEARCH #1A – GENERAL TOPIC:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

OTHER LIMITERS:
English
Human
Adult (19 years+)

SEARCH STRATEGY:
"antidepressive agents, second-generation"[mh] OR "fluoxetine"[mh] OR "sertraline"[mh] OR "paroxetine"[mh] OR "citalopram"[mh] OR "fluvoxamine"[mh] OR "bupropion"[mh] OR "nefazodone"[nm] OR "mirtazapine"[nm] OR "venlafaxine"[nm] OR "escitalopram"[tw] OR "duloxetine"[nm] OR "trazodone"[mh] OR antidepressive agents, second-generation OR fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR citalopram[mh] OR fluvoxamine[mh] OR bupropion[mh] OR nefazodone[nm] OR mirtazapine[nm] OR venlafaxine[nm] OR escitalopram OR duloxetine[nm] OR trazodone[mh]
AND
"depressive disorder"[mh] OR "depressive disorder, major"[mh] OR "depression, involutional"[tw] OR "dysthymic disorder"[mh] OR "subsyndronal depressive disorder"[tw] OR depressive disorder[mh] OR depressive disorder, major[mh] OR depression, involutional[tw] OR dysthymic disorder[mh] OR subsyndronal depressive disorder[tw]
AND
"quality of life"[mh] OR "hospitalization"[mh] OR quality of life[mh] OR hospitalization[mh]
NOT
"randomized controlled trial"[pt] OR "randomized controlled trials"[mh] OR "single-blind method"[mh] OR "double-blind method"[mh] OR "random allocation"[mh] OR randomized controlled trial[pt] OR randomized controlled trials[mh] OR single-blind method[mh] OR double-blind method[mh] OR random allocation[mh]

TOTAL NUMBER OF ITEMS RETRIEVED: 8

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SEARCH #1B – GENERAL TOPIC:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO – 2006–2008

OTHER LIMITERS:
English
Human

SEARCH STRATEGY:
su= "antidepressant drugs" OR de= "antidepressant drugs" OR kw: fluoxetine OR kw: sertraline OR kw: paroxetine OR kw: citalopram OR kw: fluvoxamine OR kw: bupropion OR kw: nefazodone OR kw: mirtazapine OR kw: venlafaxine OR kw: escitalopram OR kw: duloxetine OR kw: trazodone
AND
de: depressi* OR su: depressi* OR kw: dysthymi*
AND

(kw: quality AND kw: life) OR kw: hospitaliz* OR kw: hospitalis*
NOT
kw: random* OR kw: single-blind* OR (kw: single AND kw: blind*) OR kw: double-blind* OR (kw: double AND kw: blind*)

TOTAL NUMBER OF ITEMS RETRIEVED: 45

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane – All databases

OTHER LIMITERS:
English
Human

SEARCH STRATEGY:
(fluoxetine or sertraline or paroxetine or citalopram or fluvoxamine or bupropion or nefazodone or mirtazapine or venlafaxine or escitalopram or duloxetine or trazodone).mp. OR antidepressive agents, second-generation.mp.
AND
(depression or depressive or depressed).ti,sh,hw.

TOTAL NUMBER OF ITEMS RETRIEVED: 484

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SEARCH #2A – ADVERSE EVENTS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

OTHER LIMITERS:
English
Human
Adult (19 years+)

SEARCH STRATEGY:
"antidepressive agents, second-generation"[mh] OR "fluoxetine"[mh] OR "sertraline"[mh] OR "paroxetine"[mh] OR "citalopram"[mh] OR "fluvoxamine"[mh OR "bupropion"[mh] OR "nefazodone"[nm] OR "mirtazapine"[nm] OR "venlafaxine"[nm] OR "escitalopram"[tw] OR "duloxetine"[nm] OR "trazodone"[mh] OR antidepressive agents, second-generation OR fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR citalopram[mh] OR fluvoxamine[mh] OR bupropion[mh] OR nefazodone[nm] OR mirtazapine[nm] OR venlafaxine[nm] OR escitalopram OR duloxetine[nm] OR trazodone[mh]
AND
"depressive disorder"[mh] OR "depressive disorder, major"[mh] OR "depression, involutional"[tw] OR "dysthymic disorder"[mh] OR "subsyndronal depressive disorder"[tw] OR depressive disorder[mh] OR depressive disorder, major[mh] OR depression, involutional[tw] OR dysthymic disorder[mh] OR subsyndronal depressive disorder[tw]
AND
"adverse events"[tw] OR "drug hypersensitivity"[mh] OR "drug toxicity"[mh] OR hyponatremia[mh] OR seizures[mh] OR suicide[mh] OR "weight gain"[mh] OR "gastroesophageal reflux"[mh] OR libido[mh] OR hepatoxicity[tw] OR adverse events[tw] OR drug hypersensitivity[mh] OR drug toxicity[mh] OR

hyponatremia[mh] OR seizures[mh] OR suicide[mh] OR weight gain[mh] OR gastroesophageal reflux[mh] OR libido[mh] OR hepatoxicity[tw]
NOT
"randomized controlled trial"[pt] OR "randomized controlled trials"[mh] OR "single-blind method"[mh] OR "double-blind method"[mh] OR "random allocation"[mh] OR randomized controlled trial[pt] OR randomized controlled trials[mh] OR single-blind method[mh] OR double-blind method[mh] OR random allocation[mh]

TOTAL NUMBER OF ITEMS RETRIEVED: 58

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SEARCH #2B – ADVERSE EVENTS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO – 2006–2008

OTHER LIMITERS:
English

SEARCH STRATEGY:
su= "antidepressant drugs" OR de= "antidepressant drugs" OR kw: fluoxetine OR kw: sertraline OR kw: paroxetine OR kw: citalopram OR kw: fluvoxamine OR kw: bupropion OR kw: nefazodone OR kw: mirtazapine OR kw: venlafaxine OR kw: escitalopram OR kw: duloxetine OR kw: trazodone
AND
de: depressi* OR su: depressi* OR kw: dysthymi*
AND
kw: side w effect OR kw: side w effects) OR (kw: adverse or kw: hypersensitiv* OR kw: toxic* OR kw: hyponatremi* OR kw: seizure* OR kw: suicid* OR kw: weight OR kw: reflux OR kw: libido OR kw: hepatoxic*
NOT
kw: random* OR kw: single-blind* OR (kw: single AND kw: blind*) OR kw: double-blind* OR (kw: double AND kw: blind*)

TOTAL NUMBER OF ITEMS RETRIEVED: 288

SEARCH #3A – LONGITUDINAL STUDIES:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

OTHER LIMITERS:
English
Human
Adult (19 years+)

SEARCH STRATEGY:
"antidepressive agents, second-generation"[mh] OR "fluoxetine"[mh] OR "sertraline"[mh] OR "paroxetine"[mh] OR "citalopram"[mh] OR "fluvoxamine"[mh OR "bupropion"[mh] OR "nefazodone"[nm] OR "mirtazapine"[nm] OR "venlafaxine"[nm] OR "escitalopram"[tw] OR "duloxetine"[nm] OR "trazodone"[mh] OR antidepressive agents, second-generation OR fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR

citalopram[mh] OR fluvoxamine[mh] OR bupropion[mh] OR nefazodone[nm] OR mirtazapine[nm] OR venlafaxine[nm] OR escitalopram OR duloxetine[nm] OR trazodone[mh]
AND
"depressive disorder"[mh] OR "depressive disorder, major"[mh] OR "depression, involutional"[tw] OR "dysthymic disorder"[mh] OR "subsyndronal depressive disorder"[tw] OR depressive disorder[mh] OR depressive disorder, major[mh] OR depression, involutional[tw] OR dysthymic disorder[mh] OR subsyndronal depressive disorder[tw]
AND
longitudinal studies[mh] OR cohort studies[mh] OR case-control studies[mh] OR **comparative study[pt]** OR "observational studies"[tw] OR longitudinal studies[mh] OR cohort studies[mh] OR case-control studies[mh] OR **comparative study[pt]** OR observational studies[tw]
NOTE: ORIGINAL SEARCH USED COMPARATIVE STUDY AS A MESH TERM[MH]; SHOULD HAVE BEEN PUBLICATION TYPE[PT]
NOT
"randomized controlled trial"[pt] OR "randomized controlled trials"[mh] OR "single-blind method"[mh] OR "double-blind method"[mh] OR "random allocation"[mh] OR randomized controlled trial[pt] OR randomized controlled trials[mh] OR single-blind method[mh] OR double-blind method[mh] OR random allocation[mh]

TOTAL NUMBER OF ITEMS RETRIEVED: 102

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SEARCH #3B – LONGITUDINAL STUDIES:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO – 2006–2008

OTHER LIMITERS:
English

SEARCH STRATEGY:
su= "antidepressant drugs" OR de= "antidepressant drugs" OR kw: fluoxetine OR kw: sertraline OR kw: paroxetine OR kw: citalopram OR kw: fluvoxamine OR kw: bupropion OR kw: nefazodone OR kw: mirtazapine OR kw: venlafaxine OR kw: escitalopram OR kw: duloxetine OR kw: trazodone
AND
de: depressi* OR su: depressi* OR kw: dysthymi*
AND
kw: longitudinal OR kw: cohort* OR (kw: case and kw: control) OR kw: case-control OR kw: comparative OR kw: observational
NOT
kw: random* OR kw: single-blind* OR (kw: single AND kw: blind*) OR kw: double-blind* OR (kw: double AND kw: blind*)

TOTAL NUMBER OF ITEMS RETRIEVED: 62

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SEARCH #4A – DRUG INTERACTIONS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

OTHER LIMITERS:

English
Human
Adult (19 years+)

SEARCH STRATEGY:
"antidepressive agents, second-generation"[mh] OR "fluoxetine"[mh] OR "sertraline"[mh] OR "paroxetine"[mh] OR "citalopram"[mh] OR "fluvoxamine"[mh] OR "bupropion"[mh] OR "nefazodone"[nm] OR "mirtazapine"[nm] OR "venlafaxine"[nm] OR "escitalopram"[tw] OR "duloxetine"[nm] OR "trazodone"[mh] OR OR antidepressive agents, second-generation OR fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR citalopram[mh] OR fluvoxamine[mh] OR bupropion[mh] OR nefazodone[nm] OR mirtazapine[nm] OR venlafaxine[nm] OR escitalopram OR duloxetine[nm] OR trazodone[mh]
AND
"depressive disorder"[mh] OR "depressive disorder, major"[mh] OR "depression, involutional"[tw] OR "dysthymic disorder"[mh] OR "subsyndronal depressive disorder"[tw] OR depressive disorder[mh] OR depressive disorder, major[mh] OR depression, involutional[tw] OR dysthymic disorder[mh] OR subsyndronal depressive disorder[tw]
AND
drug interactions[mh]
NOT
"randomized controlled trial"[pt] OR "randomized controlled trials"[mh] OR "single-blind method"[mh] OR "double-blind method"[mh] OR "random allocation"[mh] OR
randomized controlled trial[pt] OR randomized controlled trials[mh] OR single-blind method[mh] OR double-blind method[mh] OR random allocation[mh]

TOTAL NUMBER OF ITEMS RETRIEVED: 14

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SEARCH #4B – DRUG INTERACTIONS:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

OTHER LIMITERS:
English

SEARCH STRATEGY:
su= "antidepressant drugs" OR de= "antidepressant drugs" OR kw: fluoxetine OR kw: sertraline OR kw: paroxetine OR kw: citalopram OR kw: fluvoxamine OR kw: bupropion OR kw: nefazodone OR kw: mirtazapine OR kw: venlafaxine OR kw: escitalopram OR kw: duloxetine OR kw: trazodone
AND
de: depressi* OR su: depressi* OR kw: dysthymi*
AND
kw: interact*
NOT
kw: random* OR kw: single-blind* OR (kw: single AND kw: blind*) OR kw: double-blind* OR (kw: double AND kw: blind*)

TOTAL NUMBER OF ITEMS RETRIEVED: 71

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SEARCH #5 – RECURRENCE:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

OTHER LIMITERS:
English
Human
Adult (19 years+)

SEARCH STRATEGY:
"antidepressive agents, second-generation"[mh] OR "fluoxetine"[mh] OR "sertraline"[mh] OR "paroxetine"[mh] OR "citalopram"[mh] OR "fluvoxamine"[mh OR "bupropion"[mh] OR "nefazodone"[nm] OR "mirtazapine"[nm] OR "venlafaxine"[nm] OR "escitalopram"[tw] OR "duloxetine"[nm] OR "trazodone"[mh] OR antidepressive agents, second-generation OR fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR citalopram[mh] OR fluvoxamine[mh] OR bupropion[mh] OR nefazodone[nm] OR mirtazapine[nm] OR venlafaxine[nm] OR escitalopram OR duloxetine[nm] OR trazodone[mh]
AND
"depressive disorder"[mh] OR "depressive disorder, major"[mh] OR "depression, involutional"[tw] OR "dysthymic disorder"[mh] OR "subsyndronal depressive disorder"[tw] OR depressive disorder[mh] OR depressive disorder, major[mh] OR depression, involutional[tw] OR dysthymic disorder[mh] OR subsyndronal depressive disorder[tw]
AND
"recurrence"[mh] OR remission[tw] OR relapse[tw] OR recurrence[mh] OR remission[tw] OR relapse[tw]
NOT
"randomized controlled trial"[pt] OR "randomized controlled trials"[mh] OR "single-blind method"[mh] OR "double-blind method"[mh] OR "random allocation"[mh] OR randomized controlled trial[pt] OR randomized controlled trials[mh] OR single-blind method[mh] OR double-blind method[mh] OR random allocation[mh]

TOTAL NUMBER OF ITEMS RETRIEVED: 52

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SEARCH #5B – RECURRENCE:

DATABASES SEARCHED & TIME PERIOD COVERED:
PsycINFO –2006–2008

OTHER LIMITERS:
English

SEARCH STRATEGY:
su= "antidepressant drugs" OR de= "antidepressant drugs" OR kw: fluoxetine OR kw: sertraline OR kw: paroxetine OR kw: citalopram OR kw: fluvoxamine OR kw: bupropion OR kw: nefazodone OR kw: mirtazapine OR kw: venlafaxine OR kw: escitalopram OR kw: duloxetine OR kw: trazodone
AND
de: depressi* OR su: depressi* OR kw: dysthymi*
AND
kw: recur* OR kw: remission* OR kw: relaps*
NOT
kw: random* OR kw: single-blind* OR (kw: single AND kw: blind*) OR kw: double-blind* OR (kw: double AND kw: blind*)

TOTAL NUMBER OF ITEMS RETRIEVED: 196

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SEARCH #6 – SSRI's

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed – 2006–2008

OTHER LIMITERS:
Humans
English
Adult (19+ yrs of age)

SEARCH STRATEGY:
serotonin uptake inhibitors
AND
"depressive disorder"[mh] OR "depressive disorder, major"[mh] OR "depression, involutional"[tw] OR "dysthymic disorder"[mh] OR "subsyndronal depressive disorder"[tw] OR depressive disorder[mh] OR depressive disorder, major[mh] OR depression, involutional[tw] OR dysthymic disorder[mh] OR subsyndronal depressive disorder[tw]
AND
"recurrence"[mh] OR remission[tw] OR relapse[tw] OR recurrence[mh] OR remission[tw] OR relapse[tw]
NOT
"randomized controlled trial"[pt] OR "randomized controlled trials"[mh] OR "single-blind method"[mh] OR "double-blind method"[mh] OR "random allocation"[mh] OR randomized controlled trials as topic OR randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR single-blind method[mh] OR double-blind method[mh] OR random allocation[mh]

TOTAL NUMBER OF ITEMS RETRIEVED: 65

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SEARCH #7A – LIMITED SEARCH STRATEGY:

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2000–2008

OTHER LIMITERS:
Publication types:
Editorial
Review
Comment

SEARCH STRATEGY:
"antidepressive agents, second-generation"[mh] OR "fluoxetine"[mh] OR "sertraline"[mh] OR "paroxetine"[mh] OR "citalopram"[mh] OR "fluvoxamine"[mh OR "bupropion"[mh] OR "nefazodone"[nm] OR "mirtazapine"[nm] OR "venlafaxine"[nm] OR "escitalopram"[tw] OR "duloxetine"[nm] OR "trazodone"[mh] OR antidepressive agents, second-generation OR fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR citalopram[mh] OR fluvoxamine[mh] OR bupropion[mh] OR nefazodone[nm] OR mirtazapine[nm] OR venlafaxine[nm] OR escitalopram OR duloxetine[nm] OR trazodone[mh]
AND

"annals of internal medicine" OR "british medical journal" OR "jama" OR "lancet" OR "new england journal of medicine" OR "archives of general psychiatry" OR "american journal of psychiatry"

TOTAL NUMBER OF ITEMS RETRIEVED: 15

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SEARCH #7B – LIMITED SEARCH STRATEGY (Revised):

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed – 2006–2008

OTHER LIMITERS:
Publication types:
Editorial
Letter
Comment

SEARCH STRATEGY:
"antidepressive agents, second-generation"[mh] OR "fluoxetine"[mh] OR "sertraline"[mh] OR "paroxetine"[mh] OR "citalopram"[mh] OR "fluvoxamine"[mh OR "bupropion"[mh] OR "nefazodone"[nm] OR "mirtazapine"[nm] OR "venlafaxine"[nm] OR "escitalopram"[tw] OR "duloxetine"[nm] OR "trazodone"[mh] OR antidepressive agents, second-generation OR fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR citalopram[mh] OR fluvoxamine[mh] OR bupropion[mh] OR nefazodone[nm] OR mirtazapine[nm] OR venlafaxine[nm] OR escitalopram OR duloxetine[nm] OR trazodone[mh]
AND
"annals of internal medicine" OR "british medical journal" OR "jama" OR "lancet" OR "new england journal of medicine" OR annals of internal medicine OR british medical journal OR jama OR lancet OR new england journal of medicine OR "archives of general psychiatry" OR "american journal of psychiatry" OR archives of general psychiatry OR american journal of psychiatry

TOTAL NUMBER OF ITEMS RETRIEVED: 49

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SEARCH #7C – LIMITED SEARCH STRATEGY (Revised to include all publication types):

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed – 2006–2008

SEARCH STRATEGY:
"antidepressive agents, second-generation"[mh] OR "fluoxetine"[mh] OR "sertraline"[mh] OR "paroxetine"[mh] OR "citalopram"[mh] OR "fluvoxamine"[mh OR "bupropion"[mh] OR "nefazodone"[nm] OR "mirtazapine"[nm] OR "venlafaxine"[nm] OR "escitalopram"[tw] OR "duloxetine"[nm] OR "trazodone"[mh] OR antidepressive agents, second-generation OR fluoxetine[mh] OR sertraline[mh] OR paroxetine[mh] OR citalopram[mh] OR fluvoxamine[mh] OR bupropion[mh] OR nefazodone[nm] OR mirtazapine[nm] OR venlafaxine[nm] OR escitalopram OR duloxetine[nm] OR trazodone[mh]
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Arch Gen Psychiatry"[Journal:__jrid744] OR american journal of psychiatry[ta]

TOTAL NUMBER OF ITEMS RETRIEVED: 135

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SEARCH #7D – LIMITED SEARCH STRATEGY:

DATABASES SEARCHED & TIME PERIOD COVERED:
PscyINFO –2006–2008

OTHER LIMITERS:
English
Publication types:
Editorial
Letter
Comment

SEARCH STRATEGY:
su= "antidepressant drugs" OR de= "antidepressant drugs" OR kw: fluoxetine OR kw: sertraline OR kw: paroxetine OR kw: citalopram OR kw: fluvoxamine OR kw: bupropion OR kw: nefazodone OR kw: mirtazapine OR kw: venlafaxine OR kw: escitalopram OR kw: duloxetine OR kw: trazodone
AND
de: depressi* or su: depressi* or kw: dysthymi*
AND
(kw: annals w1 internal w1 medicine) OR (kw: british w medical w journal) OR kw: jama OR kw: lancet OR (kw: new w england w journal w1 medicine) or (kw: archives w1 general w1 psychiatry) OR (kw: american w journal w1 psychiatry)

TOTAL NUMBER OF ITEMS RETRIEVED: 143

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SEARCH #7E – LIMITED SEARCH STRATEGY – Revised to increase date coverage:

DATABASES SEARCHED & TIME PERIOD COVERED:
PscyINFO – 2000–2008

OTHER LIMITERS:
English

SEARCH STRATEGY:
su= "antidepressant drugs" OR de= "antidepressant drugs" OR kw: fluoxetine OR kw: sertraline OR kw: paroxetine OR kw: citalopram OR kw: fluvoxamine OR kw: bupropion OR kw: nefazodone OR kw: mirtazapine OR kw: venlafaxine OR kw: escitalopram OR kw: duloxetine OR kw: trazodone
AND
de: depressi* or su: depressi* or kw: dysthymi*
AND
(kw: annals w1 internal w1 medicine) OR (kw: british w medical w journal) OR kw: jama OR kw: lancet OR (kw: new w england w journal w1 medicine) or (kw: archives w1 general w1 psychiatry) OR (kw: american w journal w1 psychiatry)

TOTAL NUMBER OF ITEMS RETRIEVED: 298

CER 9 – CABG VERSUS PCI – 2008 UPDATE
SEARCH METHODOLOGY

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

SEARCH STRATEGY:
balloon angioplasty OR (balloon AND dilat* AND coronary) OR (coronary AND atherectom*) OR (balloon AND angioplast*) OR "Angioplasty, Transluminal, Percutaneous Coronary"[Mesh] OR (percutaneous[tiab] AND coronary AND transluminal AND angioplast*) OR ptca[tiab] OR transluminal coronary angioplasty[mh] OR pci[tiab] OR (percutaneous AND coronary AND intervention*[tiab]) OR transluminal coronary angioplasty OR percutaneous coronary intervention OR stents OR stent OR stent[tiab] OR stents[tiab] OR stenting[tiab]
AND
coronary artery bypass OR coronary bypass OR cabg OR coronary artery bypass surgery[mh] OR coronary artery bypass graft
AND
randomized controlled trial* OR randomized controlled trials OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt] OR triple blind* OR triple-blind* OR single blind* OR single-blind* OR double blind* OR double-blind* OR treble blind* OR treble-blind* OR placebo*
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Am J Cardiol"[Journal:__jrid408] OR "Circulation"[Journal:__jrid2979] OR "J Am Coll Cardiol"[Journal:__jrid4429] OR "Heart"[Journal:__jrid20297]

TOTAL NUMBER OF ITEMS RETRIEVED: 114

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane DARE – No date limit allowed

SEARCH STRATEGY:
(balloon angioplasty OR (balloon and dilat$ and coronary) OR (coronary and atherectom$) OR (balloon and angioplast$) OR Angioplasty, Transluminal, Percutaneous Coronary OR ((percutaneous and coronary and transluminal and angioplast$) OR ptca OR (percutaneous coronary intervention) OR stents OR stent OR stenting).mp. [mp=title, full text, keywords]
AND
(coronary artery bypass or coronary bypass or cabg or coronary artery bypass surgery or coronary artery bypass graft).mp.

TOTAL NUMBER OF ITEMS RETRIEVED: 71

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Database of Systematic Reviews – 2006-2008

SEARCH STRATEGY:
(balloon angioplasty OR (balloon and dilat$ and coronary) OR (coronary and atherectom$) OR (balloon and angioplast$) OR Angioplasty, Transluminal, Percutaneous Coronary OR ((percutaneous and coronary and transluminal and angioplast$) OR ptca OR (percutaneous coronary intervention) OR stents OR stent OR stenting).mp. [mp=title, full text, keywords]
AND
(coronary artery bypass or coronary bypass or cabg or coronary artery bypass surgery or coronary artery bypass graft).mp.

TOTAL NUMBER OF ITEMS RETRIEVED: 17

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Central (Controlled Trials Register) – 2006-2008

SEARCH STRATEGY:
(balloon angioplasty OR (balloon and dilat$ and coronary) OR (coronary and atherectom$) OR (balloon and angioplast$) OR Angioplasty, Transluminal, Percutaneous Coronary OR ((percutaneous and coronary and transluminal and angioplast$) OR ptca OR (percutaneous coronary intervention) OR stents OR stent OR stenting).mp. [mp=title, full text, keywords]
AND
(coronary artery bypass or coronary bypass or cabg or coronary artery bypass surgery or coronary artery bypass graft).mp.

TOTAL NUMBER OF ITEMS RETRIEVED: 83

CER 10 – ANGIOTENSIN-CONVERTING ENZYME INHIBITORS – 2008 UPDATE
SEARCH METHODOLOGY

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

SEARCH STRATEGY:
"Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin II Type 1 Receptor Blockers"[Mesh] OR losartan OR valsartan OR telmisartan OR eprosartan OR candesartan OR irbesartan OR olmesartan OR losartan[mh] OR cozaar OR micardis OR atacand OR teveten OR avapro OR benicar OR diovan OR quinapril OR perindopril OR ramipril OR captopril OR enalapril OR benazepril OR trandolapril OR fosinopril OR moexipril OR enalaprilat OR cilazapril OR lisinopril OR angiotensin converting OR (ace AND inhibitor*) OR (angiotensin AND block*)
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Am J Cardiol"[Journal:__jrid408] OR "Circulation"[Journal:__jrid2979] OR "J Am Coll Cardiol"[Journal:__jrid4429] OR "Heart"[Journal:__jrid20297] OR "Hypertension"[Journal:__jrid4217] OR "Stroke"[Journal:__jrid7613]
AND
randomized controlled trial* randomized controlled trials[mh] OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt])

TOTAL NUMBER OF ITEMS RETRIEVED: 290

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane DARE – No date limit allowed

SEARCH STRATEGY:
Angiotensin-Converting Enzyme Inhibitors OR Angiotensin II Type 1 Receptor Blockers OR losartan OR valsartan OR telmisartan OR eprosartan OR candesartan OR irbesartan OR olmesartan OR cozaar OR micardis OR atacand OR teveten OR avapro OR benicar OR diovan OR quinapril OR perindopril OR ramipril OR captopril OR enalapril OR benazepril OR trandolapril OR fosinopril OR moexipril OR enalaprilat OR cilazapril OR lisinopril {No Related Terms}
AND
hypertension OR hypertensive OR hypertense OR high blood pressure OR lower blood pressure {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 27
TOTAL NUMBER OF RELEVANT ITEMS IDENTIFIED: 1

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Database of Systematic Reviews – 2006-2008

SEARCH STRATEGY:
Angiotensin-Converting Enzyme Inhibitors OR Angiotensin II Type 1 Receptor Blockers OR

losartan OR valsartan OR telmisartan OR eprosartan OR candesartan OR irbesartan OR olmesartan OR cozaar OR micardis OR atacand OR teveten OR avapro OR benicar OR diovan OR quinapril OR perindopril OR ramipril OR captopril OR enalapril OR benazepril OR trandolapril OR fosinopril OR moexipril OR enalaprilat OR cilazapril OR lisinopril {No Related Terms}
AND
hypertension OR hypertensive OR hypertense OR high blood pressure OR lower blood pressure {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 69
TOTAL NUMBER OF RELEVANT ITEMS IDENTIFIED: 1

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DATABASES SEARCHED & TIME PERIOD COVERED:
Cochrane Central (Controlled Trials Register) – 2006-2008

SEARCH STRATEGY:
Angiotensin-Converting Enzyme Inhibitors OR Angiotensin II Type 1 Receptor Blockers OR
losartan OR valsartan OR telmisartan OR eprosartan OR candesartan OR irbesartan OR olmesartan OR cozaar OR micardis OR atacand OR teveten OR avapro OR benicar OR diovan OR quinapril OR perindopril OR ramipril OR captopril OR enalapril OR benazepril OR trandolapril OR fosinopril OR moexipril OR enalaprilat OR cilazapril OR lisinopril {No Related Terms}
AND
hypertension OR hypertensive OR hypertense OR high blood pressure OR lower blood pressure {No Related Terms}

TOTAL NUMBER OF ITEMS RETRIEVED: 27

CER 11 – RHEUMATOID / PSORIATIC ARTHRITIS – 2008 UPDATE
SEARCH METHODOLOGY

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2006–2008

LIMITERS:
English
Human

SEARCH STRATEGY:
psoriatic arthritis[MeSH] OR "psoriatic arthritis"[all fields] OR rheumatoid arthritis[MeSH] OR "rheumatoid arthritis"[all fields]
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "Br J Rheumatol"[Journal:__jrid1901] OR "J Rheumatol"[Journal:__jrid5243] OR "J Rheumatol Suppl"[Journal:__jrid5244] OR "Arthritis Rheum"[Journal:__jrid881]
AND
randomized controlled trial* OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt]

TOTAL NUMBER OF ITEMS RETRIEVED: 340

CER 12 – OSTEOPOROSIS/LOW BONE DENSITY – 2008 UPDATE
SEARCH METHODOLOGY

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2005–2008

LIMITERS:
English

SEARCH STRATEGY:
osteoporosis or osteopenia or osteopaenia or fracture* or bone mineral OR fractures[mh] OR bone density OR fractures, bones
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] 19:15:50 367459 OR "Bone"[Journal:__jrid1710] OR "J Bone Miner Res"[Journal:__jrid104]) OR "Osteoporos Int"[Journal:__jrid2061]) OR "Endocr Rev"[Journal:__jrid3558]
AND
randomized controlled trial* OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt])

TOTAL NUMBER OF ITEMS RETRIEVED: 576

CER 13 – PROSTATE CANCER – 2008 UPDATE
SEARCH METHODOLOGY

DATABASES SEARCHED & TIME PERIOD COVERED:
PubMed –2004–2008

SEARCH STRATEGY:
prostatic neoplasms OR prostate cancer
AND
randomized controlled trial* OR randomized controlled trials OR rct* OR random allocation OR randomi* OR double blind OR double-blind OR single blind OR single-blind OR letter* OR editorial* OR comment* OR letter[pt] OR editorial[pt] OR comment[pt] OR randomized controlled trial[pt] OR triple blind* OR triple-blind* OR single blind* OR single-blind* OR double blind* OR double-blind* OR treble blind* OR treble-blind* OR placebo*
AND
"JAMA"[Journal:__jrid5346] OR "N Engl J Med"[Journal:__jrid5985] OR "Lancet"[Journal:__jrid5470] OR "Br Med J"[Journal:__jrid1912] OR "Br Med J (Clin Res Ed)"[Journal:__jrid1913] OR "BMJ"[Journal:__jrid2274] OR "Ann Intern Med"[Journal:__jrid596] OR "J Urol"[Journal:__jrid5331] OR "Cancer"[Journal:__jrid2771] OR "J Clin Oncol"[Journal:__jrid5023]
NOT
animals NOT humans

TOTAL NUMBER OF ITEMS RETRIEVED: 540

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[i] Hackam, D. G., D. Thiruchelvam and D. A. Redelmeier (2006). "Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study." Lancet **368**(9536): 659-65.
[ii] Hall, A. S. and M. H. Strauss (2007). "More about the "ARB MI paradox"." Heart **93**(9): 1011-4.
[iii] Elliott, W. J. and P. M. Meyer (2007). "Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis." Lancet **369**(9557): 201-7.