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## **Evidence Updates:**

- (a) New Oral Anticoagulants &**
- (b) Neuropathic Pain**

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# CADTH's Programs

**HTA** Health Technology Assessment



= Assessment



= Advice



= Recommendation



= User tools

**CDR** Common Drug Review



**COMPUS** Canadian Optimal Medication Prescribing and Utilization Service



# What is a Health Technology?

**Any medical intervention utilized in health treatment and maintenance across the whole spectrum of medical and health practices.**

## **Designed to:**

- Improve health
- Prevent, diagnose or treat disease
- Aid in rehabilitation or long term care

## **Includes:**

- Drugs and Vaccines
- Blood products
- Diagnostic tests
- Devices and equipment
- Medical and surgical procedures

# Hierarchical Evidence Pyramid



# Additional CADTH Services

- Free access to reports: [www.cadth.ca](http://www.cadth.ca)
- Drug Interventions Database: [www.rxforchange.ca](http://www.rxforchange.ca)
- Rapid Response Service (Health Technology Inquiry Service)  
(self web access to database coming soon!)
- Local Liaison Officer support to aid interpretation of evidence, link with others pan-Canadian, and place new requests for information



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## Health Technology Inquiry Service

Health Technology Assessment HTA



### HTIS Topic Summary

March 2010

Devices and Systems					
#	Technology	Question	Level	Date Complete	Org Type
1	Intermittent Pneumatic Compression Stockings and Thromboembolytic Deterrent Stockings for Perioperative Patients: Clinical Effectiveness and Guidelines*	<p>1. What are the evidence-based guidelines regarding patient indications and timing of use for intermittent pneumatic compression stockings and/or thromboembolytic deterrent stockings during a surgery that requires general anesthesia?</p> <p>2. What are the evidence-based guidelines regarding the use of both intermittent pneumatic compression stockings and thromboembolytic deterrent stockings compared to using one or the other during surgery that requires the delivery of anesthesia?</p> <p>3. What is the clinical effectiveness of placing intermittent pneumatic compression stockings and/or thromboembolytic deterrent stockings before the delivery of general anesthesia?</p> <p>4. What is the evidence regarding the need to use both intermittent pneumatic compression stockings and thromboembolytic deterrent stockings?</p>	Level 1	March 1	HOS



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**Evidence Update:**

**Rivaroxaban and Dabigatran**

# Venous Thrombo- Embolism (VTE) Post-Surgical Risk

Patients undergoing major orthopedic surgery — elective total hip replacement (THR), elective total knee replacement (TKR), and hip fracture surgery (HFS) — have elevated risk

Without primary thromboprophylaxis, VTE has been reported to occur in:

- 42% to 57% of patients undergoing THR
- 41% to 85% of patients undergoing TKR
- <35% to 50% of patients undergoing HFS (overall mortality highest)

Of patients developing DVT, fatal PE has been reported in 0.1% to 2.0% of patients undergoing THR and 0.1% to 1.7% of patients undergoing TKR.

# VTE Prevention Post-Orthopedic S

## NOT Recommended prophylaxis options:

- Low dose unfractionated heparin
- Aspirin
- Graduated compression stocking
- Intermittent pneumatic compression (IPC) devices
  - **NOTE: IPC devices and venous foot pumps appear to provide some protection, but evidence is limited.**
  - **They are also less effective than the anticoagulant alternatives. IPC devices should be used for patients with valid absolute contraindications to anticoagulants, and should be replaced with anticoagulant prophylaxis if/when contraindications resolve**



# Thrombo-prophylaxis

## Post-Hip and Post-Knee surgery

The following methods of thromboprophylaxis have been validated as effective choices for total hip or knee arthroplasty:

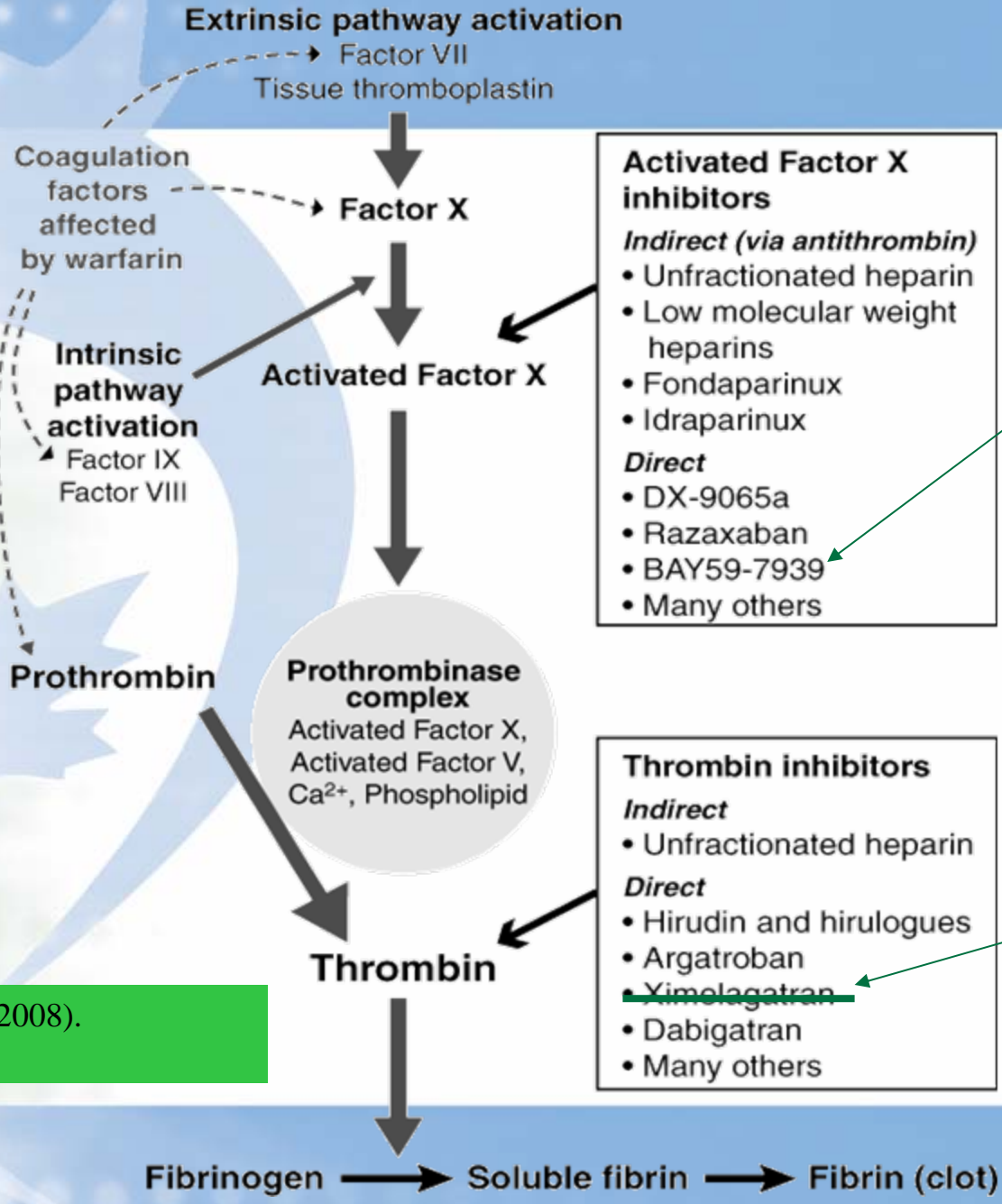
- A low molecular weight heparin (LMWH) once or twice daily SC dosing
- Warfarin in doses to prolong the INR to 2.0 - 3.0
- The pentasaccharide (fondaparinux) once daily SC dosing.
- A Direct thrombin inhibitor (dabigatran etexilate) once daily oral dosing.
- A Direct Xa inhibitor (rivaroxaban) once daily oral dosing.

# Newer Anticoagulants

Dabigatran etexilate (Pradax™ Boehringer-Ingelheim) and rivaroxaban (Xarelto™ Bayer) are anticoagulants that were approved by Health Canada in 2008 for the prevention of VTE in patients who have undergone elective THR or TKR.

Compared to other anticoagulants, dabigatran and rivaroxaban offer potential advantages

- **fixed once-daily dosing**
- **oral administration**
- **rapid onset of action**
- **low potential for interactions with other drugs**
- **no requirement for ongoing anticoagulation monitoring.**



Rivaroxaban

No FDA Approval

Medscape Cardiology (2008).  
[www.medscape.com](http://www.medscape.com)

Parameter	Dabigatran (Pradax™)	Rivaroxaban (Xarelto®)	Fondaparinux (Arixtra®)	LMWH		UFH (Hepalean®)	Warfarin (Coumadin®)
				Enoxaparin (Lovenox®)	Dalteparin (Fragmin®)		
<b>Target</b>	Factor IIa (thrombin)  Direct	Factor Xa  Direct	Factor Xa  Indirect	Factor Xa and Factor IIa (thrombin)  Indirect		Antithrombin III	Vitamin K epoxide reductase
<b>Route</b>	Oral	Oral	SC	SC		SC	Oral
<b>Peak Plasma Levels (Healthy Volunteers)*</b>	0.5 to 2 hours  <i>Post-surgery:</i> 7 to 9 hours	2 to 4 hours	2 to 3 hours	3 to 5 hours	4 hours	1 to 3 hours	4 hours Therapeutic effect in 5 to 7 days
<b>Half-Life Elimination* (h)</b>	11  <i>Post-surgery:</i> 14 to 17	5 to 9  <i>Post-surgery:</i> 7 to 11	17 to 21	4 to 7	3 to 4	1 to 2	20 to 60
<b>Dosing for Thromboprophylaxis After Orthopedic Surgery</b>	<i>Initial:</i> 110 mg 1 to 4 hours after surgery  <i>Maintenance:</i> 220 mg once daily  <i>Duration:</i> 10 days for knee replacement or 28 to 35 days for hip replacement	<i>Initial:</i> 10 mg 6 to 10 hours after surgery  <i>Maintenance:</i> 10 mg once daily  <i>Duration:</i> 14 days for knee replacement or 35 days for hip replacement	2.5 mg once daily 6 to 24 hours after surgery  <i>Duration:</i> Up to 11 days following hip or knee replacement or up to 32 days following hip fracture surgery	30 mg twice daily within 12 to 24 hours after surgery  <i>Duration:</i> 7 to 14 days	5,000 IU daily starting the evening before surgery  <i>Duration:</i> 5 to 7 days minimum	5,000 units every 8 to 12 hours starting 1 to 2 hours after surgery  <i>Duration:</i> 5 to 7 days	Individualized once daily dosing based on target INR 2.5 (range 2 to 3) started preoperatively or the evening of surgery  <i>Duration:</i> 10 to 35 days

Parameter	Dabigatran (Pradax™)	Rivaroxaban (Xarelto®)	Fondaparinux (Arixtra®)	LMWH		UFH (Hepalean®)	Warfarin (Coumadin®)
				Enoxaparin (Lovenox®)	Dalteparin (Fragmin®)		
<b>Routine Coagulation Monitoring Required</b>	No	No	No	No		No	Yes
<b>Use With Renal Insufficiency</b>	<i>Moderate:</i> Dosage adjustment (150 mg daily)	<i>Moderate:</i> Use caution	<i>Moderate:</i> Use caution	<i>Moderate:</i> Use caution		<i>Moderate:</i> Yes	<i>Moderate:</i> Use with caution
	<i>Severe:</i> Contraindicated	<i>Severe:</i> Not recommended	<i>Severe:</i> Contraindicated	<i>Severe:</i> Dosage Adjustment		<i>Severe:</i> Use with caution	<i>Severe:</i> Use with caution
<b>Use With Hepatic Insufficiency</b>	Not recommended	Contraindicated	Use with caution	Use with caution		Use with caution	Use with caution
<b>Potential for HIT</b>	No	No	No	Low		High	No
<b>Drug Interactions<sup>†</sup></b>	Quinidine, amiodarone, antacids, potent P-gp inhibitors (e.g., verapamil, clarithromycin)	Potent inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, voriconazole, ritonavir, rifampicin), strong CYP3A4 inducers (e.g. phenytoin, carbamazepine)	No clinically significant drug interactions known	No clinically significant drug interactions known		No clinically significant drug interactions known	Multiple drugs
<b>Reversal of Anticoagulant Effect</b>	rFVIIa, APCC (in rats) <sup>33</sup>	rFVIIa, APCC (in rats and primates) <sup>34,35</sup>	rFVIIa (partial) <sup>36</sup>	Protamine sulfate (partial)		Protamine sulfate	Vitamin K <sub>1</sub> , FFP, PCC

# HTIS Search Results: Dabigatran

## DABIGATRAN 1999-2009

One systematic review pooled results from RE-NOVATE, RE-MODEL, and RE-MOBILIZE (8,210 participants) revealed no statistically significant differences between dabigatran and enoxaparin in any of the end points that were used in the evaluation of safety or efficacy of thromboprophylaxis after THR or TKR

Wolowacz SE, Roskell NS, Plumb JM, Caprini JA, Eriksson BI. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. *Thromb Haemost* 2009;101(1):77-85.

### Dabigatran

RE-NOVATE (11) Non-inferiority <sup>5</sup>	THA	D <sub>1</sub> 1 × 220, D <sub>2</sub> 1 × 150 mg/d, 1 × 40 mg/d, 28-35 (33) days 28-35 (32, 33) days; Start: 1-4 h after surgery with 1/2 dose	Start: 12 h before surgery, in some centers after surgery	MITT: D <sub>1</sub> = 880, D <sub>2</sub> = 874, E = 897	D <sub>1</sub> = 1146, D <sub>2</sub> = 1163, E = 1154; Follow-up 2 mo after last dose	Efficacy: D <sub>1</sub> , D <sub>2</sub> = E Safety: D <sub>1</sub> , D <sub>2</sub> = E
RE-MODEL (12)	TKA	D <sub>1</sub> 1 × 220, D <sub>2</sub> 1 × 150 mg/d, 6-10 (8,8) days; Start: as above	1 × 40 mg/d, 6-10 (7) days Start: as above	MITT: D <sub>1</sub> = 503, D <sub>2</sub> = 526, E = 512	D <sub>1</sub> = 679, D <sub>2</sub> = 703, E = 694; As above	Efficacy: D <sub>1</sub> , D <sub>2</sub> = E Safety: D <sub>1</sub> , D <sub>2</sub> = E
RE-MOBILIZE (13)	TKA	D <sub>1</sub> 1 × 220, D <sub>2</sub> 1 × 150 mg/d, 12-15 (14,14) days; Start: 6-12 h after surgery with 1/2 dose	2 × 30 mg/d, 12-15 (14) days Start: 12-24 h after surgery	MITT: D <sub>1</sub> = 604, D <sub>2</sub> = 649, E = 643	D <sub>1</sub> = 857, D <sub>2</sub> = 871, E = 868; As above	Efficacy: D <sub>1</sub> , D <sub>2</sub> < E Safety: D <sub>1</sub> , D <sub>2</sub> = E

# Dabigatran Bottom Line

Of the published phase 3 trials, two showed the non-inferiority of dabigatran in the prevention of VTE after THR or TKR (RE-MODEL; RE-NOVATE), but the trial comparing dabigatran with the Health Canada-approved regimen for enoxaparin showed dabigatran to be Inferior (RE-MOBILIZE)

As a result, the Canadian Expert Drug Advisory Committee (CEDAC) recommended that dabigatran **not be listed** in publicly funded drug plans.

Additional trials comparing dabigatran with the Health Canada-approved dose of enoxaparin are needed.

# Clinical Trial Phases

Each “phase” of drug approval processes provides a piece of the knowledge puzzle

- Pre-clinical studies (in-vitro/test-tube) and (in-vivo / animal or cell culture)
- Phase 0 (first-in-humans trials; micro-dosing)
- Phase I (small N healthy volunteers; pharmacovigilance)
  - safety, tolerability, pharmacokinetics, pharmacodynamics
- Phase II (larger N; dosing requirements; and drug efficacy at prescribed doses)
- Phase III (randomized, multicentre trials; larger N; drug effectiveness)
- Phase IV (post-market surveillance; pharmacovigilance)

# HTIS Search Results - Rivaroxaban

**TABLE 1.** Pivotal efficacy/safety trials (multinational, randomized, double-blind) of rivaroxaban (R) and dabigatran etexilate (D) for prevention of venous thromboembolism after total hip (THA) or knee (TKA) arthroplasty in comparison with enoxaparin sodium (E)\*

Trial/ hypothesis	Setting	Test po + placebo injection <sup>†</sup>	Enoxaparin sc + oral placebo <sup>†</sup>	Efficacy population	Safety population	Main findings
<b>Rivaroxaban</b>						
RECORD 1 (7) Non-inferiority Superiority <sup>†</sup>	THA	R 1 × 10 mg/d, 31-39 (33) days Start: 6-8 h after surgery	1 × 40 mg/d, 31-39 (34) days Start: 12 h before surgery, then 6-8 h after	PP: R= 1537, E= 1492 MITT: R= 1595, = 1558	R= 2209, E= 2224 Follow-up 30-35 d after last dose	Efficacy: R>E Safety: R=E
RECORD 2 (8)	THA	R 1 × 10 mg/d, 31-39 (34) days Start: as above	1 × 40 mg/d, 10-14 (12) days Start: as above	PP: R= 812, E= 803 MITT: R= 864, E= 869	R= 1228, E= 1229 Follow-up as above	Efficacy: R>E Safety: R=E
RECORD 3 (9)	TKA	R 1 × 10 mg/d, 10-14 (12) days Start: as above	1 × 40 mg/d, 10-14 (13) days Start: as above	PP: R= 793, E= 838 MITT: R= 824, E= 878	R= 1220, E= 1239 Follow-up as above	Efficacy: R>E Safety: R=E
RECORD 4 (10)	TKA	R 1 × 10 mg/d, 11-15 (11) days Start: as above	2 × 30 mg/d 11-15 (11) days Start: 12-24 h after surgery	PP: R= 864, E= 878 MITT: R= 965, E= 959	R= 1526, E= 1508 Follow-up as above	Efficacy: R>E Safety: R=E

Six RCT's: 3 phase 2 RCTs, and 3 phase 3RCTs evaluated rivaroxaban compared to enoxaparin

Turpie et al (2005); Eriksson et al (2006); Eriksson et al (2006); Eriksson et al (2008); Kakkar et al (2008); Lassen et al (2008)

# Rivaroxaban Bottom Line

Results from three phase 3 trials indicate superior clinical effectiveness of rivaroxaban compared with enoxaparin for the prevention of VTE after THR or TKR.

Based on these results, CEDAC recommended that rivaroxaban **be listed in publicly funded drug plans** for the prophylaxis of VTE after TKR or THR for up to two weeks as an alternative to LWMH.

## **SASKATCHEWAN DRUG PLAN LISTING:**

**rivaroxaban, tablet, 10mg (Xarelto-BAY)**

- (a) For prophylaxis following total knee arthroplasty for up to 14 days following the procedure.
- (b) For prophylaxis in patients undergoing total hip replacement for up to 14 days following the procedure.

# New Anticoagulant Research Limitations

- Patients with severe renal insufficiency, severe liver disease, or at high risk of bleeding were excluded from trials
- Low numbers of patients with a previous history of VTE, >age 75 years, or at extremities of weight were studied
- Studies only included patients 18 years and older
- Clinically important outcomes such as post-DVT complications, length of hospital stay, health related quality of life, and surgical outcomes were not assessed.
- Definitions of major bleeding events differed significantly between the dabigatran and rivaroxaban clinical trials
- There are no head-to-head trials comparing rivaroxaban with dabigatran, or comparing either drug directly to other anticoagulants. As a result, indirect comparisons within trials must be interpreted with caution because of differences in the methods for assessing outcomes
- There is no evidence to support the use of dabigatran or rivaroxaban in patients undergoing Hip fracture surgery



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## **Case Study - Management of Neuropathic Pain**

# Neuropathic Pain Case Study

RP, a 55 year old male, is one of your regular clients in your pharmacy.

## Medical history:

- Type 2 diabetes x 20 years
- Hypercholesterolemia x 10 years
- Osteoarthritis of the knee x 5 years

## Social history:

- 1.5 to 2 PPD smoker
- Occasional drinker
- BMI = 31.7

# Neuropathic Pain Case Study

## Current Medications:

- Metformin 1000mg bid
- Atorvastatin 20mg daily
- ECASA 81mg daily
- Acetaminophen 1000mg qid

## Lab Work:

- A1c: 8.3%
- Total Cholesterol: 5.7mmol/L

# Neuropathic Pain Case Study

**RP has prescription drug coverage through Social Assistance.**

**He comes into the pharmacy today and explains to you that he just came from an appointment with his GP.**

**He had been experiencing a sharp, stabbing pain in his feet, which was aggravated by walking.**

**His GP told him that his symptoms were due to “diabetic neuropathy”.**

**He presents a prescription for pregabalin 75mg twice daily.**

# Neuropathic Pain Case Study

**You determine that pregabalin has Exception Drug Status under the Saskatchewan Drug Plan as follows:**

**pregabalin, capsule, 25mg, 50mg, 75mg, 150mg, 300mg (Lyrica-PFI)**

- (a) For the treatment of neuropathic pain in patients unresponsive following treatment with adequate doses of tricyclic antidepressants (TCA) as indicated on the patient profile by 2 consecutive prescriptions for a TCA within 6 months of the EDS request, or
- (b) For the treatment of neuropathic pain in patients intolerant or contraindicated to tricyclic antidepressants.

# Neuropathic Pain Case Study

**You explain to RP that pregabalin is only covered as an exception drug, after a different medication is tried first and found to be ineffective or poorly tolerated.**

**You further explain that the you could phone his doctor to recommend changing the medication to one that is covered or he can pay for pregabalin out of pocket.**

**RP states that he cannot afford pregabalin and would like to try another medication that he does not have to pay for.**

# Pharmacological management of chronic neuropathic pain<sup>1</sup>

**Table 1: Pharmacological Management of Chronic Neuropathic Pain<sup>12</sup>**

First Line	Second Line	Third Line	Fourth Line
<ul style="list-style-type: none"> <li>• TCAs</li> <li>• Anticonvulsants                             <ul style="list-style-type: none"> <li>• Gabapentin</li> <li>• Pregabalin</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• SNRIs                             <ul style="list-style-type: none"> <li>• Venlafaxine</li> <li>• Duloxetine*</li> </ul> </li> <li>• Topical lidocaine                             <ul style="list-style-type: none"> <li>• 5% patch<sup>†</sup></li> <li>• 5% or 10% gel or cream</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Tramadol</li> <li>• Opioid analgesics</li> </ul>	<ul style="list-style-type: none"> <li>• Cannabinoids</li> <li>• Methadone</li> <li>• SSRI                             <ul style="list-style-type: none"> <li>• Citalopram</li> <li>• Paroxetine</li> </ul> </li> <li>• Other anticonvulsants                             <ul style="list-style-type: none"> <li>• Lamotrigine</li> <li>• Topiramate</li> <li>• Valproic acid</li> </ul> </li> <li>• Miscellaneous agents                             <ul style="list-style-type: none"> <li>• Mexiletine</li> <li>• Clonidine</li> </ul> </li> </ul>

SNRI=serotonin noradrenaline reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressants.

\*Unavailable in Canada when this project was initiated, duloxetine was selected for estimating overall clinical efficacy of SNRIs.

<sup>†</sup>Unavailable in Canada; 5% or 10% gel or cream can be compounded by pharmacists.

# Neuropathic Pain Case Study

Based on the Exception Drug Status guidelines for coverage and practice guidelines for Chronic Neuropathic Pain, you call RP's GP and recommend a trial of amitriptyline 10mg hs, increasing to a maximum of 150mg per day, based upon treatment response.

RP's GP explains that much of his clinical experience in treating neuropathic pain is with pregabalin and asks "how effective amitriptyline is in the management of neuropathic pain?"



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**Where could you find the answer to this question?**

# Neuropathic Pain Case Study

## Antidepressants for neuropathic pain (Review)

Saarto T, Wiffen PJ



**THE COCHRANE  
COLLABORATION®**

# Antidepressants for Neuropathic Pain

## Objective:

- To determine the analgesic effectiveness and adverse effects of antidepressant drugs in the treatment of neuropathic pain

## Methods:

- Systematic review of RCTs
- Antidepressants to placebo, other drugs or interventions
- Adults with neuropathic pain
- Outcomes: patient-reported improvement or pain relief, quality of life, adverse effects, sleep quality, or depression scores
- Meta-analysis

Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.:CD005454. DOI: 10.1002/14651858.CH005454.pub2.

# Antidepressants in Neuropathic Pain

## Results

- 61 RCTs involving 20 antidepressants (TCA, SSRI/SNRI, other)
- 26 parallel design, 35 cross-over studies
- 89% double blind
- 74% placebo controlled
- 28% diabetic neuropathy, 18% postherpetic neuralgia
- Central pain, atypical facial pain, HIV-related, mixed pain
- Placebo controlled studies had a higher median quality score than the active control studies

# Antidepressants in Neuropathic Pain

## Tricyclic antidepressants (TCAs)

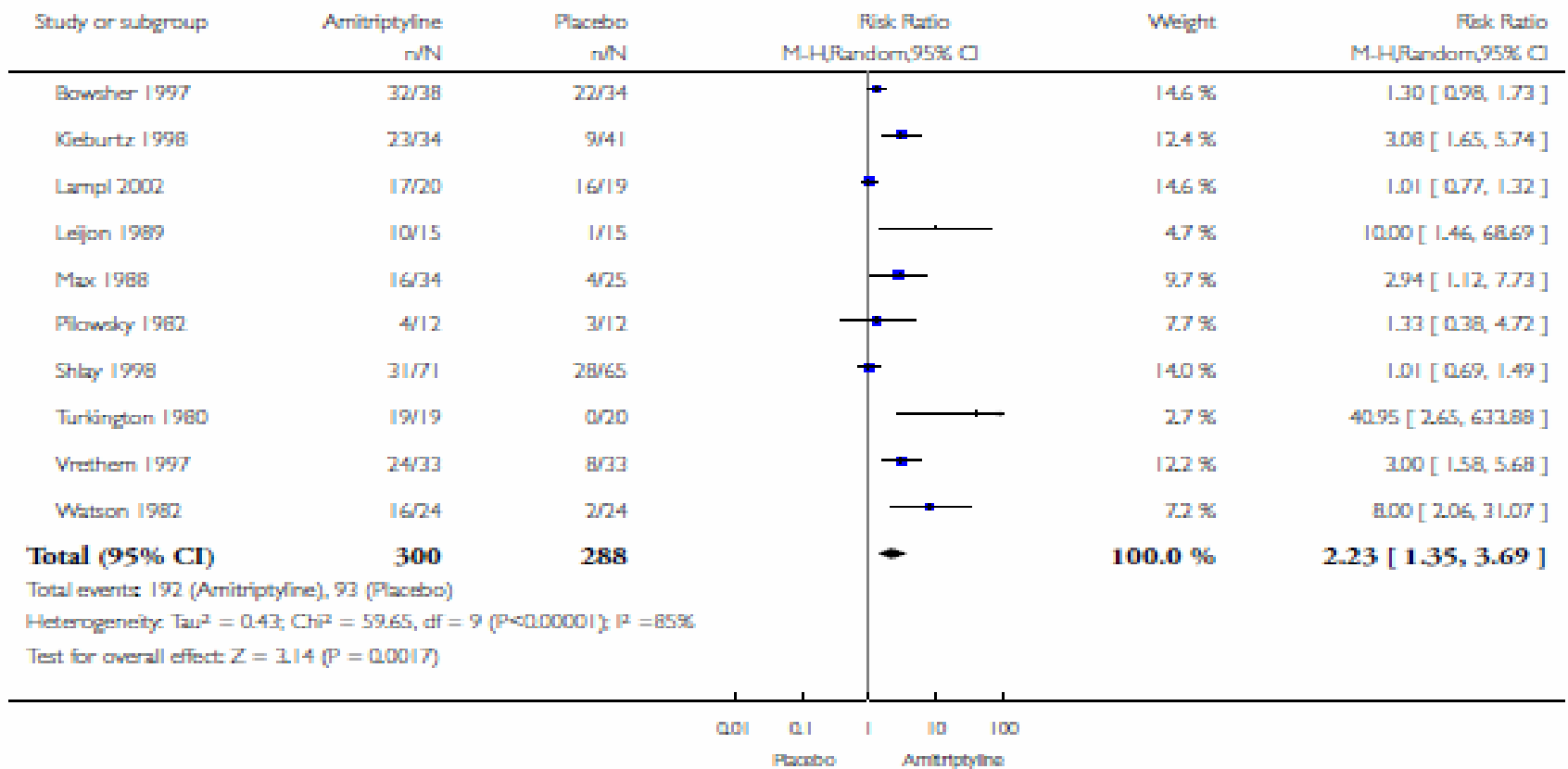
- 31 placebo controlled RCTs
- TCAs more effective than placebo for achieving moderate global improvement or pain relief
- TCAs: NNT 3.6 (95% CI 3.0 to 4.5) to achieve moderate pain relief
- Amitriptyline doses up to 150 mg daily: NNT 3.1 (2.5 to 4.2)

**Analysis 1.1. Comparison 1 Global improvement - number of patients with moderate pain relief or better, Outcome 1 Amitriptyline versus placebo.**

Review: Antidepressants for neuropathic pain

Comparison: 1 Global improvement - number of patients with moderate pain relief or better

Outcome: 1 Amitriptyline versus placebo



# Antidepressants for Neuropathic Pain

## Diabetic neuropathy

- 13 RCTs evaluated pain
- 5 small studies, TCAs were more effective than placebo for achieving moderate global improvement or pain relief
- NNT 1.3 (95% CI 1.2 to 1.5)

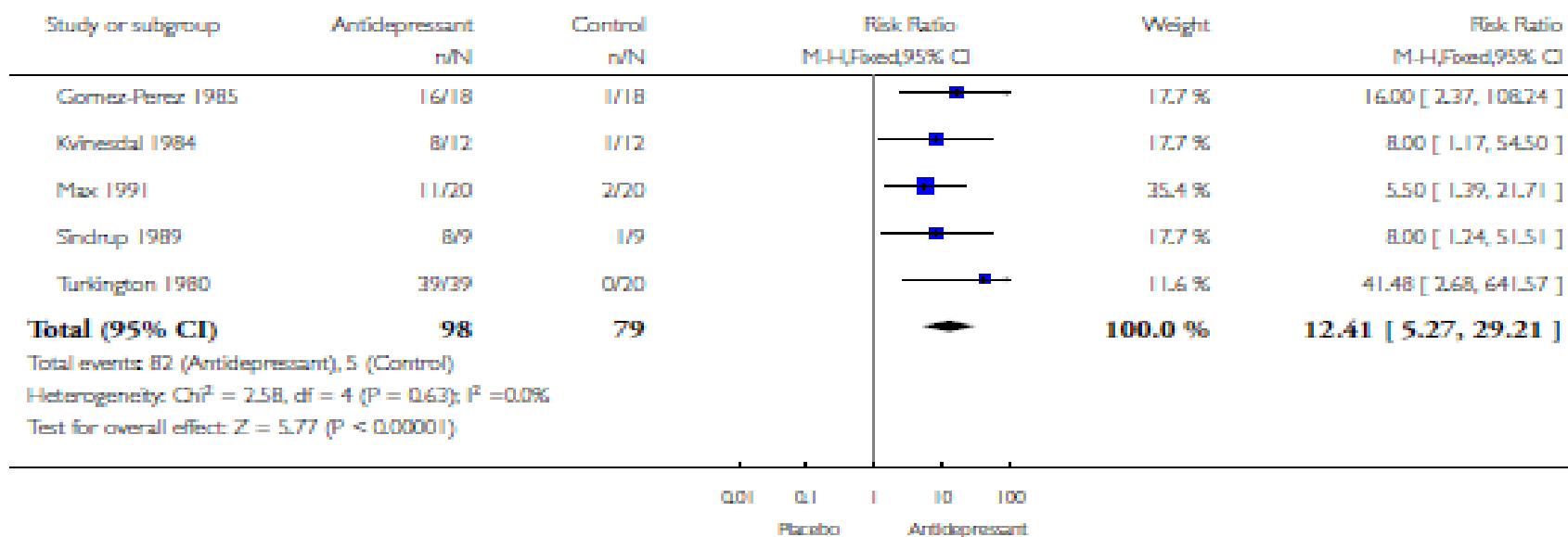
# Antidepressants in Neuropathic Pain

## Analysis 2.1. Comparison 2 Diabetic neuropathy, Outcome 1 Antidepressant vs placebo. Number of patients with moderate pain relief or better.

Review: Antidepressants for neuropathic pain

Comparison: 2 Diabetic neuropathy

Outcome: 1 Antidepressant vs placebo. Number of patients with moderate pain relief or better



# Antidepressants in Neuropathic Pain

## Adverse effects

- Major harm leading to study withdrawal
- Amitriptyline: NNH 28 (95% CI 17 to 68)
  
- Minor harm: drowsiness, dizziness, dry mouth, constipation etc
- Amitriptyline: NNH 6 (4.2 to 10.7)

# Antidepressants in Neuropathic Pain

## Conclusions and Implications for Practice

- Antidepressants are effective for the treatment of neuropathic pain
- Best evidence of pain relief with TCAs and amitriptyline (NNT 3)
- Limited data of effectiveness of SSRIs
- Promising new data on venlafaxine
- Effectiveness is usually seen within a few days

# Neuropathic Pain Case Study

**Based upon this report, what would you tell RP's GP about the effectiveness of amitriptyline in the management of neuropathic pain?**

**What factors might you consider in applying the results of this report to RP?**

**In addition to clinical effectiveness, what other factors may impact the selection of medication to manage RP's neuropathic pain?**



***Questions?***