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Evidence-Based Series 13-8 EDUCATION AND INFORMATION 2013

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

The Use of Gabapentin and Tricyclic Antidepressants in the Treatment of Neuropathic Pain in Cancer Patients

L. Librach, N. Lloyd, V. Jarvis, D. Warr, A. R. Jadad, J. Wilson, M. Brouwers, R. Wong, and members of the Supportive Care Guidelines Group

Report Date: October 11, 2006

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Section 1: Clinical Practice Guideline
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EBS Citation (Vancouver Style): Librach L, Lloyd N, Jarvis V, Warr D, Jadad AR, Wilson J, et al. The use of gabapentin and tricyclic antidepressants in the treatment of neuropathic pain in cancer patients. Toronto (ON): Cancer Care Ontario; 2006 Oct 11 [Education and Information 2011 Sep]. Program in Evidence-based Care Evidence-based Series: 13-8 Education and Information 2013

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Evidence-based Series #13-8: Section 1

The Use of Gabapentin and Tricyclic Antidepressants in the Treatment of Neuropathic Pain in Cancer Patients: A Clinical Practice Guideline

L. Librach, N. Lloyd, V. Jarvis, D. Warr, A. R. Jadad, J. Wilson, M. Brouwers, R. Wong, and members of the Supportive Care Guidelines Group

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Education and Information

Questions

What are the roles of gabapentin and tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, and nortriptyline) in terms of efficacy for pain relief and side effects in cancer patients with neuropathic pain? Is one superior to the other?

Target Population

These recommendations apply to adult cancer patients experiencing neuropathic pain.

Recommendations

- Gabapentin or tricyclic antidepressants are recommended as options for the treatment of neuropathic pain in cancer patients.
- While there is limited evidence comparing different tricyclic antidepressant drugs with this population, amitriptyline has been shown to have some beneficial effect, although the tolerability of that agent may be a concern with some patients. In the opinion of the Supportive Care Guidelines Group, other tricyclic antidepressants may be expected to have similar efficacy as amitriptyline with fewer side effects.
- There is insufficient evidence demonstrating the superiority of either gabapentin or tricyclic antidepressants over the other in neuropathic pain management.

Qualifying Statements

- Evidence for the effectiveness of gabapentin compared with tricyclic antidepressants in cancer populations is limited to two small trials; however, evidence from non-cancer populations was also considered in the development of the guideline and supports the recommendations.
- Given the complexity of assessment of pain syndromes in cancer patients, it is the opinion of the Supportive Care Guidelines Group that individual patient assessment should determine the appropriate treatment option and gabapentin and tricyclic antidepressants

may be used alone, sequentially, or with other analgesic agents, including opioids, in the treatment of neuropathic cancer pain.

- Evidence on treatment dosing was not systematically reviewed; however, in the expert opinion of the Supportive Care Guidelines Group, the doses commonly used in clinical practice and represented in the trials included in the systematic review are reasonable options.

  Gabapentin: starting total daily dose of 300-600 mg, titrating up by 300 mg every 5-7 days until patient pain is significantly reduced, intolerable adverse effects occur, or a maximum daily dose of 2400 mg is reached.

  Tricyclic antidepressants: starting daily dose of 10-25 mg, titrating up until patient pain is significantly reduced, intolerable adverse effects occur, or a maximum daily dose of 100 mg is reached.

Key Evidence

- Two randomized trials and two systematic reviews, each including one cancer trial, were eligible for inclusion.
- The randomized trials were comprised of a combined total of 50 patients with diabetic neuropathy and compared gabapentin to amitriptyline. In one open-label randomized trial, patients allocated to receive gabapentin experienced significantly greater pain reduction compared to those in the amitriptyline group (mean change in pain intensity 1.9 versus 1.3 points below baseline; p=0.026). Side effects were also less severe in the gabapentin arm. Alternatively, no significant differences in pain relief or overall side effects were detected between gabapentin and amitriptyline in a double-blind randomized crossover trial.
- One systematic review examined the utility of gabapentin through 14 reports of 15 studies which had a combined total of 1468 patients. Data from a synthesis of seven studies found greater reductions in pain scores for patients receiving gabapentin compared to a placebo (42% versus 19% of patients, respectively, experienced pain relief). In the only trial comparing gabapentin to a placebo among 121 patients with neuropathic pain due to cancer, the reduction in mean global pain scores was also found to be greater among those allocated to gabapentin compared to a placebo (mean follow-up pain score, 4.6 versus 5.4, p=0.025). No significant differences in adverse events were found between groups.
- The other systematic review examined the effect of antidepressants on pain through 50 trials which included a combined total of 2515 patients. Fourteen of the 25 placebo-controlled studies that examined the effect of tricyclic antidepressants on pain used measures of global improvement or moderate improvement; patients in the tricyclic antidepressant group experienced significantly greater pain reduction. In one small trial focusing solely on cancer patients, amitriptyline was found to significantly reduce pain compared to a placebo in 20 breast cancer patients (median post-treatment pain intensity on a visual analogue scale: 0.2 versus 3.1, at the breast scar and 0.5 versus 5.0, in the arm).

Future Research

Large, double-blind randomized controlled trials comparing gabapentin to amitriptyline, desipramine, imipramine, or nortriptyline are needed to establish the role of gabapentin in the cancer patient population.

Funding

The PEBC is supported by CCO and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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Evidence-based Series #13-8: Section 2

The Use of Gabapentin and Tricyclic Antidepressants in the Treatment of Neuropathic Pain in Cancer Patients: A Systematic Review

L. Librach, N. Lloyd, V. Jarvis, D. Warr, A. R. Jadad, J. Wilson, M. Brouwers, R. Wong, and members of the Supportive Care Guidelines Group

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QUESTIONS

What are the roles of gabapentin and tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, and nortriptyline) in terms of efficacy for pain relief and side effects in cancer patients with neuropathic pain? Is one superior to the other?

INTRODUCTION

The number of Canadians diagnosed annually with cancer is increasing, and overall survival periods are extending (1). Approximately, 30-90% of patients with a diagnosis of cancer will experience pain at some time during their illness, with more advanced cancers exhibiting more severe and complex pain syndromes (2). Of those patients, approximately 34% will develop neuropathic pain (3). Although the treatment of nociceptive pain has improved substantially over the last 20 years, effective treatment for neuropathic pain remains elusive.

Neuropathic pain can occur in the non-cancer patient as a result of lesions or trauma in the central or peripheral nervous systems producing a variety of pain syndromes, such as phantom limb pain, trigeminal neuralgia, or diabetic peripheral neuropathy, to name just a few (4,5). In the cancer patient, both disease and therapies can damage the peripheral and central nervous systems, precipitating complex neuropathic pain syndromes (2,4,6). Indeed, many cancer patients develop neuropathic pain that is not directly related to tumour invasion but rather to treatments, be they surgical, chemical, or radiation (2,6). The mechanism of neuropathic pain may differ depending on the origin of the pain and the assessment of pain as nociceptive, inflammatory, neuropathic, or of mixed origin can be complex. However, the *treatment* of neuropathic pain does not differ, as the assessment of pain dictates the treatment options (2,7).

Unfortunately, neuropathic pain is often refractory to conventional analgesics, such as opioids (2,7) and non-steroidal anti-inflammatory drugs (NSAIDs). For this reason co-analgesic administration of tricyclic antidepressants with or without anticonvulsants, such as gabapentin (Neurontin®), an 'off-label' indication, constitute the most common treatments for patients with

neuropathic pain. That issue has economic implications as well, as gabapentin costs $0.2520 per 100mg capsule, compared to the tricyclic antidepressant amitriptyline (Elavil®, Endep®), which costs $0.0059 per 10mg tab (8). The purpose of this guideline is to examine the evidence regarding the role of gabapentin and tricyclic antidepressants in the management of neuropathic pain and to provide recommendations regarding their use.

METHODS

This systematic review was developed by the Cancer Care Ontario (CCO) Program in Evidence-based Care (PEBC). It is a convenient and up-to-date source of the best available evidence on the treatment of neuropathic pain with tricyclic antidepressants or gabapentin. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the SCGG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by, but editorially independent of, CCO and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

The MEDLINE database was searched from 1966 to November 2005 and CINAHL was searched from 1982 to November 2005 using treatment-specific text words and subject headings (gabapentin, neurontin, antidepressive agents, tricyclic, desipramine, imipramine, nortriptyline, amitriptyline) combined with the CAS registry number for gabapentin and combining these terms with those specific to study design and publication type (meta-analysis, randomized controlled trial(s), practice guideline). The Excerpta Medica database (EMBASE) was also searched up to November 2005 using agent-specific EMTREE terms (gabapentin, tricyclic antidepressant agent). Those terms were then combined with the search terms for the following study design and publication types: practice guidelines, randomized controlled trials, systematic reviews, and meta-analyses.

Issue 4 (2005) of the Cochrane Library, Issue 4 (2005) of the Database of Abstracts of Reviews of Effects (DARE), and on-line conference proceedings from the American Society of Clinical Oncology (http://www.asco.org/ac/1,1003,_12-002634-00_18-0034,00.asp; 1995-2005) were also searched. The Canadian Medical Association InfoBase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Inclusion Criteria

Articles were eligible for inclusion in this systematic review of the evidence if they met all of the following criteria:

1. The study population included adult patients with neuropathic pain of any aetiology. Trials including cancer or non-cancer patients were considered eligible.
2. The article was a systematic review, meta-analysis, evidence-based practice guideline, or a fully published or abstract report of a randomized or non-randomized controlled trial.
3. The trial compared gabapentin versus one of four tricyclic antidepressants (amitriptyline, desipramine, imipramine, and nortriptyline) or the systematic review focused on the use of gabapentin and/or tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, and nortriptyline).
4. One of the outcomes reported was pain relief. Other outcomes of interest were paresthesia score and adverse effects.

Education and Information

Exclusion Criteria

1. Letters and editorials were not considered.
2. Papers published in a language other than English were not considered.

Synthesizing the Evidence

It was decided not to pool the results of the trials because the eligible trials examined different measures of pain.

RESULTS

Two recent systematic reviews developed by members of the Cochrane Collaboration (9,10) and two randomized trials, also found in the two Cochrane reviews, were found and served as the primary evidence for this document. One of the systemic reviews focused on the role of gabapentin and the second one on the role of antidepressants (all kinds) on the management of neuropathic pain. The results are organized into three sections: the first examining gabapentin, the second examining tricyclic antidepressants, and the third comparing gabapentin to tricyclic antidepressants.

1. Gabapentin

Literature Search Results

One recently updated Cochrane systematic review by Wiffen and colleagues was found that met inclusion criteria (9). Its objective was to measure the analgesic effectiveness and adverse effects of gabapentin for pain management in clinical practice.

Systematic Review Characteristics and Quality

Fully published randomized controlled trials that measured the analgesic effects of gabapentin versus placebo or active control in patients with a pain assessment outcome were included in the systematic review (9). Searches of MEDLINE, EMBASE and the Cochrane Pain Palliative and Supportive Care Trials Register were completed up to December 2003 and the Cochrane Central Register of Controlled Trials was searched (2004, Issue 1). The searches identified 14 reports of 15 studies that included 1468 patients with acute (one study) or chronic pain (post-herpetic neuralgia, two studies; diabetic neuropathy, seven studies in six reports; phantom limb pain, one study; Guillain-Barre, one study; spinal cord pain, one study; cancer related pain, one study; and various neuropathic pain types, one study). Pain was measured in a variety of ways. The one trial examining cancer-related pain is highlighted in more detail below. The median quality scores of the trials were five out of five, based on the Jadad scale.

Overall Outcomes

Pain Relief

Data could be synthesized for seven of the 14 chronic pain studies to calculate an overall numbers needed-to-treat (NNT), which indicates the number of patients that need to be treated to avoid one negative outcome. The overall NNT for improvement, which was defined differently across individual studies, was 4.3 (95% confidence interval [CI], 3.5–5.7). Relative risk (RR) was 2.2 (95% CI, 1.8–2.7), with an RR>1 representing greater pain relief with gabapentin. Forty-two percent of participants improved on gabapentin compared to 19% on placebo.

Adverse Effects

Adverse effects were inconsistently reported in the studies and the review did not provide detailed data, but the relative frequencies were given as: dizziness 24%, somnolence 20%, headache 10%, diarrhea 10%, confusion 7%, and nausea 8%. The number needed-to-

Education and Information

harm (NNH) for adverse events leading to withdrawal from a trial was not significant (assessed across five trials) and for minor harm was 3.7 (95% CI, 2.4-5.4) based on data from two trials.

Cancer Trial Outcomes

One trial in this systematic review focused on cancer-related pain (11). That trial was described as a multicentre, double blind, placebo-controlled parallel design. Caraseni (11) randomized 121 consecutive patients with neuropathic pain due to cancer at a 2:1 ratio to gabapentin (starting dose 600 mg/day; titration up to 1,800 mg/day) or placebo for 10 days. All patients had an active cancer lesion causing pain either by nerve compression or tumour infiltration. The most common primary disease sites were breast, lung, and colon. Previous analgesic and adjuvant therapies were unchanged. Patients' assessments of global pain (primary outcome), shooting/lancinating pain, burning pain, and dysesthesias were rated daily for 10 days on a 10-point scale and averaged. The trial description and results are summarized in Tables 1 and 2.

Fifty-eight of the 80 patients allocated to the treatment arm and 31 of 41 allocated to the control arm completed the study. Reasons for withdrawal included need for prohibited therapy, adverse events, consent withdrawal, or protocol violation. One hundred twenty patients were included in the intention-to-treat (ITT) analysis.

Mean follow-up global pain scores were lower for patients allocated to the gabapentin group versus placebo group (4.6 versus 5.4, p=0.025, with baseline scores as covariates). Dysesthesia scores were lower in the gabapentin group than the placebo group (4.3 versus 5.2, p=0.0077). Other symptoms did not show a significant difference between the two groups.

The rate of adverse events leading to withdrawal was similar between the two groups: six patients in the treatment group (four with events attributed to the drug, including two serious events) and three patients in the placebo group. Most frequent side effects not leading to drug discontinuation were mild to moderate somnolence (23% versus 10% of patients) and dizziness (9% versus 0%), which were more common in the gabapentin arm.

2. Tricyclic Antidepressants

Literature Search Results

One recently updated Cochrane systematic review by Saarto and Wiffen was found that met inclusion criteria (10). Its objective was to measure the effectiveness and safety of antidepressants for management of neuropathic pain. That systematic review examined a range of antidepressants (including tricyclics) and included randomized controlled trials comparing antidepressants with placebo or with any other antidepressant or with any other active control drug or with any other intervention. All diseases were included except chronic headache or migraine.

Systematic Review Characteristics and Quality

Searches were conducted up to January 2004 (System for Information on Grey Literature, SIGLE) and November 2004 (MEDLINE, EMBASE), as well as in Issue 4 (2004) of the Cochrane Central Register of Controlled Trials. Overall, fifty randomized studies (20 parallel design and 30 crossover design) of 19 different antidepressants that included 2515 participants were included in the systematic review. The method of pain assessment could be clearly ascertained in 34 of the studies, and was patient-reported in 32 of those studies. Thirty-six studies were placebo controlled. Six studies were open, single blinded or blinding was unclear; the remaining studies were double blinded. For the purposes of this review, just those findings related to tricyclic antidepressants are presented. More detail is provided where the trial focused on cancer-related pain.

For education and information

Table 1. RCTs of gabapentin or tricyclic antidepressants for the treatment of neuropathic pain: trial descriptions.

Author, Year (reference)	Number of Patients Randomized (evaluable)	Treatment Arms	Patient Characteristics	Study Duration	Outcomes Assessed (scale)	Study Design/ Blinding	Jadad Score
Gabapentin vs. placebo							
Caraceni 2004 (11)	80 (79) 41 (41)	Gabapentin Placebo	Active cancer lesion causing pain by infiltration or compression of nervous structures	10 days	Pain intensity (0-10) for global pain, shooting / lancinating pain, burning pain, and dysesthesia.	RCT / double-blind	4
Tricyclic antidepressants vs. placebo							
Kalso 1995 (12)	20 (15) total 13 ipsilateral arm pain 12 breast scar pain	Amitriptyline Placebo	Moderate to severe neuropathic pain following treatment for breast cancer	10 weeks	Pain intensity (0-10, VAS) Pain intensity (0-7, VRS) Pain relief (0-4, VRS) McGill pain questionnaire	RCT crossover / double-blind	3
Gabapentin vs. tricyclic antidepressants							
Dallocchio 2000 (13)	13 (13) 12 (12)	Gabapentin Amitriptyline	Type-II diabetes; lower limb polyneuropathy with pain and paresthesia lasting at least 6 months	12 weeks	Pain intensity (0-4)[1] Paresthesia (0-4)	RCT / open	2
Morello 1999 (14)	**Treatment 1:** Group A: 12 (9) Group B: 13 (10) **Treatment 2:** Group A: 11 (10) Group B: 11 (11)	 Gabapentin Amitriptyline Amitriptyline Gabapentin	Diabetes mellitus; chronic daily pain >3 months	13 weeks (two 6 week treatment periods with 1 week washout)	Pain relief (Pain Scale Rating System[2]; Global Rating Scale[3])	RCT crossover / double-blind	4

Abbreviations: RCT, randomized controlled trial; VAS, visual analogue scale; VRS, verbal rating scale; vs., versus.

1 – Pain intensity: 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain, 4=excruciating pain.
2 – Patients chose from a scale of 13 words describing pain intensity, ranging from none to extremely intense; verbal descriptors were quantified based on a ratio-scale technique.
3 – Patient-reported global rating of their overall pain relief (complete, a lot, moderate, slight, none, or pain worse) at the end of each treatment compared to their baseline pain score.

Education and Information

Table 2. RCTs of gabapentin or tricyclic antidepressants for the treatment of neuropathic pain: trial results.

Author, Year (reference)	Treatment Arms	Pain Relief				Adverse Events N (%)
		Mean Baseline Pain Intensity	Post-treatment Pain Intensity Score	Mean Baseline Paresthesia	Post-treatment Paresthesia Score	
Gabapentin vs. placebo						
Caraceni 2004 (11)	Gabapentin Placebo	7.0 (SD 1.4) 7.7 (SD 1.3)	Mean adjusted score with baseline score as covariate 4.6 (SE 0.25) 5.4 (SE 0.32) **p=0.025**	Dysesthesia 6.4 (SD 2.1) 6.0 (SD 2.4)	Mean adjusted score with baseline score as covariate 4.3 (SE 0.26) 5.2 (SE 0.32) **p=0.0077**	Gabapentin vs. Placebo [1] Dizziness: 7 (9%) vs. 0 Somnolence: 18 (23%) vs. 4 (10%) Nausea/vomiting: 5 (6%) vs. 0 Infection: 2 (3%) vs. 1 (2%) Fever: 2 (3%) vs. 0
Tricyclic antidepressants vs. placebo						
Kalso 1995 (12)	Breast scar Amitriptyline [2] Placebo	Median 3.3 / 3.0 for VAS / VRS across both groups	Median VAS VRS 0.2 1.9 3.1 2.7 **p<0.05** Pain relief, 3 vs. 1.5, **p<0.05** in favour of amitriptyline	NR	NR	Amitriptyline 100 mg[3] vs. Placebo Tired: 12 (92%) vs. 8 (62%), p<0.05 Dry mouth: 12 (92%) vs. 5 (38%), p<0.05 Headache: 2 (15%) vs. 5 (38%) Constipation: 8 (62%) vs. 1 (8%), p<0.01 Nightmares: 6 (46%) vs. 5 (38%) Sweaty: 12 (92%) vs. 8 (62%), p<0.05 Palpitation: 6 (46%) vs. 4 (31%) Nausea: 0 vs. 2 (15%) Appetite loss: 3 (23%) vs. 3 (23%) Urinary: 3 (23%) vs. 1 (8%)
	Ipsilateral Arm Amitriptyline [2] Placebo	Median 5.0 / 4.0 for VAS / VRS across both groups	Median VAS VRS 0.5 1.8 5.0 3.0 **p<0.05 p<0.05** Pain relief, 3 vs. 2, **p<0.05** in favour of amitriptyline			
Gabapentin vs. tricyclic antidepressants						
Dallocchio 2000 (13)	Gabapentin Amitriptyline	2.9 (SD 0.8) 2.8 (SD 0.8)	Change, baseline to final visit -1.9 (SD 0.8) -1.3 (SD 0.6) **p=0.026**	3.0 (SD 0.7) 2.5 (SD 0.8)	Change, baseline to final visit -1.8 (SD 0.7) -0.9 (SD 0.5) [4]**p=0.004**	Gabapentin vs. Amitriptyline Dizziness: 2 (15%) vs. 5 (42%) Somnolence: 1 (8%) vs. 6 (50%) Dry mouth: 0 (0%) vs. 5 (42%) Ataxia: 1 (8%) vs. 0 (0%) Constipation: 0 (0%) vs. 4 (33%) Weight gain 0 (0%) vs. 2 (17%) Orthostatic hypotension 0 (0%) vs. 1 (8%)
Morello 1999 (14)	Gabapentin Amitriptyline	NR	Pain Scale Rating System: no significant difference in pain intensity between groups, p=0.26 Pain relief on Global Rating Scale[5]: 52% vs. 67% (p>0.1)	NR	NR	Gabapentin vs. Amitriptyline Dizziness: 7 (28%) vs. 2 (8%) Sedation: 12 (48%) vs. 8 (32%) Dry mouth: 4 (16%) vs. 8 (32%) Ataxia: 5 (20%) vs. 2 (8%) Lethargy: 4 (16%) vs. 5 (20%) Weight gain: 0 (0%) vs. 6 (24%), p=0.01 Postural hypotension: 6 (24%) vs. 5 (20%)

Abbreviations: NR, not reported; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; VAS, visual analogue scale; VRS, verbal rating scale; vs., versus.
1 – Events occurring in more than one patient and not leading to treatment discontinuation. Events leading to treatment discontinuation occurred in only one patient each.
2 – Results reported for amitriptyline 100 mg, the maximum dose achieved by 13 of the 15 patients included in the final analysis.
3 – The adverse effects were similar for amitriptyline 50 mg except for headache, which was more frequent with amitriptyline 50 mg than placebo (5 vs. 3 patients).
4 – Significance level inconsistently reported as p=0.004 in the original report abstract and text and p=0.04 in the report table.
5 – Moderate or greater pain relief at end of treatment period (% patients), gabapentin vs. amitriptyline.

Education and Information

Overall Outcomes: Tricyclic Antidepressants versus Placebo

Twenty-five placebo-controlled studies examined the role of tricyclic antidepressants in the management of neuropathic pain across several clinical conditions (10). An overall effectiveness benefit in favour of tricyclic antidepressants compared to placebo (RR 2.37, 95% CI 1.96–2.87) was found for the 14 studies with measures of either global improvement or moderate improvement. The NNTs to achieve moderate pain relief or better were 2 (95% CI 1.7–2.5) for amitriptyline (7 studies, 341 patients, dose up to 150 mg daily) and 2.1 (95% CI 1.5–3.2) for desipramine (2 studies, 78 patients). For the 10 studies that reported mean data only, only three of the 13 comparisons did not show a benefit for tricyclic antidepressants over placebo using vote counting.

Cancer Trial Outcomes: Tricyclic Antidepressants versus Placebo

One of the 25 placebo-controlled studies examined the role of tricyclic antidepressants (amitriptyline) versus placebo and focused on patients with postoperative neuropathic pain after breast cancer surgery and radiotherapy (12). The description and results of the trial are summarized in Tables 1 and 2.

The study was a double blind placebo controlled crossover design that incorporated two four-week treatment periods and a two-week washout period, with an amitriptyline starting dose of 25mg/day, titrating up to 100mg/day (12). The use of other adjuvant analgesic agents was not reported. Twenty patients treated for breast cancer and with neuropathic pain in the anterior chest wall, axilla, or medial upper arm were recruited to participate but four withdrew because of adverse effects (tiredness), and one patient was removed because of non-compliance. Several pain outcomes were evaluated, including the McGill Pain Questionnaire words, McGill Pain Questionnaire score, visual analogue scale, and verbal rating scales.

Median pain intensity and relief were significantly improved with 100 mg amitriptyline compared with baseline and amitriptyline, at doses of 25 mg to 100 mg also significantly reduced mean pain intensity and increased mean pain relief compared with placebo in both the arm (13 patients) and breast scar (12 patients). In addition, eight of 15 evaluable patients achieved ≥50% reduction in intensity of arm or breast scar pain with a median dose of 50 mg. The remaining seven patients who had a less than 50% effect had drug concentrations equalling those of patients with a more favourable response. As previously noted, four patients discontinued amitriptyline during the first week of treatment because of incapacitating tiredness. Other adverse effects that occurred significantly more often with amitriptyline compared with placebo included dry mouth, constipation, and sweating. Only 3 of the 15 study patients wanted to continue treatment with amitriptyline.

Overall Outcomes: Tricyclic Antidepressants versus Tricyclic Antidepressants

Nine studies compared two different tricyclic antidepressant regimens across several clinical conditions (10). In five studies that reported global improvements or pain relief measures, no significant difference between regimens was found (RR 1.22, 95% CI 0.92-1.60). In four studies reporting only mean data, clomipramine was reported to be more effective than nortriptyline and more efficacious than desipramine, while imipramine was found to be more effective than mianserin. No difference was reported between amitriptyline and desipramine.

Cancer Trial Outcomes: Tricyclic Antidepressants versus Tricyclic Antidepressants

No studies met the inclusion criteria that specifically examined cancer-related pain.

3. Gabapentin versus Tricyclic Antidepressants

Literature Search Results

Two randomized trials comparing gabapentin versus amitriptyline in patients with painful diabetic neuropathy were considered eligible and are summarized in Tables 1 and 2 (13,14).

Education and Information

Those trials were also found in the gabapentin and antidepressant systematic reviews (9,10). No trials comparing gabapentin to a tricyclic antidepressant in cancer patients were identified.

Study Quality

The Jadad quality scale was used to evaluate the studies (15). The Dallocchio trial (13) was assigned a score of two, and the Morello trial (14) was rated four out of five on the Jadad scale. Both trials were reported as randomized and the Morello study (14) stated that a double-blinding strategy was used. Neither of the trials reported funding sources, although the authors of one trial included associates from the manufacturer of gabapentin (13).

Trial Characteristics

Mean daily dosages in the Dallocchio trial (13) were 1785 $\pm$ 351mg/day (starting dose, 400mg/day; titration up to 2400mg/day) for gabapentin and 53 $\pm$ 16mg/day (starting dose, 10mg/day; titration up to 90mg/day) for amitriptyline. Pain intensity and paresthesia were assessed weekly on a four-point Likert-type scale ranging from zero (no pain/paresthesia) to four (excruciating pain/paresthesia). Use of other adjuvant analgesic agents was not allowed during the study. Toxicity was measured by recording the number of adverse events in each treatment group.

In the trial by Morello (14), the mean dosages of gabapentin and amitriptyline after dosage titration based on individual response were 1565mg (range 900-1800mg/day) and 59mg (range 25-75mg/day), respectively. Two scales were used to measure patients' pain at baseline and during the last week of each treatment. The validated Pain Scale Rating System (PSRS) (16,17) has patients choose from 13 words describing pain intensity. The Global Rating Scale asks patients to make a global rating of their overall pain relief from baseline using a six-point scale (complete relief to worse pain). Regular use of analgesics, other than acetaminophen, was not allowed during the study.

Outcomes

Pain Relief

Results from the two included trials detected conflicting outcomes in the efficacy of gabapentin versus amitriptyline for pain relief in patients with diabetic neuropathy. With the Dallocchio (13) trial, significant reductions in pain scores from baseline were found for both patients randomized to the gabapentin (from 2.9 to 1.0, $p<0.01$) and the amitriptyline groups (from 2.8 to 1.5, $p<0.01$). However, gabapentin was significantly more efficacious in reducing pain compared to amitriptyline ($p=0.026$). The gabapentin group also had significantly lower paresthesia scores compared to the amitriptyline group ($p=0.004$). On the other hand, Morello (14) found no significant difference between groups on either the PSRS scale ($p=0.26$) or the Global Rating Scale ($p>0.1$), although significant pain relief from baseline was observed in both treatment arms ($p<0.001$) (14).

Adverse Effects

There were no dropouts in the trial by Dallocchio (13). In that trial, a statistically significant difference between groups was detected in the overall frequency of side effects favouring gabapentin (4 patients versus 11 patients, $p=0.003$). The most common adverse effects were dizziness, somnolence, constipation, and dry mouth.

In the Morello trial, four patients withdrew because of adverse effects, protocol violation, or voluntary withdrawal (2 under each treatment), and three were crossed over early because of intolerable side effects or pain (2 while receiving gabapentin and one while receiving amitriptyline) (14). A total of 19 patients completed both six-week treatment periods. Eighteen patients receiving gabapentin and 17 patients receiving amitriptyline experienced adverse effects. With the exception of weight gain, which was more frequent with amitriptyline ($p=0.01$),

Education and Information

no statistically significant differences in adverse effects were detected between treatment groups ($p>0.05$). The most prevalent adverse effects were sedation, dry mouth, dizziness, postural hypotension, weight gain, ataxia, and lethargy.

DISCUSSION

Two systematic reviews, one focused on gabapentin (9) and one on antidepressants including tricyclics (10), and two trials comparing the two agents against each other (13,14), were identified that met our inclusion criteria. There is an absence of large high-quality trials that focus on patients with cancer.

There is some evidence supporting a role for gabapentin in the treatment of neuropathic pain in general. In the Wiffen systematic review and meta-analysis, the NNT to achieve relief was 4.3 in favour of gabapentin and 42% of patients in the gabapentin treatment group saw improvement in their pain compared with 19% in the placebo group (9). In the trial with cancer patients only (11), improvement with gabapentin versus placebo was found with some measures, including global pain scores and dysesthesia.

In addition, the systematic review by Saarto and Wiffen (10) found global improvement and moderate improvement in neuropathic pain with tricyclic antidepressants compared to placebo. The NNT to achieve at least moderate pain relief was 2 for amitriptyline and 2.1 for desipramine. In the only study focused specifically on reductions in cancer pain with tricyclic antidepressants, amitriptyline was found to significantly reduce pain compared to a placebo in 20 breast cancer patients (12).

In comparing gabapentin to tricyclic antidepressants, the evidence is not consistent. One study demonstrated superiority with gabapentin, and the second study did not detect a difference between the two treatments (13,14). A possible reason for the discrepant results could be that both trials were too small and inadequately powered to reliably detect significant differences between treatment groups on pain relief. In addition, one study was not blinded (13) and, as with all non-blinded trials, patients are at higher susceptibility for bias with the answers they may provide regarding those treatments (18,19), thereby weakening the validity of the results and the ability to base clinical recommendations solely on those results.

The mean treatment effects detected for both amitriptyline and gabapentin were generally small but statistically significant; however, it is difficult to interpret the clinical significance of those benefits. The level of change in pain scores that represents a minimal clinically important difference (MCID) has been estimated at 1.5-2.2 on a 0-10 scale (20-22); however, the MCID varies by measurement scale (21) and may vary according to baseline pain intensity (21,22). In addition, it is not currently possible to determine which patients will respond well to treatment and even small average improvements may translate into considerable benefits for individual patients; therefore, at the current time, statistically significant improvements in pain levels may also be considered clinically important.

Patient tolerance to both gabapentin and tricyclic antidepressants is generally good and adverse effects are moderate and manageable. Although amitriptyline is the only tricyclic antidepressant compared with gabapentin to date, there is evidence of benefit for other tricyclic antidepressants compared with placebo and the choice of treatment may depend on patient preferences and the medication side effect profiles. Data specific to patients with cancer are incomplete.

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched in June 2006 for reports of new or ongoing trials, but none were identified.

For information and interpretation

CONCLUSIONS

In general, there is a role for either gabapentin or tricyclic antidepressants in the management of neuropathic pain. However, there is a need to examine the role of these treatments, and other options, with cancer patients in large well-conducted double-blind randomized trials.

CONFLICT OF INTEREST

The authors disclosed potential conflicts of interest relating to the topic of this report. No potential conflicts were declared.

ACKNOWLEDGEMENTS

The SCGG would like to thank Mr. Adam Haynes and Ms. Jean Mackay for assistance in the development of the report.

For a complete list of the SCGG members, please visit the CCO Web site at http://www.cancercare.on.ca/

Funding

The PEBC is supported by CCO and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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Evidence-based Series #13-8: Section 3

The Use of Gabapentin and Tricyclic Antidepressants in the Treatment of Neuropathic Pain in Cancer Patients: Guideline Development and External Review - Methods and Results

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A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: October 11, 2006

Education and Information

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

- *Section 3: Guideline Development and External Review - Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Supportive Care Guidelines Group (SCGG) of CCO's PEBC. The SCGG comprises medical, radiation, and surgical oncologists; psychiatrists; palliative care physicians; nurses; radiation therapists; methodologists; administrators; a psychologist; and an anesthetist. The series is a convenient and up-to-date source of the best available evidence on the use of gabapentin and tricyclic antidepressants (TCAs) in the treatment of neuropathic pain in cancer patients, developed through systematic review, evidence synthesis, and input from practitioners in Ontario. A list of current members of the SCGG and completed guidelines can be found at http://www.cancercare.on.ca/index_supportive careguidelines.htm.

External Review by Ontario Clinicians

Following review and discussion of Sections 1 and 2 of this evidence-based series, the SCGG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations that were distributed for external review.

BOX 1: DRAFT RECOMMENDATIONS (external review report of December 6, 2005)

Target Population

These recommendations apply to adult cancer patients experiencing neuropathic pain.

Draft Recommendations

- Gabapentin is recommended as an option for the treatment of neuropathic pain in cancer patients.
- Tricyclic antidepressants are recommended as an option for cancer patients with neuropathic pain. While there is limited evidence comparing different drugs with this population, amitriptyline and venlafaxine have been shown to have some effect.
- There is insufficient evidence demonstrating the superiority of either gabapentin or tricyclic antidepressants over the other in neuropathic pain management.

Methods

Feedback was obtained through a mailed survey of 122 health care providers in Ontario including 70 palliative care physicians, 22 psychiatrists, 18 nurses, 5 radiation therapists, 4 pharmacists, 2 family medicine specialists, and 1 medical oncologist. One member of the SCGG, a palliative care physician who was an author on the report, was included in the survey sample in error but was not included in the analysis. The survey consisted of items evaluating the methods, results, and discussion used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on February 1st and 2nd 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). In addition, the draft report and survey were distributed to attendees of the Cancer Care Ontario 2006 Signature

Education Information

Event (March 6th, 2006, Toronto), which was on palliative care. One attendee returned a survey and was included in the following analysis. The SCGG reviewed the results of the survey.

Results

In total, 54 responses were received out of the 122 surveys sent (44% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Forty-three respondents, including 30 palliative care physicians, 5 nurses, 4 psychiatrists, 1 family medicine specialist, 1 pharmacist, 1 medical oncologist, and 1 radiation therapist, indicated that the report was relevant to their clinical practice and completed the survey. Key results of the external review survey are summarized in Table 1.

Table 1. Responses to eight items on the external review survey.

Item	Number (%) [a]		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear. [b1]	36 (84%)	2 (5%)	4 (9%)
There is a need for a guideline on this topic.	37 (86%)	4 (9%)	2 (5%)
The literature search is relevant and complete. [b2]	26 (60%)	12 (28%)	3 (7%)
The results of the trials described in the report are interpreted according to my understanding of the data. [b1]	37 (86%)	3 (7%)	2 (5%)
The draft recommendations in the report are clear. [b1]	38 (88%)	3 (7%)	1 (2%)
I agree with the draft recommendations as stated. [b1]	33 (77%)	5 (12%)	4 (9%)
This report should be approved as a practice guideline. [b1]	32 (74%)	6 (14%)	4 (9%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice? [b2]	Very likely or likely	Unsure	Not at all likely or unlikely
	31 (72%)	7 (16%)	3 (7%)

a Percentages may not total 100% due to rounding errors.
bx 'x' individuals did not respond to this question.

Among the 30 palliative care physicians, responses were similar: 73% agreed with the draft recommendations as stated and that the report should be approved as a practice guideline; 67% indicated they would be likely to use the practice guideline in their own practice. Ten percent disagreed with each of those statements.

Summary of Practitioner Comments and the Responses of the SCGG

Twenty respondents (47%) provided written comments related to the content of the report. The main points contained in the written comments are summarized below, along with responses of the SCGG.

Comments on the Recommendations

1. Two respondents commented that gabapentin was always mentioned first (in the report title and in the recommendations), which implies superiority over TCAs, when the evidence presented suggests the opposite (number needed to treat, NNT, for benefit of 2.0 and 4.3 for TCAs and gabapentin, respectively). One respondent recommended starting with a TCA, which is also cheaper than gabapentin, and one indicated that was their current practice.

   The recommendations explicitly state that neither treatment option is clearly superior and comparing the NNTs across analyses can be misleading since

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many factors, including patient populations, selected comparison treatments, selected outcome threshold, etc. may influence the results in individual studies. The recommendations have been revised to more clearly indicate that both agents are considered reasonable treatment options. Tricyclic antidepressants may be considered first for patients without any contraindications because they are used more widely, are more accessible under the Ontario provincial formulary, and cost less than gabapentin; however, based on the available evidence, neither option is recommended over the other.

2. One respondent felt that recommending amitriptyline and venlafaxine while not recommending desipramine (with a true NNT equivalent to amitriptyline) or clomipramine (which was more effective than nortriptyline, which was, in turn, more effective than desipramine) was not supported.

   Amitriptyline is the only TCA that has been examined in a cancer population to date and is, therefore, the only option explicitly indicated in the recommendations. However, the SCGG acknowledge that other TCAs may be expected to have a similar effect to amitriptyline and have added a statement to that effect in the Recommendations section of the report.

3. One respondent indicated that the recommendations do not mention that either of the options presented are only second line co-analgesic options, citing the Oxford Handbook of Palliative Care, 2005, in support of this statement. ("Remember that most cancer pain which seems to be predominantly neuropathic will also probably have a nociceptive opioid element, i.e. try WHO analgesic ladder first", p.206) (3).

   While acknowledging that opioids are often part of the treatment plan for neuropathic cancer pain and, with or without additional treatments, are the standard treatment for mixed pain of nociceptive origin, the choice of an appropriate treatment depends upon the pain assessment. However, a Qualifying Statement has been added to the Clinical Practice Guideline to indicate that, in the opinion of the SCGG, gabapentin or tricyclic antidepressants may be used alone, or as co-analgesics, in the treatment of neuropathic cancer pain.

4. One respondent suggested that the size of the expected analgesic effect should be indicated in the recommendations. They noted that for gabapentin, the expected analgesic efficacy appears to be in the order of a mean pain intensity reduction of 1 over 10 compared to pain intensity baseline.

   The analgesic effects of the agents considered in this review are reported in the Key Evidence section of the Clinical Practice Guideline and are generally small, even when they are statistically significant. Further discussion of the clinical importance of the treatment effect size has been added to the Discussion section of the Systematic Review (section 2).

5. Several respondents indicated that venlafaxine is not a TCA and that the recommendations should be revised to reflect that.

   Since non-TCAs were not considered in this guideline, the recommendations and systematic review were revised to exclude reference to venlafaxine.

6. Several respondents commented on the need for medication dose recommendations.

   Evidence on optimal dosing of treatments for pain management were not reviewed in this report; however, the SCGG have added a Qualifying Statement

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on medication dosing based on clinical expertise and the doses used in the trials reviewed in this report.

Comments on the Evidence

7. Limitations of the evidence were noted by a number of respondents, both in terms of quantity (number of trials) and quality (power of trials to detect a difference given their size and drop-out rates). Some respondents felt that these limitations were not emphasized enough and questioned whether recommendations should be made based on trials of 20 patients. Others questioned the generalizability of the data from non-cancer populations to cancer populations and across different types of neuropathic pain and suggested that the extrapolation of data across populations in the development of the recommendations was not sufficiently emphasized.

   A Qualifying Statement has been added to the Clinical Practice Guideline to highlight the fact that, given the limited evidence available for the use of gabapentin and tricyclic antidepressants in cancer patients, data from non-cancer populations was considered in the review of evidence and development of recommendations. The SCGG recognize that the etiology of neuropathic pain is heterogeneous and this is acknowledged in the Introduction section of the Systematic Review; however, the limited data available from cancer populations is similar to that from non-cancer populations with neuropathic pain of varied origins and supports the recommendations.

8. It was suggested that a clear distinction be made, in the research trials and the patient groups for whom treatment is intended, between cancer pain that is site-specific, type-specific, or cause unspecified, as well as non-cancer neuropathic pain.

   Where available, data on cancer pain sources has been added to the Results section of this report.

9. One respondent commented that the magnitude of improvement on gabapentin was not always clear and that, even in the 'Cancer Trial Result' section, the difference in pain scores was given as well as the difference in dysesthesia scores between gabapentin and placebo groups but this difference was not large (<1) and pain and dysesthesia scores in the groups prior to treatment were not provided (were they different to start with?).

   Both the magnitude of benefit associated with treatment and the baseline treatment comparisons are important in evaluating study outcomes and are reported in the Results section of this report where available.

10. One respondent identified two key articles that they felt should be referenced (4,5).

    Both of the articles identified were reviews published after the last literature search update for this report was conducted. The review by Lynch and Watson (4) was not clearly systematic and would not meet the inclusion criteria for this report. The Finnerup review (5), whose results were consistent with the data reported here, was systematic and will be included in the next revision of this report.

Other comments

11. It was noted that the limitations of the EBM approach are not acknowledged or discussed. The context of the debate is missing, e.g. financial and social interests of each medication, why these two classes of medication are expected to be effective, etc., and the report does not provide enough information to elicit genuine reflection.

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While acknowledging that there are a range of non-clinical issues that may be of interest to some constituents, the scope and corresponding focus of the current report, treatment efficacy and side effects, is clearly indicated in the research question.

12. One respondent felt the title of the guideline and the paragraph in the Methods section describing the report as a review of "the best available evidence on the treatment of neuropathic pain" were misleading, since only two of the numerous co-analgesic options available in the pharmacological management of neuropathic pain in cancer patients are reviewed. Several respondents questioned why anticonvulsants other than gabapentin were not considered e.g. carbamazepine (Tegretol, Tegretol CR) and pregabalin (Lyrica), suggesting that the latter is largely replacing gabapentin in effectiveness and has the relevant indication. Other suggested new antiepileptics look interesting for neuropathic pain and should be compared to tricyclics and gabapentin.

    The scope of this report included the key agents commonly used in addition to opioids in the treatment of neuropathic cancer pain, gabapentin and tricyclic antidepressants, and both the title and Methods section of the report have been revised to clearly indicate that. The SCGG acknowledge the increasing interest in the use of newer anticonvulsants in the treatment of neuropathic pain and the potential interest in antiepileptic agents and will consider broadening the scope of this report when there is evidence on the use of these agents in cancer populations.

13. Several respondents thought the report was clear, well done, or a very valuable resource. One found the tables of the trials very helpful and suggested that data from all trials discussed should be summarized in the same way.

    For clarity, data from all individual trials discussed in the systematic review have been added to the data tables.

14. One respondent noted there is little discussion about mode of action, suspecting that there are many different pathways for neuropathic pain. They suggested that discussing only clinical efficacy is like comparing succinylcholine with tubocurarine: similar effect but vastly different mechanisms.

    While recognizing that the mode of action of the two treatments may differ, the focus of the report is treatment efficacy and evidence relating to treatment mode of action was not reviewed.

15. One respondent indicated that the guideline should be used to lobby for decreased costs and increased coverage for gabapentin for neuropathic pain. Another commented that since gabapentin is very expensive and often not covered by insurance or drug plans, other less expensive researched options for the treatment of neuropathic pain should be considered. Several respondents questioned whether gabapentin would receive an Ontario Ministry of Health Limited Use (L.U.) Code as a result of the recommendations

    While health care policies, particularly treatment funding policies, do have important implications for health care providers in Ontario, the focus of this report is on the clinical efficacy aspects of treatment. However, the report is publicly available and may be used to inform policy decisions within the province. It will also be submitted to the Ontario Committee to Evaluate Drugs for consideration of funding of gabapentin for the treatment of neuropathic pain in cancer patients.

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Report Approval Panel

In December 2005, the evidence-based series report was reviewed by one member of the PEBC Report Approval Panel with expertise in clinical and methodology issues. The other Panel member contributed to the development of the report and was not eligible to provide feedback. Overall, the report was considered very well conceived, thoroughly researched, and likely to be helpful to clinicians.

The Panel member suggested that it would be beneficial to include a section in the report on issues related to outcome assessment and measurement specific to this topic, particularly in relation to the magnitude of benefit associated with pain assessment instruments. For example, where there are statistically significant differences between randomized groups in pain scores, is it possible to qualify what these differences mean to a patient? Does an NNT of 2 reflect mild pain reduction or eradication of pain? Although outcome assessment is a complex topic in its own right, readers would benefit from the SCGG interpretation of magnitude.

In addition, the Panel member also suggested that expert advice on dose, schedule, and duration of therapy would be helpful. Although such recommendations would be informed by the evidence rather than strictly evidence-based, readers may benefit from the SCGG expertise.

The feedback from the Report Approval Panel was consistent with that received through the external review process. In response, the SCGG added further discussion of the complexity of pain assessment and the evaluation of clinically important differences, and have included a Qualifying Statement on medication dosing, based on clinical expertise and the trials reviewed in the report. The Report Approval Panel formally approved the Evidence-based Series Report in October 2006.

ONGOING DEVELOPMENT AND MAINTENANCE

This report reflects the integration of the draft recommendations with feedback obtained from the internal and external review processes and has been approved by the SCGG. PEBC reports are reviewed within five years of completion and updated reports will be posted on the CCO web site at: www.cancercare.on.ca.

Funding

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Education and Information