Evaluation of dosing guidelines for use of controlled-release codeine in chronic noncancer pain

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OBJECTIVE: The clinical utility of guidelines for conversion of patients from a combination analgesic preparation of acetaminophen 300 mg plus codeine 30 mg every 4h to 6h as needed to scheduled controlled-release (CR) codeine every 12h was evaluated.

METHODS: Adult patients with chronic noncancer pain underwent a two-week evaluation on acetaminophen plus codeine, followed by eight weeks of treatment with CR codeine. Patients taking four to six tablets of acetaminophen plus codeine per day were transferred to 50 mg CR codeine every 12 h; those on seven to nine tablets were transferred to 100 mg every 12 h; those on 10 to 12 tablets were transferred to 150 mg every 12 h; and those on greater than 12 tablets were transferred to 200 mg every 12 h. Subsequent dose adjustments were permitted. Acetaminophen (325 mg) was available for rescue. Pain intensity (five-point categorical and 100 mm visual analog scale), pain related disability, adverse events and acceptability were assessed.

RESULTS: Of the 140 patients enrolled, 95 completed eight weeks of treatment with CR codeine. During month 1 and month 2, the mean CR codeine daily doses were 295.7±119.1 mg and 390.3±163.4 mg, respectively. Pain scores during both CR codeine month 1 and 2 were significantly lower than on acetaminophen plus codeine (53.6±20.9 mm and 49.7±23.7 mm versus 59.6±17.5 mm; P=0.0003, P=0.0001, respectively). CR codeine treatment was rated as moderately or highly acceptable by 82% of patients compared with 50% for acetaminophen plus codeine (P=0.001). Only seven patients (5.9%) discontinued CR codeine treatment because of adverse events.

CONCLUSION: The results confirm the safety, efficacy and patient acceptability of the initial conversion and maintenance dosing recommendations for CR codeine from a combination opioid/nonopioid analgesic.

Key words: *Chronic pain; Controlled-release codeine*

L'évaluation des lignes directrices sur les doses d'utilisation de codéine à libération contrôlée en cas de douleur non cancéreuse chronique

OBJECTIF : Est évaluée l'utilité clinique des lignes directrices pour faire passer le traitement des patients d'une association de préparation analgésique de 300 mg d'acétaminophène et de 30 mg de codéine toutes les quatre à six heures au besoin à de la codéine à libération contrôlée (LC) programmée toutes les 12 heures.

MÉTHODOLOGIE : Des patients adultes souffrant de douleur non cancéreuse chronique ont subi une évaluation de deux semaines pendant qu'ils prenaient de l'acétaminophène associée à de la codéine, suivie par un traitement de huit semaines à la codéine à LC. Des patients prenant de quatre à six comprimés d'acétaminophène et de codéine par jour sont passés à 50 mg de codéine à LC toutes les 12 heures, ceux qui en prenaient de sept à neuf, à 100 mg toutes les 12 heures, ceux qui en prenaient de dix à 12, à 150 mg toutes les 12 heures et ceux qui en prenaient plus de 12, à 200 mg toutes les 12 heures. Des rajustements de la posologie étaient autorisés. Il était possible de prendre de l'acétaminophène (325 mg) comme antidote électif. L'intensité de la douleur (échelle nominale de cinq points et échelle analogique visuelle de 100 mg), l'incapacité causée par la douleur, les événements indésirables et l'acceptabilité ont été évalués.

RÉSULTATS : Des 140 patients enrôlés, 95 ont terminé huit semaines de traitement à la codéine à LC. Pendant le premier et le deuxième mois, les doses quotidiennes moyennes de codéine à LC s'élevaient à 295,7±119,1 mg et à 390,3±163,4 mg, respectivement. Les échelles de douleur pendant les premier et deuxième mois sous codéine à LC étaient beaucoup plus faibles que sous acétaminophène et codéine (53,6±20,9 mm et 49,7±23,7 mm comparativement à 59,6±17,5 mm; P=0,0003, P=0,0001, respectivement). Le traitement à la codéine à LC était évalué comme modérément ou hautement acceptable par 82 % des patients par rapport à 50 % de ceux qui prenaient de l'acétaminophène associée à de la codéine (P=0,001). Seulement sept patients (5,9 %) ont mis fin au traitement à la codéine à LC en raison d'événements indésirables.

CONCLUSION : Les résultats confirment l'innocuité, l'efficacité et l'acceptabilité par le patient de la conversion initiale et des recommandations relatives à une dose d'entretien de codéine à LC en remplacement d'une association d'analgésiques opioïdes et non opioïdes.

The goal of analgesic therapy is to achieve continuous suppression of pain by administering the next dose before the effects of the previous dose have worn off (1). While there are controlled-release formulations of opioids that meet this therapeutic objective for the treatment of severe chronic pain (2-7), codeine is generally recommended for mild to moderate pain (8) but is usually used in combination with acetaminophen in immediate-release formulations. Controlled-release (CR) codeine dosed every 12 h provides an equivalent extent of absorption compared with immediate release codeine dosed

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TABLE 1
Conversion from acetaminophen plus codeine phosphate combinations to controlled-release codeine

Number of 30 mg codeine combination tablets per day	Initial dose of CR codeine (mg every 12 h)	Maintenance dose of CR codeine (mg every 12 h)
4 – 6	50	100
7 – 9	100	150
10 – 12	150	200
>12	200	300

Data from reference 30. CR Controlled-release

every 4 h to 6 h (9), and has the advantage of less frequent scheduled dosing and improved pain control without the limitations of fixed-dose combinations of short-acting opioids with nonsteroidal anti-inflammatory drugs or acetaminophen (10,11).

Fixed-dose combinations of codeine-acetaminophen-caffeine have an upper dose limit imposed by acetaminophen, which prevents titration of patients to higher opioid doses. Also, chronic use of high doses of acetaminophen (greater than 5000 mg daily) has been associated with hepatotoxicity and kidney damage (12,13) and the caffeine component may cause insomnia resulting in increased pain.

CR codeine has also been shown to result in significantly lower pain intensity scores, daily rescue analgesic consumption and Pain Disability Index (PDI) scores when compared with placebo in patients with cancer (14), chronic nonmalignant pain of varying etiology (11) and osteoarthritis (15), and has been compared with acetaminophen plus codeine in chronic back pain (16).

A dose response for CR codeine was demonstrated with both single doses and at steady state in a comparison of CR codeine and acetaminophen plus codeine in patients with cancer pain. CR codeine at approximately 150 mg every 12 h was shown to be equivalent in effect to acetaminophen plus codeine 600/60 mg every 6 h, with similar side effects (10). Arkinstall et al (11) used this equianalgesic dose ratio to convert patients with chronic nonmalignant pain to CR codeine in a placebo-controlled crossover study. In the placebo phase of this study, patients consumed approximately two tablets less per day of the acetaminophen plus codeine combination than they reported using before enrollment into the study. This suggests that an initial conversion dose of CR codeine, based on a lower dose of acetaminophen plus codeine than that reported in the patient's history, may provide an acceptable level of analgesia while minimizing the risk of early adverse effects.

This study evaluated the safety and effectiveness of proposed guidelines for the initial conversion dose and subsequent maintenance dose of CR codeine in patients currently receiving an analgesic combination of acetaminophen plus codeine.

METHODS

Patients

Male or nonpregnant female patients over 18 years of age, with chronic pain of noncancer origin, who were mentally and physically competent to provide consent, participated in this open-label evaluation. Patients were excluded if they had intractable nausea or vomiting, a clinically significant intolerance to acetaminophen or any opioid, a history of drug abuse or unstable renal function, or other serious respiratory, cardiovascular, gastrointestinal or central nervous system conditions. The study protocol and informed consent form were reviewed and approved by a research ethics board at each of the eight centres in Canada, and all patients gave written informed consent before participating in the study.

Medications

Patients underwent a minimum two week prospective evaluation on acetaminophen plus codeine (Tylenol No 3, McNeil Pharmaceuticals, Don Mills, Ontario, Canada), before initiating treatment with CR codeine (Codeine Contin, Purdue Pharma, Pickering, Ontario, Canada) with plain acetaminophen for rescue (Tylenol, McNeil Pharmaceuticals, Don Mills, Ontario, Canada). The initial dose of CR codeine was based on the average daily acetaminophen plus codeine dose during the two week baseline evaluation, using the guidelines listed in Table 1. The dose was increased from the initial dose to the maintenance dose if pain was not adequately controlled (ie, greater than mild on a five-point categorical scale and/or the patient required four or more tablets of acetaminophen per day for breakthrough pain).

CR codeine was taken every 12 h at 08:00 and 20:00, and patients were given a supply of acetaminophen to be used at a dose of one to two tablets every 4 h as required for breakthrough pain. The maximum daily dose of acetaminophen was not to exceed 12 tablets. No other opioids were permitted during the study; however, patients were allowed to continue stable doses of other analgesics (nonsteroidal anti-inflammatory drugs, corticosteroids, tricyclic antidepressants, anticonvulsants or antiarrhythmics) provided their dose had not changed for at least 14 days preceding the study. Common opioid side effects, such as nausea and constipation, were managed with appropriate drugs.

Study design

This was an open-label evaluation of guidelines for the initiation of CR codeine 50 mg, 100 mg, 150 mg or 200 mg every 12 h in patients with chronic noncancer pain, with respect to clinical effectiveness (pain intensity and rescue analgesic use), pain-related disability, pain and sleep, safety, and overall patient and investigator acceptability of treatment.

Treatment lasted eight weeks and patients returned to the clinic for evaluation every four weeks (28 to 32 days). Patients were contacted weekly to assess the need for dose adjustments in relation to the level of pain control and the occurrence of adverse effects. Patients who successfully completed the study were eligible for an additional six month, long term open-label treatment period with CR codeine.

Analgesic efficacy was assessed daily at 08:00 and 20:00 using a five-point categorical pain intensity scale (0=none, 1=mild, 2=moderate, 3=severe, 4=excruciating) and a 100 mm visual analog scale (VAS), bounded on the left by "no pain" and on the right by "excruciating pain".

Patients rated the overall acceptability of treatment and their pain-related disability at the baseline visit (before the start of acetaminophen plus codeine), the postbaseline visit (at the start of CR codeine treatment) and at the four and eight

TABLE 2
Patient disposition

Cause of pain	Percentage of patients
Injury	29.5
Arthritis	16.8
Motor vehicle accident	15.8
Surgery	14.7
Degenerative disk disease	7.4
Neuropathy	6.3
Fibromyalgia	3.2
Headache	2.1
Other	18.9

TABLE 3
Study doses

	Acetaminophen plus codeine treatment phase	CR codeine month 1 (weeks 1-4) treatment phase	CR codeine month 2 (weeks 5-8) treatment phase
Initial dose	N/A	221.5±114.0 mg	376.1±166.5 mg
Mean daily dose for period	8.3±3.3 tablets	295.7±119.1 mg	390.3±163.4 mg
Final daily dose at end of period	N/A	360.0±151.9 mg	403.7±172.9 mg
Number of days of treatment	14.4 ± 1.5	27.9±3.2	28.7±2.9
Number of dose changes	N/A	1.9±1.8	0.6±1.0

Figures are mean ± SD. CR Controlled-release; N/A Not available

TABLE 4
Distribution of controlled-release codeine doses

Dose CR codeine (mg/day)	Number of patients		
	Initial	Week 4	Week 8
50	0	1	0
100	30	2	3
150	0	0	1
200	34	22	19
300	16	23	15
400	14	25	20
500	0	6	10
600	1	15	24
700	0	1	1
800	0	0	2
Total	**95**	**95**	**95**

week visits (while receiving CR codeine). Investigators also rated the overall acceptability of treatment at the above time points. Acceptability of treatment was assessed by asking, "How would you rate the acceptability of the treatment based on the degree of pain relief and the tolerability of any side effects?" (0=not at all acceptable; 1=slightly acceptable; 2=moderately acceptable; 3=highly acceptable). The PDI (17,18) consists of seven disability subscales, each representing a different area of every day functioning: 1) family/home responsibilities, 2) recreation, 3) social activities, 4) occupation, 5) sexual behaviour, 6) self-care and 7) life-support activity. Each scale is graded from 0 to 10, where 0=no disability and 10=total disability. An overall disability score was determined by summing the numerical ratings of the seven disability scales (range: 0 to 70).

At each visit, the impact of pain on sleep was assessed with a 100 mm VAS (anchors: never to always) which included questions like "How often have you had trouble falling asleep because of pain?", "How often have you needed medication to fall asleep?", "How often have you been awakened by pain during the night?", and "How often have you been awakened by pain in the morning?".

The occurrence and severity (0=none, 1=mild, 2=moderate, 3=severe) of any adverse events were assessed at each clinic visit using a nondirected adverse events questionnaire. Rescue acetaminophen use (date and time, and the number of tablets consumed) was recorded in the patient diary.

RESULTS

A total of 140 patients were enrolled in the study, of which 22 (16%), 10 (7%), and 13 (9%) patients discontinued during treatment with acetaminophen plus codeine and during CR codeine month 1 (weeks 1 to 4) and month 2 (weeks 5 to 8) of the study, respectively. The reasons for withdrawal were: adverse events (14 patients), voluntary patient withdrawal (11 patients), patient noncompliance (6 patients) inadequate pain control (6 patients), other (5 patients) and protocol violation (3 patients). The distribution of reasons given for discontinuation did not vary dramatically across phases. Five per cent of patients withdrew during the acetaminophen plus codeine phase due to adverse events, whereas 2.5% and 4% of patients discontinued CR codeine treatment due to adverse events during month 1 and month 2, respectively. Itching, constipation, drowsiness, dry mouth, difficulty voiding, flu, diarrhea, swollen feet, disorientation, nausea and vomiting were the reasons for early discontinuation of treatment.

Ninety-five patients (46 men, 49 women; mean age 47.7±12.1 years) completed the eight week study and were evaluated for efficacy. The majority of patients had pain in the lower back (67 patients), followed by leg (57 patients), joint (50 patients) and shoulder (48 patients). Some patients had multiple sites and multiple causes of pain (Table 2). Most patients had steady pain (89 patients) and pain at rest (80 patients). Pain intensity and estimates of the benefits of their current medication did not differ as a function of site of pain. Sixty-one patients were taking acetaminophen plus codeine before enrollment and the mean duration of opioid use before the study was 5.9±5.5 years.

The initial, mean daily and final doses, treatment duration and number of dose changes are listed in Table 3. The distribution of doses at weeks four and eight is shown in Table 4. The average time to the first dose increase was 8.6±6.5 days and the maximum was 29 days (n=79). Fourteen per cent of patients had no change in their dose throughout the study. Seventy-six patients (80%) increased their dose by week 4 and 32 patients (33.7%) increased their dose from week 4 to week 8.

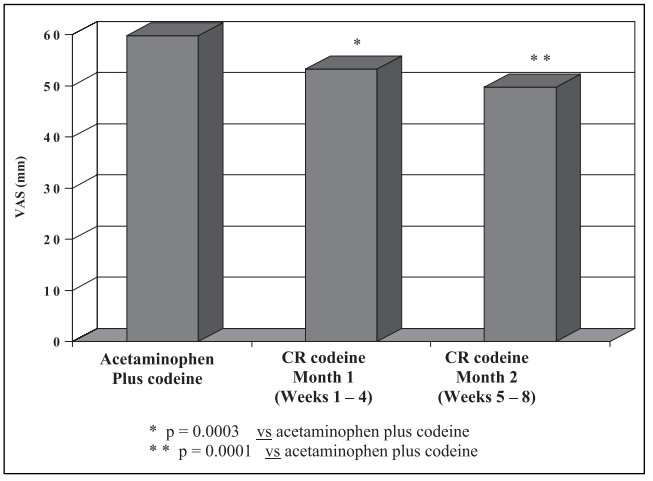

Figure 1) *Pain intensity (100 mm VAS) measured daily during the two-week acetaminophen plus codeine phase and weeks one to four and five to eight CR codeine phases. CR Controlled-release; VAS Visual analog scale*

TABLE 5
Comparison of pain intensities, pain disability index and rescue analgesic use

	Acetaminophen plus codeine (n = 95)	CR codeine month1 (weeks 1-4) (n = 95)	CR codeine month2 (weeks 5-8) (n = 95)
Pain intensity categorical (0 – 4)	2.5±0.57	2.3±0.73 **	2.2±0.79 *
Total PDI score	40.1±16.24	36.4±17.49 **	36.6±18.38 **
Rescue analgesic intake (tablets)	N/A	3.2±2.3	2.7±2.3

**P=0.0001 compared to acetaminophen plus codeine; **P=0.0005 compared with acetaminophen plus codeine. CR Controlled-release; N/A Not available*

Both categorical and VAS pain scores measured daily were significantly lower during CR codeine weeks one to four and weeks five to eight compared with the acetaminophen plus codeine phase (Figure 1, Table 5). There was an improvement in pain scores between CR codeine weeks one to four and weeks five to eight, although the difference was not statistically significant.

There were significantly fewer rescue acetaminophen tablets taken during CR codeine weeks five to eight compared with CR codeine weeks 1 to 4 (P=0.0050) (Table 5).

Patients and investigators rated acceptability significantly higher for both CR codeine phases compared with acetaminophen plus codeine (P=0.0001). There were no differences between CR codeine at week 4 and week 8.

In all cases, numerically lower (better) PDI scores were attained during the CR codeine periods compared with the acetaminophen plus codeine phase (Table 5). For all categories, differences between CR codeine week 4 and 8 were not statistically significant. Significant improvement from the acetaminophen plus codeine phase to CR codeine weeks 4 and 8 was observed for family/home responsibilities (P=0.0001, P=0.0008), recreation (P=0.0001, P=0.0049), social activity (P=0.0004, P=0.0003) and occupation (P=0.0086, P=0.0094).

TABLE 6
Adverse events

Event*	Acetaminophen plus codeine (number of patients)	CR codeine month 1 (weeks 1-4) (number of patients)	CR codeine month 2 (weeks 5-8) (number of patients)
Constipation	36	31	32
Nausea	12	6	7
Somnolence	2	12	6
Dizziness	3	10	4
Dyspepsia	3	6	1
Overall	45	59	47

**Events experienced by five or more patients. CR Controlled-release*

At the end of each phase, patients rated the degree to which their sleep was disturbed by pain. For all items, there was a rank ordering of pain and sleep scores, where CR codeine week 4 scores were lower than CR codeine week 8 scores, which were lower than acetaminophen plus codeine. For each of these items, CR codeine week 8 was superior to acetaminophen plus codeine (P<0.005) and CR codeine week 4 was superior to acetaminophen plus codeine, with the exception of 'difficulty falling asleep' (P=0.0519). Although pain and sleep scores on CR codeine were lower in week 4 compared with week 8, the difference was not statistically significant (P>0.345).

The number of incidences for the most common adverse events, for all patients enrolled, are shown in Table 6. During the eight weeks of treatment, only seven patients discontinued CR codeine due to adverse events. Serious adverse events (SAE) were reported for two patients. One patient experienced renal colic and the other patient had a urinary tract and yeast infection. Neither patient was withdrawn because of the SAE, and neither SAE was deemed related to the study medication by the investigators.

Forty-five patients went on to long term use after the end of the prospective study period and continued for an average of three months.

DISCUSSION

The objective of this study was to evaluate the clinical utility of the guidelines for the conversion of patients from a combination analgesic preparation of acetaminophen 300 mg plus codeine 30 mg administered every 4 h to 6 h to CR codeine administered every 12 h.

Other comparative studies using CR codeine and acetaminophen plus codeine resulted in equianalgesic doses of 150 mg CR codeine every 12 h and acetaminophen 600 mg plus codeine 60 mg every 6 h (300 mg codeine base versus 240 mg codeine phosphate containing 180 mg of codeine base per day, respectively) in cancer and noncancer patients (10,11). In this study, patients started CR codeine at a dose that was 50% of that calculated as equianalgesic to their baseline acetaminophen plus codeine dose and had their first dose increase approximately eight days later. By the end of the first month, patients had been titrated on CR codeine to a dose that was equivalent to their calculated equianalgesic dose, based on their baseline acetaminophen plus codeine dose. During the

two-week prospective period on acetaminophen plus codeine in this study, patients took a mean of 8.3±3.3 tablets per day, which contained approximately 180 mg of codeine base. During CR codeine months 1 and 2, the average daily codeine intakes were approximately 296 mg and 390 mg, respectively. These doses of codeine are approximately one and a half to two times greater than that received from the acetaminophen plus codeine during the two week prospective period, and fall within the estimated equianalgesic dose range. This supports the view that the acetaminophen component of acetaminophen-codeine phosphate combinations may contribute up to 50% or more of the analgesic effect (10,19-23).

Only 6% of patients dropped out due to adverse events during the eight weeks of treatment with CR codeine in this study. This is lower than in previous studies of much shorter duration (five to seven days) in which 15% of chronic noncancer pain patients (11), 24% of chronic low back pain patients (16) and 9% of cancer pain patients (14) withdrew due to adverse events. The lower initial dose and gradual titration used in the present study may explain why fewer patients withdrew due to adverse events. However, in another four week trial in which patients with osteoarthritis were initiated on a dose of 50 mg CR codeine every 12 h, and titrated at the same rate as the present study, the dropout rate due to adverse events was substantially higher (30%) (15).

Approximately 7% to 10% of the Caucasian population is designated as poor metabolizers of codeine due to a genetic polymorphism of cytochrome P450 2D6. Poor metabolizers may receive less analgesia with the same degree of side effects from codeine (24). Patients enrolled in this study were not prescreened for their ability to metabolize codeine. It is possible that the 10% of patients who dropped out of this study due to side effects or lack of efficacy may be accounted for by the percentage of poor metabolisers found in the general population.

It has been suggested that there is a ceiling effect to codeine analgesia above which adverse effects tend to increase disproportionately to pain relief (25). According to the Canadian Pain Society, there is no pharmacological rationale for a ceiling dose for opioids (26). Although patients who require doses above 800 mg of codeine daily may be better managed on a lower dose of a more potent opioid (27). If patients in this study were experiencing a ceiling effect to the pain relief provided by CR codeine, one would expect to see an increase in the adverse events reported between the first and second month of treatment along with the increase in dose; however, this was not the case.

The most common adverse events were typical opioid-related adverse events, including constipation, nausea, somnolence and dizziness. Although the incidence of somnolence and dizziness was higher for CR codeine, the incidence of nausea was twice as high for acetaminophen plus codeine. Fewer patients withdrew due to adverse events during CR codeine treatment, suggesting that the events experienced during this phase were less significant than during acetaminophen plus codeine treatment. It should also be noted that acceptability ratings by both patients and investigators were significantly higher for CR codeine than acetaminophen plus codeine, indicating that these adverse events for the CR codeine treated patients were well tolerated. The high acceptability ratings may also be due to the more stable analgesia produced by the CR formulation, leading to less interrupted sleep.

The target population for this study was patients with chronic noncancer pain of mild or moderate severity; however, the pain scores at the start of the study were high, in the order of 60 mm on a 100 mm VAS scale and 2.8 on a scale of 0 to 4, a score very close to severe (3.0). In fact, 70% of the patients rated their pain as severe or excruciating. The pain scores observed did not differ markedly from other studies examining chronic noncancer pain (11,16).

The majority of patients (83.2%) increased their dose of CR codeine during the 8-week treatment period and 98.7% of these patients cited pain as the reason. Although it is possible that the patients' pain increased over the study period, it is unlikely, considering that the patient population had chronic pain for at least three months before the study. Other long-term studies of noncancer pain patients have shown that narcotic doses increased in only 13% of patients (13 of 99) during approximately seven months of treatment (28) and increases in dose due to exacerbation of pain were brief and the patients pain usually returned to a stable baseline (29). The dose increases in this study were therefore more likely a result of the patients optimizing their pain control, and since there was not a commensurate increase in adverse events, it suggests that the dose of codeine reached was not at the analgesic ceiling.

Although the dose of CR codeine increased from month 1 to month 2 in this study, the patients pain was significantly less than during the acetaminophen plus codeine treatment, suggesting that as needed dosing in the treatment of chronic pain does not provide maximum pain relief. This may have been due to the short duration (two weeks) of acetaminophen plus codeine treatment, although one week was deemed to be an acceptable titration period in previous studies (11) and 64% of the patients completing the study had been taking acetaminophen plus codeine before the study. The improvements in pain scores and disability scores during the two months on CR codeine suggest that the dosing guidelines used in this study are appropriate for conversion of patients from acetaminophen plus codeine to CR codeine.

The higher acceptability ratings for CR codeine expressed by patients may be due to the eliminations of fluctuations in pain found over the day that occur when patients are treated with short-acting analgesics (16). The focus of treatment with short-acting analgesics tends to be pain or pain-related behaviours. Also the administration of immediate-release formulations leads to higher peak plasma concentrations compared with controlled-release formulations. This may result in a greater likelihood of adverse events and reluctance of patients to use larger doses. The benefit of time-contingent dosing is well accepted in the management of cancer pain and there is growing evidence, including the results of this study, that it is desirable in treating chronic noncancer pain (28,29).

CONCLUSION

CR codeine is an effective, well-tolerated analgesic for the long term treatment of moderately severe chronic noncancer pain. Compared with the initial baseline period, during which patients were treated with acetaminophen plus codeine, CR codeine treatment resulted in significantly lower pain, and

greater acceptability of treatment and improvement of function with a similar adverse event profile. The recommended guidelines for conversion of patients from acetaminophen plus codeine to CR codeine are: patients taking four to six tablets of acetaminophen plus codeine/day should initially transfer to 50 mg CR codeine every 12 h, seven to nine tablets to 100 mg every 12 h, 10 to 12 tablets to 150 mg every 12 h and more than 12 tablets to 200 mg every 12 h, followed by upward titration of the dose according to the patient's clinical response. These guidelines resulted in a safe and effective conversion of patients receiving acetaminophen plus codeine as needed to CR codeine every 12 h.

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