Context and policy issues:

Cannabis has been used medicinally for hundreds of years in countries such as China and India. In recent years, the pharmacology of cannabinoids has been investigated and synthetic cannabinoids developed. Anecdotal evidence has shown benefits with cannabis in chronic pain. In a survey of chronic pain clinic patients, 35% reported using marijuana with nearly one half of these patients citing pain relief as the reason.1

There is wide variation in the prevalence of chronic pain, ranging from 10% to 55%.2 In 2003, the Canadian Community Health Survey reported that 10.5% of the population had pain or discomfort that prevented them from doing few to most activities.3 In many cases chronic can be difficult to control, requiring multiple treatments and frequent visits to health care providers.1

Nabilone (Cesamet®) is an oral synthetic cannabinoid, approved for use in Canada for the management of severe nausea and vomiting associated with cancer chemotherapy.4

Research questions:

What is the evidence for the clinical effectiveness of nabilone in adults for chronic pain management?

Methods:

A limited literature search was conducted on key health technology assessment resources, including OVID MEDLINE, OVID EMBASE, The Cochrane Library (Issue 4, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and the present, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

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Summary of findings:

Clinical studies assessing the efficacy of nabilone in patients with chronic pain were limited to two randomized controlled trials (RCTs) and one case series.

In the trial by Skrabek et al.\textsuperscript{5} 40 patients with fibromyalgia and ongoing pain despite treatment were randomized to nabilone or placebo. Patients were treated for 4 weeks with an escalating dose of nabilone or placebo, and assessed at 2 weeks, 4 weeks and again 4 weeks after treatment was stopped. Patients and physicians were blinded to treatment allocation however some degree of un-blinding may have occurred due to the high incidence of adverse effects in the nabilone group. Twenty five percent of patients in the nabilone group (5/20) and 15% in the control group (3/20) stopped therapy by the first 2 weeks follow-up visit. Data from the remaining 33 patients were analyzed. At 4 weeks, the nabilone group showed statistically significant differences in two outcome measures; the change from baseline scores for pain and quality of life were significantly improved compared to placebo. No significant differences were detected at 4 weeks in the other outcomes measured (number of tender points, or the average tender point pain threshold). At the other time points measured, no significant differences were detected. Adverse effects were more common in the nabilone group (p<0.05) after 4 weeks of treatment. No serious adverse effects were reported.

Wissel et al.\textsuperscript{6} conducted a randomized double-blind cross-over trial in 13 patients with chronic upper motor neuron syndrome who experienced disabling spasticity-related pain uncontrolled by conventional treatment. Patients were randomized to receive either nabilone or placebo for four weeks and then, after a one week washout period, switched to the alternate therapy. Two patients discontinued the study during the nabilone treatment phase. It is unclear if any data from these two patients was analyzed. The results showed a significant reduction in spasticity-related pain but no change in spasticity, dexterity, or activities of daily living. Six patients reported adverse effects: transient weakness in lower limbs [1 nabilone (drop out)], drowsiness (2 nabilone, 1 placebo), dysphagia (1 placebo), acute relapse of multiple sclerosis [1 nabilone (drop out)]. No serious adverse effects were reported.

Table 1 below summarizes key study components and findings of these RCTs:
Table 1. Summary of RCTs

<table>
<thead>
<tr>
<th>Study, Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes, Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skrabek et al. 2007&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Adults with fibromyalgia and continued pain despite other medications; N=40 (33 analyzed)</td>
<td>Nabilone 0.5 mg daily to 1 mg twice daily. Dose initiated at 0.5 mg at bedtime and increased in 0.5 mg increments every 7 days to a maximum of 2 mg daily as tolerated.</td>
<td>Pain VAS score*</td>
<td>Nabilone: at 2 weeks, no significant differences detected. At 4 weeks the change from baseline was significantly different compared to placebo for VAS pain score (-1.43, p&lt;0.05) and FIQ score (-10.76, p&lt;0.01)</td>
</tr>
<tr>
<td>Randomized, blinded (patient and physician), parallel design</td>
<td>Withdrawals: Nabilone group: (2) dizziness, disorientation, nausea; (1) drowsiness and fatigue. Placebo group: (1) headaches; (1) not stated.</td>
<td>Placebo</td>
<td>Number of positive tender points</td>
<td>No significant differences noted for other outcomes.</td>
</tr>
<tr>
<td>Allocation concealment: adequate</td>
<td>Pre-existing pain control therapies were continued during the study.</td>
<td>Average tender point pain threshold</td>
<td>FIQ quality of life score†</td>
<td>Placebo: no significant changes in any outcomes compared to baseline.</td>
</tr>
<tr>
<td>No intention to treat analysis</td>
<td>Patients were assessed at baseline, after 2 and 4 weeks of treatment, and 4 weeks after treatment stopped</td>
<td>Adverse effects were more common in the nabilone group (p&lt;0.05). Most common adverse effects in the nabilone group: drowsiness (7/15), dry mouth (5/15), vertigo (4/15), ataxia (3/15).</td>
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<td>Partial industry funding received</td>
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<tr>
<td>Wissel et al. 2006&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Patients with chronic upper motor neuron syndrome with disabling spasticity-related pain refractory to treatment N=13 (11 completed) 2 patients withdrew due to acute relapse</td>
<td>Nabilone 0.5 mg daily for 7 days then 1 mg daily for 21 days.</td>
<td>11-point box test (spasticity related pain)</td>
<td>11-point box test decreased a median of 2 points with nabilone compared to placebo (p&lt;0.05)</td>
</tr>
<tr>
<td>Randomized, double blind, cross over design</td>
<td>Placebo</td>
<td>Ashworth score (spasticity)</td>
<td></td>
<td>Ashworth score (mean ± SD): Baseline 1.7 ± 1.22 Placebo 1.3 ± 1.23 Nabilone 1.0 ± 1.29, p=0.4</td>
</tr>
<tr>
<td>Allocation concealment: unclear</td>
<td>7 day washout between treatments</td>
<td>Rivermead Motor assessment (dexterity)</td>
<td></td>
<td>Rivermead Motor assessment and Barthel Index showed no change with nabilone or</td>
</tr>
<tr>
<td>Funding sources not</td>
<td>Barthel Index (activities of daily living)</td>
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</tbody>
</table>
### Study, Design
Reported

### Population
of multiple sclerosis or weakness of lower limbs after respectively 2 and 14 days of nabilone therapy.

### Intervention
Pre-existing pain control therapies were continued during the study.

### Outcomes, Assessment
Patients assessed at baseline, after first treatment, after 1 week washout, and after second treatment.

### Results
placebo.

Note: the statistical analysis of data and reporting of results were incomplete in this report.

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SD: standard deviation; *VAS=visual analogue scale (10 cm scale, 0=no pain, 10=worst pain imaginable)*

†FIQ=Fibromyalgia Impact Questionnaire (Assesses physical function, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being for patients with fibromyalgia. Higher scores indicate a greater impact of disease on quality of life. Total possible score 100.)
One retrospective chart review of 20 patients with chronic non-cancer pain was also identified in the search. The patients had a wide range of different chronic pain disorders and all had tried multiple therapies before nabilone treatment was added. The doses of nabilone used varied from 1 mg to 4 mg per day. Pain intensity was measured using a numerical rating scale (0=no pain, 10=worst pain imaginable). Missing pain score data was imputed from the last measured score. No significant differences were detected between baseline (before nabilone) and final pain scores for current pain level, average pain level for past week, highest or lowest pain level for past week. Nine of the 20 patients subjectively reported some pain relief, 10 reported improved sleep and five reported a reduction in nausea or vomiting. Three patients stopped therapy within one week due to adverse effects. Nine of the patients (45%) continued to take nabilone and the average duration of therapy was 1.5 years. Four of these patients had no decrease in pain but continued nabilone for other reasons.

Conclusions and implications for decision or policy making:

There is a paucity of evidence to support the use of nabilone for the management of chronic pain. In the two RCTs identified, the total number of patients enrolled was small (n=53), the population was limited to patients with fibromyalgia (n = 40) and patients with chronic upper motor neuron syndrome (n = 13), and treatment duration was limited to four weeks. Although both studies were reported as double blind, some degree of un-blinding may have occurred due to the high incidence of adverse effects in the nabilone group, which could have introduced bias. Benefits were based on pain scores and quality of life measurements. Although statistically significant reductions in pain scores were reported, the clinical significance of these findings is unclear. Both studies had a relatively high number of patients withdraw from nabilone treatment (5/20 and 2/13). Considering the small number of patients enrolled, exclusion of these patients’ data may have biased the results.

Based on these observations, there is considerable uncertainty around the short-term effectiveness of nabilone in the treatment of chronic pain in adults. Adverse effects are common. The limited evidence available on the long-term effectiveness of nabilone in chronic pain is of poor quality and is inconclusive.

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References:


Appendix:

Review articles


