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New Use Criteria for Dronabinol and 5-HT$_3$ Receptor Antagonists

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On April 1, 2003, dronabinol (Marinol) will require prior authorization and quantity limits will be enforced for 5-HT$_3$ receptor antagonists (9 dosage units per week) for fee-for-service ("open-card") members of the Oregon Health Plan. The policy changes were recommended by the Oregon Drug Use Review Board in response to recent drug utilization evaluations (DUE) and evidence-based evaluations of the literature.

DRONABINOL

Dronabinol is a controlled substance that contains delta-9-tetrahydrocannabinol (THC), a major active ingredient found in marijuana. Dronabinol is approved for appetite stimulation in AIDS-related anorexia and treatment of chemotherapy-induced nausea and vomiting in patients who have failed to respond to conventional antiemetic therapies.[1] Medicinal applications of dronabinol have expanded beyond its approved indications based on anecdotal reports and small, clinical studies.

A DUE of prescription claims for dronabinol of Oregon Medicaid fee-for-service claims from 1/1/2001 – 12/31/2001 was reviewed. There were a total of 1679 claims for dronabinol, at a cost over $1 million. Table 1 summarizes the claims.

Table 1 - Dronabinol DUE Data

Number of patients	134
HIV infection diagnosis	68%
Average claim cost	$547
Prescription claim cost	(n=)
>$1000	248
$2000-$4000	24
>$4000	2

It is difficult to make inferences about the indications for dronabinol from prescription claims. However, given that doses of 2.5mg bid and 5 mg/m^2 for 4-6 doses/day were used in clinical trials for AIDS-related anorexia and treatment of chemotherapy-induced nausea and vomiting, respectively, the monthly costs should be in the region of $210 per month. The DUE data indicates that dronabinol may have been prescribed outside of its approved indications in some instances, and additionally, it was prescribed in high dose for many patients.

AIDS-related anorexia - Clinical trials have shown that dronabinol increases appetite, but its effect on weight gain is inconsistent. When weight gain does occur, it is primarily an accumulation of water; sometimes fat; but not of lean body mass. Furthermore, the weight gain produced by dronabinol has not been shown to be associated with an improved immunologic status or clinical outcome, such as improvement on survival. Patients in clinical studies have usually noted a delayed onset of appetite stimulant effect and reported central nervous system complaints.[2,3] Adding dronabinol to another appetite stimulant, such as megestrol, produces no additional weight gain effect.[4] The duration of treatment in these studies has been relatively short; 5 weeks to 12 months. The maximum dose used was 10mg bid. Table 2 provides a summary of clinical trials.

Chemotherapy-induced nausea and vomiting - The efficacy of THC for chemotherapy-induced emesis has been investigated since the mid-1970s. A meta-analysis of 30 randomized controlled trials showed that cannabinoid in various dosage forms and formulations were slightly more efficacious than active comparators (e.g. prochlorperazine) and placebo in patients who received low emetogenic chemotherapy.[8] However, cannabinoid therapy was associated with increased neuropsychiatric adverse effects, leading to significantly large number of cannabinoid-treated subjects withdrawn early from these studies. There are no studies comparing cannabinoid with 5-HT$_3$ receptor antagonists.

Comprehensive review of available literature indicates that evidence to support the use of dronabinol in multiple sclerosis, migraine, pain, glaucoma, movement disorder, and cancer-related anorexia is lacking.[11-21] The use of cannabinoid has been associated with disorders of motivation, judgment, and cognition.[2] In addition to its psychoactive effects, dronabinol can cause significant cardiovascular effects such as palpitations, tachycardia or hypotension.[1,2] The use of dronabinol, outside of its approved indications, should be discouraged. Other pharmacological agents that have been evaluated more extensively in terms of efficacy and safety are available, for these indications.

Table 2 - Summary of AIDS-related Anorexia Clinical Trials

Author	Study Design	Treatment Arm	Efficacy	Safety
Beal JE[5] 1995	MC, DB, placebo-controlled, parallel-group 139 patients w/ AIDS-related anorexia - 88 evaluable patients Duration - 6 weeks	Dronabinol 2.5 mg bid or placebo Reduced dose to 2.5 mg qd if not tolerated	1. Increased in appetite Dronabinol 38% Placebo 8% (p=0.015) 2. Mean weight change Dronabinol +0.1 kg Placebo –0.4 kg (p=0.14)	43% dronabinol vs. 13% placebo w/ AE Most common AE: euphoria, dizziness, thinking abnormalities, somnolence 17 patients required dose reduction to 2.5 mg qd; 6 patients withdrew due to AE
Beal JE[6] 1997	MC, open-label follow-up 94 patients from previous 6-wk, controlled trial of dronabinol; 46 previously received dronabinol Duration - 12 months	Dronabinol 2.5 mg qd – 20 mg qd	93 evaluable patients; 22 patients completed 12-mth (mean 5.8 mth) 1. Increase in appetite 27.3% to 69.9% 2. Mean weight change at 12 months: -0.8 kg to +1.4 kg	41 patients had at least one treatment-related AE 19 patients withdrew due to AE
Struwe M[7] 1993	RCT, DB, placebo-controlled, crossover 12 men w/ HIV Duration – 12 weeks	Dronabinol 5 mg bid x 5 weeks 2 weeks washout placebo x 5 weeks 5 completed & evaluable patients	1. Median weight change Dronabinol +0.5 kg (0.2 to 0.98 kg) Placebo –0.7kg (-1.1 kg to 0.9 kg) (p=0.13) 2. Median appetite score* Dronabinol –5.7 Placebo –19.6 (p=0.14)	2 patients withdrew due to AE

MC=multicenter, DB=double-blinded, AE=adverse event, RCT=randomized clinical trial *lower or negative value represents increase in appetite

5-Hydroxytryptamine$_3$ (5-HT$_3$) Receptor Antagonists

The 5-HT$_3$ receptor antagonists are selective serotonin inhibitors, competitively inhibiting the binding of serotonin to 5-HT$_3$ receptor sites. Their antiemetic effects are postulated to be due to the blockade of these receptor sites, located on the nerve terminals of the vagus in the periphery and in the chemoreceptor trigger zone of the area postrema centrally. These drugs have little or no affinity for other 5-HT receptors; alpha or beta-adrenergic; dopaminergic; or histamine receptors.[22-24] Although they are metabolized through the cytochrome P-450 enzyme system, they do not induce or inhibit the P-450 enzymes. No major drug-drug interactions have been reported in the post-marketing period.[22-24]

Generally, these drugs are safe and well tolerated. Their adverse effect profiles are similar. All three drugs have demonstrated cardiac effects of asymptomatic EKG changes in clinical trials. Dolasetron may cause prolongation of the QTc interval while granisetron and ondansetron may cause arrhythmia such as sinus bradycardia. Common adverse effects are headache, dizziness, constipation, abdominal pain and transient AST elevation.[22-24]

Ondansetron, granisetron and dolasetron have essentially equivalent antiemetic activity and safety profile based on several large, randomized controlled clinical trials.[25,26] Clinical guidelines developed in 1999 from the American Society of Health System Pharmacists (ASHP) and the American Society of Clinical Oncology (ASCO) concur that the use of these agents as antiemetics are cost-effective in the following clinical scenarios: 1) prevention of moderately to highly emetogenic chemotherapy-induced nausea/vomiting, and 2) prevention of radiation-induced nausea/vomiting. However, there is lack of evidence to support the use of 5-HT$_3$ receptor antagonists 24 hours beyond the last dose of radiation. Furthermore, metoclopramide is considered first-line over the 5-HT$_3$ receptor antagonists in combination with corticosteroids for prevention of delayed chemotherapy-induced nausea/vomiting due to better efficacy and cost-effectiveness.[27-31] Similarly, 5-HT$_3$ receptor antagonists are effective in the treatment of breakthrough chemotherapy-induced nausea and vomiting, but their superiority over more traditional, less expensive agents (e.g. metoclopramide, prochlorperazine, etc.) has not been demonstrated.[25,26]

Approximately 30% of patients will develop post-operative nausea and vomiting (PONV) during the first 24 hours after surgery.[25] This overall incidence of PONV can vary considerably depending on preoperative patient characteristics, factors related to operative procedures and anesthesia, and postoperative management.[25,32] The decision to provide prophylactic therapy can be based on the presence of risk factors for nausea and vomiting and the potential for serious sequelae from vomiting, such as aspiration, esophageal rupture, or wound dehiscence.[25,32] Because of the lack of clear benefit of 5-HT$_3$ receptor antagonists and due to cost, traditional antiemetics (i.e. metoclopramide, prochlorperazine) are considered as first line agents.[27] However, if side effect profile is of concern, then oral ondansetron and dolasetron, or intravenous granisetron may be considered as alternatives. Table 3 provides a summary of clinical studies.

A review of the prescription claims for the last half of 2002 for OMAP fee-for-service patients reveals that 5-HT$_3$ receptor antagonists are used for an average of 9 days per claim at an average cost of $565. The total cost of 5-HT$_3$ receptor antagonists during the same time period was $679,670 (n=430 patients).

Summary

The rationale for implementing prior authorization of dronabinol and a weekly quantity limit of 9 dosage units for 5-HT$_3$ receptor antagonists is to promote cost-effective drug prescribing. Based on the review of clinical evidence, dronabinol use for AIDS-related anorexia provides inconsistent effect on weight gain with no improvement in clinical outcomes. Dronabinol has demonstrated only modest effect for chemotherapy-induced nausea and vomiting and was associated with significant, intolerable neuropsychiatric adverse effects. Therefore, dronabinol use for these approved indications should be considered as the last resort only. The 5-HT$_3$ receptor antagonists are considered as first-line antiemetics for prevention and treatment of chemotherapy-induced nausea and vomiting. However, for delayed chemotherapy-induced nausea and vomiting, these agents in combination with corticosteroids have not been shown to be better than metoclopramide in combination with corticosteroids or corticosteroid monotherapy. Finally, the lack of clear benefit of 5-HT$_3$ receptor antagonists over traditional antiemetics for prophylactic PONV makes traditional antiemetics first line agents due to cost.

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Complete reference list is posted to the DUR Board website at: http://pharmacy.oregonstate.edu/drug_policy/newsletter_email.html.

Table 3 - Summary of 5HT$_3$ Receptor Antagonists PONV Clinical Trials

Author	Study Design	Treatment Arm	Efficacy	Safety
Jokela R. et al [33] 2002	RCT, DB 179 female patients Thyroid or parathyroid surgery Gen. anesthesia	a. OND 16mg PO b. TRO 5 mg PO c. MET 10 mg PO Given 1 hr prior to surgery Post-op analgesics provided PRN	1. Incidence of no PONV (0-24hr) OND: 32% TRO: 42% MET: 25% p=>0.05 among therapy groups 2. Incidence of need for rescue antiemetics OND: 64% TRO: 50% MET: 71% p=0.024 between OND / MET	OND / TRO / MET Headache 63% / 63% / 54% Dizziness 45% / 28% / 36% Pruritis 18% / 13% / 10% p=>0.05 among therapy groups
Wilson E. et al [34] 2001	RCT 232 patients Laparoscopic cholecystectomy Gen. anesthesia	a. OND 4 mg IV b. MET 10 mg IV c. PBO Given prior to induction of anesthesia	1. PACU OR DAY SURGERY: Incidence of N/V OND 45% MET 33% PBO 46% p>0.05 between OND / MET Incidence of need for rescue antiemetics OND 38% MET 26% PBO 39% p>0.05 between OND / MET 2. FOLLOW-UP AT 24 HRS: Incidence of N/V OND 21% MET 24% PBO 32% p>0.05 between OND / MET	AE not reported
Thomas R et al[35] 2001	RCT 177 female patients Day case GYN surgery Gen. Anesthesia	1. OND 4 mg IV 2. DEX 8 mg IV 3. OND 4 mg IV + DEX 8 mg IV Given immediately after induction of anesthesia	Overall incidence of subjects classified failures* OND 42.4% DEX 48.3% Combo 34.5% *incidence of nausea, retching, vomiting, use of rescue antiemetics (0-24hr)	Common AEs: fatigue, dizziness, headache Incidence of AEs among grps NS

PONV=postoperative nausea/vomiting, RCT=randomized clinical trials, DB=double-blinded, AE=adverse event, OND=ondansetron, MET=metoclopramide, TRO=Tropisetron, DEX=dexamethasone, PBO=Placebo, PACU=postanesthesia care unit, N/V=nausea and vomiting, NS=not statistically significant

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