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<u>INDEX</u>	
Methadone Counter-Signature Extension	2
Budesonide Turbuhaler Interpretation	2
Loxapine Subcutaneous Administration	2
Oral Meperidine Interchange to Oral Morphine	3
Sumatriptan cross-sensitivity to sulfa drugs	4
SSRI Abrupt Withdrawal Syndrome	4

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CHANGES TO FORMULARY

Additions

1. **Apraclonidine 0.5% ophthalmic drops (Iopidine®)**
 - ocular alpha-adrenergic agent used to prevent increases in intraocular pressure following laser surgery
 - cost: \$11.27/5mL bottle

2. **All-trans Retinoic Acid 10mg capsule (Vesanoid®)**
 - indicated in the therapy (remission induction) of Acute Promyelocytic Leukemia (APL)
 - restricted to BMT/Leukemia program hematologists
 - cost ~\$80.00/day

3. **Diltiazem controlled delivery 120mg, 180mg, 240mg, 300mg capsules (Cardizem CD®)**
 - once daily dosage form of diltiazem
 - cost comparison:
Diltiazem CD®180mg daily \$0.80
Diltiazem SR® 90mg bid \$0.88
Diltiazem 60mg tid \$0.60

Deletions**1. Cortisone Acetate 50mg/mL Injection**

Alternatives: Methylprednisolone acetate, Triamcinolone

2. Meperidine tablets (Demerol®)

Alternatives: Morphine, Anileridine
see Policy & Procedures pg 3

UPDATED POLICY AND PROCEDURES**1. Diazepam in Emulsion (Diazemuls®) Administration**

The administration of Diazemuls® has been extended for use to include the Radiology Department.

2. Midazolam (Versed®) Administration

The administration of midazolam has been extended for use to include the Spinal Cord ICU.

3. Methadone Counter-signature

The authorizing physician's counter-signature to a verbal authorization of methadone has been extended from 24 hours to 72 hours.

4. "d" = ? "days" or "doses"

e.g. "Cefazolin 1g q8h IV x 3 d".

The abbreviation "d" is not acceptable as this letter can be interpreted as days or doses. Please specify in full the intended duration of therapy.

5. Correction from Volume 2, #3 Budesonide turbuhaler (Pulmicort®) Prescription Interpretation Protocol

Budesonide turbuhaler is available in three strengths: 100mcg/dose, 200mcg/dose and 400mcg/dose. If this drug is ordered without a strength indicated, the 200mcg/dose strength will be dispensed. Please note that terbutaline (Bricanyl®) turbuhaler is only available in a 500mcg/dose strength.

6. Loxapine Subcutaneous

The administration of loxapine by the subcutaneous (SC) route has been approved for administration by qualified personnel in all areas of the hospital. There is no compatibility information regarding loxapine, and thus loxapine cannot be mixed with any other drug in syringe. As with all SC medications where compatibility is not established, a separate SC butterfly must be used for this drug to prevent mixing with other medications.

6. Oral Meperidine Interchange to Oral Morphine

Effective September 18, 1995, all orders for oral meperidine will be automatically interchanged to an equivalent dose of oral morphine at the same interval.¹ Meperidine is less potent than morphine; an equianalgesic dose for morphine 20-30mg is meperidine 300mg (Table 1).²

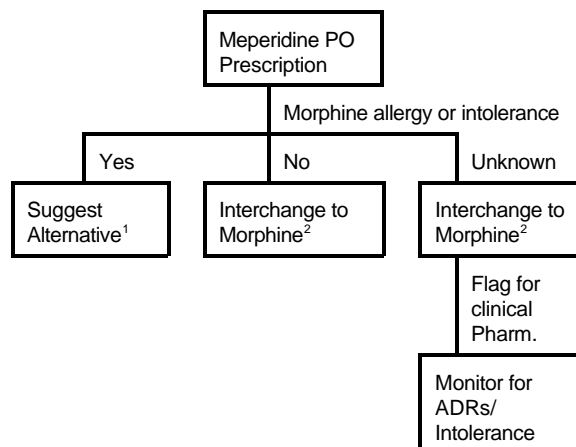
Table 1. Oral Conversion of Meperidine to Morphine

Oral Meperidine Dose	Oral Morphine Equivalent Dose
25 mg	2.5 mg
50 mg	5.0 mg
75 mg	7.5 mg
100 mg	10 mg

Oral meperidine offers no advantage over other formulary narcotic agents.³ Meperidine has a shorter duration of analgesic action than morphine (2-3 hrs versus 3-5 hrs, respectively) and, therefore, requires more frequent dosage administration for pain relief. As the bioavailability of oral meperidine is less than 50%, typical post-operative orders written for meperidine iv/po (same dose) will result in patients receiving inadequate oral meperidine doses. Meperidine is also metabolized to an active metabolite, normeperidine, which has convulsant effects.⁴ This metabolite is renally excreted and can accumulate with multiple doses in patients with renal failure or in the elderly resulting in CNS excitation and convulsions.

All oral meperidine orders will be interchanged to an equivalent oral morphine dose at the same interval if there is no known morphine allergy or intolerance documented on the allergy form (Figure 1). If a patient has a known morphine allergy or intolerance, a suitable alternative needs to be selected. Formulary alternatives include meperidine via im/iv/sc route or oral anileridine. Pharmacy will contact the physician for a new order in patients with an allergy or intolerance to morphine. This policy has been recommended by

the Drugs & Therapeutics Committee and approved by the Medical Advisory Committee (March 1995).

Figure 1. Meperidine Interchange Algorithm

¹ alternatives: meperidine im/iv/sc, anileridine po

² oral morphine dose = 10% meperidine dose

References

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QUESTIONS AND ANSWERS

Question 1.

Is there a cross-sensitivity between Sumatriptan (Imitrex®) and sulfonamides?

Sumatriptan contains a sulphonamide group in its chemical structure and as such may display cross-sensitivity to other sulphonamide compounds. There have been reports of patients with known hypersensitivities to sulphonamides exhibiting an allergic reaction following sumatriptan administration ranging from

rash to anaphylaxis.

Thus caution should be exercised when using sumatriptan in patients with a history of sulpha allergy, especially in those with known anaphylactic reactions.

Question 2.

Is there an abrupt withdrawal syndrome with Selective Serotonin Reuptake Inhibitors?

Answer: Selective Serotonin Reuptake Inhibitors (SSRI) are a relatively new group of antidepressants which have gained popularity because of a low incidence of side effects in comparison to older antidepressants. SSRIs that are marketed in Canada include fluoxetine (Prozac[®]), fluvoxamine (Luvox[®]), paroxetine (Paxil[®]), and sertraline (Zoloft[®]); the former three drugs are formulary at VHHSC.

SSRIs bind specifically to the presynaptic serotonin reuptake carrier in the central nervous system causing accumulation of serotonin (5HT) in the synaptic cleft¹. The increase in serotonin is thought to be responsible for the efficacy of SSRIs in the treatment of depression, obsessive compulsive disorder, and panic disorder.

The SSRIs are metabolized by the liver and have relatively long half-lives (Table 2).¹⁻³ Fluoxetine is the only SSRI which has a fully active metabolite with a half-life of seven days. The most common adverse reactions experienced with SSRIs are gastrointestinal disturbances (nausea, decreased appetite, diarrhea) and central nervous system disturbances

(insomnia, sedation, anxiety, headache, tremor).

Table 2. Comparison of SSRI half-lives

SSRI	Half-life (hours)	Metabolite
Fluoxetine (Prozac [®])	46-84	norfluoxetine ^a
Fluvoxamine (Luvox [®])	17-22	none
Paroxetine (Paxil [®])	21-24	none
Sertraline (Zoloft [®])	26	desmethylsertraline ^b (partially active)

^a half-life of norfluoxetine is 7 days

^b half-life of desmethylsertraline is 2.5-4 days

Evidence exists in the literature that an abrupt withdrawal syndrome can occur with fluvoxamine, paroxetine, and sertraline.

Black *et al* performed an unblinded withdrawal of fourteen patients with panic disorder treated with fluvoxamine 100 to 300mg daily for eight months⁴. By day five, 78.6% of patients experienced dizziness and incoordination, 35.7% reported a headache, and 28.6% experienced nausea and irritation. All symptoms peaked on day five and decreased significantly by day fourteen. Mallya *et al* retrospectively assessed seventeen patients who were part of a fluvoxamine trial for obsessive compulsive disorder.⁵ Patients received fluvoxamine in doses of 100 to 300mg for 12 to 15 months; immediately after discontinuation, four (28%) developed dizziness. Two of the four patients also developed nausea, headache, confusion, memory problems, decreased energy and weakness.

Paroxetine has also been reported to cause an abrupt withdrawal syndrome. Keuthen *et al* noted unexpected withdrawal symptoms in 5/13 (38.5%) of patients enrolled in a clinical trial who received paroxetine doses ranging from 20mg to 60mg for three weeks to five months.⁶ Symptoms of lightheadedness and dizziness occurred within one to three days of discontinuing paroxetine and continued for up to fourteen days. There are three case reports of patients with obsessive compulsive disorder treated with paroxetine 60mg daily for 12 weeks.⁷ Paroxetine was tapered over seven days; however three days after discontinuation, patients experienced vertigo, gait instability, nausea, emesis, and diarrhea which resolved within one week. Similarly, another case report describes a patient experiencing anorexia, nausea, diarrhea and chills three days after paroxetine 10mg daily was discontinued.⁸ These symptoms continued for three weeks. The manufacturer of paroxetine has on file a study of 222 patients receiving paroxetine for 6 weeks after which the drug was abruptly discontinued.⁹ Fifteen percent of patients experienced withdrawal symptoms as follows: dizziness (7%), depression (5%), paresthesias (3%), central nervous system stimulation (2%), gastrointestinal complaints (2%), abnormal dreams (2%).

There is only one case report of sertraline causing abrupt withdrawal syndrome.¹⁰ Louie *et al* describe a woman who was treated with sertraline 150mg daily for four weeks which was then tapered to 100mg daily for five weeks.¹⁰ Within two days of sertraline discontinuation, the

patient developed fatigue, severe abdominal cramps and distension, insomnia, increased dreaming and flu-like symptoms consisting of generalized aching, chills without fever, headache and sore eyes. This syndrome remitted upon restarting sertraline 25mg/day. A slower tapering schedule was then initiated over 14 weeks. Interestingly, the patient reported mild withdrawal symptoms, similar to the above mentioned symptoms, one and a half days after each dose reduction.

The mechanism of the SSRI withdrawal reaction has not yet been elucidated. Possible theories are that the withdrawal syndrome may be cholinergically or serotonergically mediated.^{6,7} The cholinergic theory relates the SSRI withdrawal syndrome to one with similar symptoms that may occur with tricyclic antidepressants (TCA).^{6,7} TCA withdrawal syndrome is due to cholinergic rebound and the SSRIs have activity at muscarinic cholinergic receptors. The second possible explanation for the withdrawal syndrome is through down-regulation of 5HT receptors.⁷ Interestingly, fluoxetine does not cause an abrupt withdrawal syndrome, possibly to the long half-life of its active metabolite. The partially active sertraline metabolite may also contribute to the infrequent reports of abrupt withdrawal with this drug.

In conclusion, abrupt withdrawal syndrome can occur even with low doses of fluvoxamine, paroxetine and sertraline. The syndrome has been reported in up to 78.6% of patients discontinued off fluvoxamine, 39% discontinued off

paroxetine and once in a patient discontinued off sertraline. Symptoms develop from one to five days after discontinuation of medication and most commonly consist of dizziness, incoordination, and gait instability. Nausea, headache, weakness and confusion occur less frequently. Symptoms usually resolve within two weeks. Given the high rate of occurrence, it is recommended that patients who are to be discontinued from fluvoxamine, paroxetine and sertraline should be informed of the potential withdrawal syndrome and carefully monitored for symptoms of withdrawal while doses are slowly tapered over several weeks.

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