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Fluphenazine: Product Unavailability and Potential Conversions to Alternative Long-Acting Injection Preparations

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Introduction

Long-acting injectable antipsychotics, also referred to as depot injections, offer clinicians several advantages over their respective oral formulations. Perhaps the most significant advantage is that long-acting injections address issues of medication non-compliance. Healthcare team members can easily identify patients who refuse or fail to receive their depot injection for any reason, and can take appropriate action to ensure continuity of treatment.

Another advantage relates to the nature of their controlled release profile over a defined period of time following each injection. As a consequence, plasma drug concentrations do not exhibit the daily fluctuations between peaks and troughs that occur with oral formulations. This may explain why extrapyramidal symptoms are less frequent with depot formulations of antipsychotics¹.

Lastly, regular injections offer the opportunity for increased monitoring of symptomatic response and emergence of drug-related adverse effects as patients

come for their regularly scheduled injections.

In Canada, there are six antipsychotics available as long-acting injections: fluphenazine, flupenthixol, zuclopenthixol, pipotiazine, haloperidol, and risperidone. Recently, the supply of fluphenazine decanoate (Modecate[®]) 25 mg/mL and 100mg/mL vials has been unavailable from all suppliers. The manufacturers suggest that the supply of the medication may return in April 2009. In the interim, some patients may no longer have the drug available for treatment. It is recommended that all patients on fluphenazine decanoate have an alternative antipsychotic depot therapy plan in place.

The following tables compare available antipsychotic long-acting injections on the basis of dosing and pharmacokinetics (Table 1), relative neurotransmitter-receptor occupancy rates (Table 2), and frequency of drug-related adverse effects (Table 3).

Discussion

Although there are notable differences among antipsychotic depots with respect to receptor occupancy rates and frequency of adverse reactions, there also exists significant overlap. Consequently, clinicians will face uncertainty when deciding which alternative depot best mimics fluphenazine decanoate.

If a therapeutic decision were to be made based on

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Table 1: Antipsychotic depots available in Canada

Antipsychotic	<i>Fluphenazine Decanoate (Modecate Concentrate®)</i>	<i>Flupenthixol Decanoate (Fluanxol Depot®)</i>	<i>Zuclopenthixol Decanoate (Clopixol Depot®)</i>	<i>Pipotiazine Palmitate (Piportil L4®)</i>	<i>Haloperidol Decanoate (Haldol LA®)</i>	<i>Risperidone Microspheres (Risperdal Consta®)</i>
Drug Class ²	Piperazine Phenothiazine	Thioxanthene	Thioxanthene	Piperidine Phenothiazine	Butyrophenone	Benzisoxazole
Vehicle ^{1,3,4}	Sesame oil	Vegetable oil	Coconut oil	Sesame oil	Sesame oil	Water-based polymer
Clinical Equivalency ³	25 mg q2w	40 mg q2w	200 mg q2w	50 mg q4w	100 mg q4w	Undetermined at this time
Dose Comparable to CPZ 100 mg daily ¹	0.3 mg/day 6.25 mg q3w	1.8 mg/day 50 mg q4w	4.3 mg/day 60 mg q2w	0.85 mg/day 24 mg q4w	0.7 mg/day 20 mg q4w	1.8 mg/day 25 mg q2w
Test Dose ³	12.5 (6.25 in elderly)	20	100	25	50	N/A
Dose Range ¹	12.5-100 mg q2-4w	20-100 mg q2-4w	150-300 mg q2-4w	50-250 mg q4w	50-300 mg q4w	25-50 mg q2w
Tmax ^{1,3}	8-24 h (first peak) 8-12 d	3-7 d	3-7 d	4 d	3-9 d	4-6 w
T ½ ^{1,3}	9 d (single injection) 102 d (multiple dosing)	8 d (single injection) 17 d (multiple dosing)	19 d	15 d	18-21 d	3-6 d (following microsphere erosion)
Cost per Month ²	\$15	\$25-40	\$35	\$60	\$20	\$350-650
Supplied ⁴	100 mg/mL (1 mL ampoules)	20 mg /mL (2 mL ampoules; 10 mL vials) 100 mg/mL (2 mL vials)	200 mg/mL (1 mL ampoules; 10 mL vials)	25 mg/mL (1 mL ampoules) 50mg/mL (1 and 2 mL ampoules)	50 mg/mL (5 mL vials) 100 mg/mL (1 mL ampoules; 5 mL vials)	12.5/25/37.5/50 mg vials with prefilled syringes (20 G 2") containing 2 mL diluent
Storage ⁴	Room temp; protect from light	15-25°C; protect from light	15-25°C; protect from light	15-30°C; protect from light	15-30°C; protect from light	2-8°C (can store at room temp up to 7 days); protect from light

Table 2: Effects of available antipsychotic depots on neurotransmitters/ receptors¹

Antipsychotic	<i>Fluphenazine Decanoate (Modecate Concentrate®)</i>	<i>Flupenthixol Decanoate (Fluanxol Depot®)</i>	<i>Zuclopenthixol Decanoate (Clopixol Depot®)</i>	<i>Pipotiazine Palmitate (Piportil L4®)</i>	<i>Haloperidol Decanoate (Haldol LA®)</i>	<i>Risperidone Microspheres (Risperdal Consta®)</i>
Blockade D1	+++	++++	+++++	?	+++	+++
Blockade D2	+++++	++++	+++++	+++++	+++++	+++++
Blockade D3	+++++	++++	?	+++++	++++	++
Blockade D4	++++	?	++++	?	+++++	+++++
Blockade H1	+++	+++	+++	?	+	+++
Blockade M1	+	+++	++	?	+	±
Blockade α1	+++	+++	++++	?	+++	++++
Blockade α2	+	++	++	?	+	++++
Blockade 5HT1A	+	+	+	++	+	++
Blockade 5HT2A	++++	++++	++++	+++	+++	+++++
DA reuptake	+	++	++	?	+	+

K_i values (nM): - = > 100,000; ± = 10,000-100,000; + = 1,000-10,000; +++ = 10-100, ++ = 1-10, +++++ = 0.1-1

Table 3: Frequency (%) of adverse reactions to antipsychotics at therapeutic doses¹

Antipsychotic	<i>Fluphenazine Decanoate (Modecate Concentrate®)</i>	<i>Flupenthixol Decanoate (Fluanxol Depot®)</i>	<i>Zuclopenthixol Decanoate (Clopixol Depot®)</i>	<i>Pipotiazine Palmitate (Piportil L4®)</i>	<i>Haloperidol Decanoate (Haldol LA®)</i>	<i>Risperidone Microspheres (Risperdal Consta®)</i>
Drowsiness/Sedation	> 2	> 2	> 30	> 10	> 2	> 10 ^d
Insomnia/Agitation	> 2	< 2	> 10	< 2	> 10	> 10
Parkinsonism	> 30	> 30	> 30	> 30	> 30	> 10 ^a
Akathisia	> 30	> 30	> 10	> 10	> 30	> 10 ^a
Dystonia	> 10	> 10	> 10	< 2	> 30	< 2 ^a
Orthostatic Hypotension	> 2	> 2	> 2	> 2	> 2	> 30 ^d
Tachycardia	> 10	> 2	> 2	> 2	< 2	> 10
EKG Abnormalities	> 2	> 2	< 2	> 2	< 2	< 2
QTc Prolongation (>450 ms)	> 2 ^a	< 2	< 2	> 2	< 2 ^a	< 2
Anticholinergic Effects	> 2	> 10	> 10 ^c	> 10	> 2	> 2
Sexual Dysfunction	> 2 ^b	< 2 ^b	> 2 ^b	> 10	> 2 ^b	> 10 ^b
Galactorrhea	> 10	-	-	> 30	< 2	> 2
Weight Gain	> 30	> 10	> 10	> 10	> 10	> 10
Photosensitivity	< 2	< 2	< 2	> 2	< 2	> 2
Rashes	< 2	> 2	< 2	> 2	< 2	< 2
Pigmentation	-	-	< 2	-	< 2	< 2
Lenticular Pigmentation	< 2	< 2	< 2	> 2	< 2	-
Pigmentary Retinopathy	-	< 2	-	-	-	-
Blood Dyscrasias	< 2	< 2	< 2	< 2	< 2	< 2
Hepatic Disorders	< 2	< 2	< 2	< 2	< 2	< 2
Seizures	< 2	< 2	< 2	< 2	< 2	< 2

a: higher doses pose more risk; b: priapism reported; c: sialorrhea reported; d: at start of therapy or rapid dose increase

the information derived from the tables alone, there often is no “right answer”. As with all therapeutic decision-making processes, it is important to consider the variables that each individual patient presents with: past medical and psychiatric history, current medications, past response to antipsychotics including favourable and adverse effects, current response to fluphenazine decanoate and other co-prescribed antipsychotics if applicable, allergy status, and cost concerns.

When both the pharmacology of the antipsychotics and the patient-specific factors are considered, weighing of advantages and disadvantages of

each alternative depot becomes clearer. For instance, patients with histories of developing EPS with haloperidol would benefit from trials of alternative depot agents first. Patients who already experience significant anticholinergic side effects with fluphenazine would be at increased risk with flupenthixol and zuclopenthixol. Patients who exhibit marked daytime sedation would be at increased risk with zuclopenthixol. The risperidone titration process is long, requiring oral medication to continue for a minimum of three weeks following the first injection.

When switching from depot to depot, it is acceptable practice to administer the new drug at the next

scheduled injection date. Although the clinical equivalent doses mentioned above can be used as a guideline for dose calculations, it is important to note that the elimination half-life of fluphenazine decanoate increases from eight days to over 102 days with multiple dosing. Thus, depending on the acuity of the patient's clinical presentation, age, and presence of co-morbid risk factors, it may be advisable to start at a lower than equivalent dose.

Of equal importance to selecting an appropriate alternative depot to fluphenazine decanoate is monitoring of patient response. Baseline rating scales of psychiatric symptoms, drug-related side effects and movement assessments are recommended for all patients. With the exception of risperidone long-acting injection, peak plasma levels of depot preparations are reached within seven days. Following conversion from fluphenazine depot, monitoring of patients should occur weekly for the first month, and then at each scheduled injection appointment.

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