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1. Introduction

The purposes of this paper are: (1) to identify some demographic characteristics and general patterns of utilisation associated with patients who receive atypical antipsychotic medications (APMs), and (2) identify if there is evidence of expanded atypical APM use.

This document summarises data pertaining to BC residents who received at least one filled prescription for one or more of the following five atypical APMs: s.15

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The data are from the time period, February 1, 1994 through June 15, 2009. The data are mostly grouped by fiscal year. Some of the tables and charts are limited to the most recent complete fiscal year, which as of June 2009, is 2007/2008, some data are grouped by the month in which patients received prescriptions, and death-related data are grouped by calendar year.

2. Background

Antipsychotic medications are psychoactive drugs used, for the most part, to treat psychoses associated with mental disorders, such as schizophrenia. The first atypical APM, clozapine was developed in the 1950s, and introduced into clinical practice throughout the USA, UK, and Canada. During the 1990s, clozapine was re-introduced as an atypical APM and olanzapine, risperidone and quetiapine were also introduced. In the post-2000 period, ziprasidone and aripiprazole were introduced in Canada (see ***Table 1*** below).

Table 1: atypical APMs in Canada, routes of administration, dosage, and cost (source: Gardner, et al., 2005:174)

Antipsychotic agent / Year Marketed in Canada	Forms Available	Usual target doses, mg/d	Monthly cost, $ *
Aripiprazole†	T	10–30	370–740†
Clozapine (1991)	T	300–450	310–470
Olanzapine (1996)	T, W, IMS	10–20	265–515
Quetiapine (1998)	T	300–600	145–275
Risperidone (1993)	T, L	2–6	100–250
Risperidone depot (2004)	IMD	25–50‡	640–1250
Ziprasidone§	T, IMS	80–160	–

Notes:

T = tablet, W = rapid-dissolving wafer, IMS = short-acting intramuscular injection,
L = oral liquid, IMD = long-acting intramuscular depot, C = capsule.
*Prescription retail price in Canadian dollars rounded to closest $5; includes $10 pharmacy professional fee (source: Shoppers Drug Mart, Halifax, NS, May 2005).
†Available only through special access in Canada.
‡Risperidone and flupenthixol depot formulations are usually administered every 2 weeks.
§Available in Canada, as of 2006.

In Canada, the most recent atypical APM medication is paliperidone (drug product Invega) which has been approved for use by Health Canada in 2007 (see http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/phase1-decision/drug-med/nd_ad_2008_invega_108748-eng.php). In 2005, olanzapine, quetiapine fumarate and risperidone comprised three of the top ten BC PharmaCare drugs, based on reimbursement; in 2008, olanzapine and quetiapine fumarate comprised two of the "top ten" drugs based on reimbursement (see BC Pharmacare annual reports).

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Figure 1: some highlights in the chronology of antipsychotic drug development

1856	Perkin synthesized mauve;
1896	Caro synthesized methylene blue, a phenothiazine derivative;
1878	Berthsen synthesized phenothiazine;
1891	Paul Ehrlich observed that methylene blue helped patients with malaria;
1944	Gilman et ai. found a lack of antimalarial effect for phenothiazines;
1950	Laborit and Huguenard used promethazine in anesthesia;
1951	Laborit and Huguenard produced artificial hibernation with chlorpromazine;
1952	Hamon et al. and Delay et al. showed chlorpromazine's antipsychotic effect;
1953	Staihelin and Kielholz confirmed chlorpromazine's antipsychotic efficacy in Germany;
1954	Chlorpromazine marketed in the US by Smith, Kline and French Laboratories as an anti-vomiting agent; Lehmann and Hanrahan confirmed chlorpromazine's antipsychotic efficacy in Montreal; Winkelman confirmed chlorpromazine's antipsychotic efficacy in the USA; Steck described EPS induced by chlorpromazine and reserpine;
1958	Haloperidol introduced to the market;
1959	Sigwald et al. describe tardive dyskinesia;
1960	Veterans Administration Collaborative Study reported its double-blind results for antipsychotic agents;
1961	Ayd reported EPS incidence of 38.9%;
1962	Carlsson and Lindquist demonstrated dopaminergic blocking effect of antipsychotic drugs;
1975	Molindone introduced to the US market;
1990	Clozapine approved bythe FDA;
1994	Risperidone approved by the FDA;
1996	Olanzapine approved by the FDA;
1997	Quetiapine approved by the FDA.

A point that is noted in Shen's analysis is that most of the activities surrounding the development of antipsychotic medications have been "closely" financed by pharmaceutical companies; currently, the resources for antipsychotic development "still originate from private industrial support rather than from public research organisations" (Shen, 1999:411-12).

Over the past ten years or so, the demography of atypical APM patients has changed -- due, in part, to "off-label" use. Some research indicates that young and youth-age patients (particularly children with behavioural and developmental problems) and patients who are older than age 65 (particularly elderly patients who live in nursing homes with behavioural symptoms of dementia) comprise an increasing proportion of atypical APM patients (Crystal, et al., 2009). According to Leslie, et al., (2009) some of the most common off-label uses of atypical APMs are treatment of agitation in dementia and treatment of depression, obsessive compulsive disorder, post traumatic stress disorder, personality disorders, Tourette's syndrome, and autism -- in spite of "very little strong evidence in the literature that these drugs were effective in treating these disorders" (Leslie, et al., 2009:1175). Second-generation APMs have, for the most part,

replaced older phenothiazine, thioxanthene and butyrophenone neuroleptics in clinical practice (see Gardner, et al., 2005:1703).

Each antipsychotic medication has a unique side effect profile. The first generation of antipsychotic drugs were linked to adverse effects such as obesity, agranulocytosis, tardive dyskinesia, tardive akathisia, tardive psychoses, and tardive dysphrenia, and sexual dysfunctions (see, for example, Wright and O'Flaherty, 2003:24-37). Atypical APMs, however, are also linked to adverse effects including impaired cognition, extra pyramidal symptoms, weight gain (e.g., Varley and McClellan, 2009:1811-1812), hyperlipidemia and hyperglycemia, increased risk of polymorphic ventricular tachycardia, agranulocytosis and sudden cardiac death (see Bagnall, et al., 2003). Based on a considerable body of research, the claim that atypical APMs entail less risk of adverse effects than conventional antipsychotic drugs lacks validity. Rather, risks appear to be of a different kind, i.e., qualitative, rather than "more" or "less," i.e., quantitative. As pointed out by Gardener, et al., (2005:1706-7) the much promoted advantage of reduced risk of extrapyramidal symptoms associated with modern antipsychotic drugs needs to be balanced against other adverse effects.

Gardner, et al., (2005) review the pharmacology, therapeutic effectiveness, tolerability, adverse effects and costs of atypical APMs (versus conventional antipsychotic drugs). The authors report that minor differences exist between agents in clinical effectiveness and tolerability, and that because of growing concerns about potential adverse long-term health consequences of some modern agents, "it is reasonable to consider both older and newer drugs for clinical use, and it is important to inform patients of relative benefits, risks and costs of specific choices" (Gardner, et al., 2005:1709).

From the literature relating to atypical APMs, the increased utilisation and the adverse effects associated with the utilisation of the medication are two central issues. This draft document focuses on the former issue: atypical APM patients' characteristics and associated patterns of utilisation using data from British Columbia.

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