Modern antipsychotic drugs: a critical overview

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Abstract

CONVENTIONAL ANTIPSYCHOTIC DRUGS, used for a half century to treat a range of major psychiatric disorders, are being replaced in clinical practice by modern "atypical" antipsychotics, including aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone among others. As a class, the newer drugs have been promoted as being broadly clinically superior, but the evidence for this is problematic. In this brief critical overview, we consider the pharmacology, therapeutic effectiveness, tolerability, adverse effects and costs of individual modern agents versus older antipsychotic drugs. Because of typically minor differences between agents in clinical effectiveness and tolerability, and 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.

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Antipsychotic drugs are useful for treating a range of severe psychiatric disorders. Applications include the short-term treatment of acute psychotic, manic and psychotic-depressive disorders as well as agitated states in delirium and dementia and the long-term treatment of chronic psychotic disorders including schizophrenia, schizoaffective disorder and delusional disorders. Newer, "second-generation" antipsychotic drugs have largely replaced older phenothiazine, thioxanthene and butyrophenone neuroleptics in clinical practice (Table 1).[1,2] The development of modern antipsychotic drugs was stimulated by a landmark 1988 study that showed clozapine to be superior in efficacy to chlorpromazine in schizophrenia patients resistant to high doses of haloperidol and to have none of the adverse neurologic effects typical of older antipsychotic agents.[3] Clozapine was considered "atypical" in having a very low risk of adverse extrapyramidal symptoms. This term has since been applied broadly and uncritically to antipsychotic drugs marketed in the past decade, despite their striking chemical, pharmacologic and clinical heterogeneity.[4] In this overview we consider the neuropharmacology, efficacy and adverse effects of conventional antipsychotics and specific modern antipsychotic drugs.

Neuropharmacology

The venerable hypothesis that schizophrenia is caused by increased cerebral activity of the neurotransmitter dopamine was based primarily on the finding that dopamine agonists produced or worsened psychosis and that antagonists were clinically effective against psychotic and manic symptoms.[5] Blocking dopamine D_2 receptors may be a critical or even sufficient neuropharmacologic action of most clinically effective antipsychotic drugs, especially against hallucinations and delusions, but it is not necessarily the only mechanism for antipsychotic activity. Moreover, this activity, and subsequent pharmacocentric and circular speculations about altered dopaminergic function, have not led to a better understanding of the pathophysiology or causes of the several still idiopathic psychotic disorders, nor have they provided a non-empirical, theoretical basis for the design or discovery of improved treatments for psychotic disorders.

The neuropharmacodynamics of specific modern antipsychotic drugs vary greatly, with little evidence for a unifying theory of antipsychotic activity or of drug design (Table 2). Clozapine in particular is complex: it binds loosely and transiently to D_2 receptors and interacts at dopamine (D_1, D_3 and D_4), histamine (H_1), acetylcholine muscarinic (M_1) and serotonin (5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7) receptors and α_1 adrenoceptors.[6–8] This complexity leaves the very low risk of extrapyramidal symptoms and unexcelled antipsychotic effectiveness of clozapine unexplained.[9] Postural dizziness, sedation and increased appetite may reflect actions of clozapine and some other antipsychotic agents at α_1, H_1 and 5-HT_{2C} receptors respectively. Olanzapine demonstrates significant anti-M_1 and moderate H_1 affinity. Risperidone is a potent antagonist at 5-HT_{2A}, D_2 and α_1 receptors. Ziprasidone is a potent antagonist at D_2, D_3, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_7 receptors; it also has 5-HT_{1A}-agonist actions that may alleviate anxiety and depression, and a moderate inhibitory effect on neuronal transport inactivation of serotonin like that of selective serotonin reuptake inhibitor antidepressants.[10] Aripiprazole has a particularly low risk of acute extrapyramidal symptoms despite high levels of occupation of D_2 receptors (> 90%) at therapeutic doses, which probably reflects its partial-agonist activity at those receptors.[11]

Conventional antipsychotic drugs, especially those of high potency with high affinity and avidity for D_2 receptors (e.g., haloperidol and fluphenazine), markedly interfere with dopaminergic neurotransmission and carry relatively high risks of extrapyramidal symptoms, even at moderate doses. These adverse neurologic responses include distressing motor restlessness (akathisia), acute dystonias and dyskinesias and gradually evolving parkinsonian bradykinesia

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as well as tardive dyskinesias and dystonias. Although the pathophysiology of these extrapyramidal syndromes is ill-defined, parkinsonism, at least, is probably related to decreased dopaminergic transmission in the forebrain basal ganglia.[8] Clinical computed positron-emission tomography (PET) studies have indicated that 60%–80% occupation of D_2 receptors is associated with antipsychotic efficacy and that higher occupation levels are associated with an increased risk of acute extrapyramidal symptoms as well as with hyperprolactinemia from the blocking of D_2 receptors on anterior-pituitary mammotrophic cells that normally are tonically inhibited by dopamine produced in the hypothalamic arcuate nucleus.[12–15]

Table 1: Routes of administration, dosage and cost of antipsychotics in Canada

Antipsychotic agent (year marketed in Canada)	Forms available	Usual target doses, mg/d	Monthly cost, $*
Modern "atypical" antipsychotics			
Aripiprazole†	T	10–30	370–740†
Clozapine (1991)	T	300–450	310–470
Olanzapine (1996)	T, W, IM_S	10–20	265–515
Quetiapine (1998)	T	300–600	145–275
Risperidone (1993)	T, L	2–6	100–250
Risperidone depot (2004)	IM_D	25–50‡	640–1250
Ziprasidone§	T, IM_S	80–160	–
Representative conventional antipsychotics			
Chlorpromazine (1953)	T, L, IM_S	75–400	25–50
Flupenthixol (1983)	T, L	9–24	65–160
Flupenthixol decanoate (1983)	IM_D	20–60‡	40–80
Fluphenazine (1960)	T, L, IM_S, IM_D	4–20	25–35
Haloperidol (1966)	T, L, IM_S, IM_D	4–12	15–35
Loxapine (1978)	T, L, IM_S	20–100	30–45
Perphenazine (1957)	T, L	16–48	10–15
Thiothixine (1968)	C	15–30	20–60
Trifluoperazine (1958)	T	5–20	15–35

Note: T = tablet, W = rapid-dissolving wafer, IM_S = short-acting intramuscular injection, L = oral liquid, IM_D = 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.
§Not available in Canada.

The atypically low risk of extrapyramidal symptoms associated with some modern antipsychotic agents (e.g., clozapine, olanzapine, ziprasidone) may reflect their greater affinity for 5-HT_{2A} receptors over dopamine D_2 receptors.[16,17] However, this pattern is not followed by all modern agents and is found in some older drugs (e.g., loxapine).[18,19] Also, PET studies have shown that some modern antipsychotic agents (including clozapine, olanzapine, quetiapine and ziprasidone, but not aripiprazole or risperidone) have moderate affinity and relatively low avidity (rapid dissociation) at basal ganglia D_2 receptors (Table 2).[18,19] The anticholinergic effects of some modern agents (e.g., clozapine, olanzapine) may also limit the risk of extrapyramidal symptoms and avoid the need to add an antimuscarinic-antiparkinsonism agent (e.g., benztropine, biperiden, procyclidine or trihexyphenidyl), as is often required with older antipsychotic agents to rebalance critical dopaminergic–cholinergic functions in the basal ganglia.[8,20]

Efficacy: modern versus older antipsychotic agents

So-called "positive" psychotic symptoms (particularly agitation, aggression, delusions and hallucinations) are especially responsive to antipsychotic treatment, whereas "negative" symptoms of chronic psychotic illnesses (e.g., social withdrawal, lack of motivation) and impaired cognition (e.g., deficient working memory, verbal fluency) are typically less responsive to treatment and contribute to long-term disability.[8,21] To compare individual drugs for their clinical efficacy, tolerability and safety, we examined

Table 2: Receptor potencies (Ki values, nM) of selected antipsychotic agents*†

Agents	Dopamine D_{2L}	Serotonin 5-HT_{2A}	ACh muscarinic	Adrenergic α_1	Adrenergic α_2	Histaminic H_1
Perphenazine	1.4	5.6	1500	10	510	–
Risperidone	3.3	0.2	> 10 000	2	55.6	58.8
Aripiprazole	3.4	3.4	> 10 000	57	–	61
Haloperidol	4	36	> 20 000	6.2	3800	1890
Ziprasidone	4.8	0.4	≥ 10 000	10.5	–	46.8
Olanzapine	11	4	1.9	19	230	7.1
Chlorpromazine	19	1.4	60	0.6	750	9.1
Loxapine	71.4	1.7	62.5	27.8	2400	5
Quetiapine	160	294	120	62.5	2500	11
Clozapine	180	1.6	7.5	9	160	2.8

Note: ACh = acetylcholine. Data are in descending order of potency at dopamine D_{2L} (predominant long form, based on gene splice variants) receptors.
*Data are in Ki values (nM) determined by radioligands for binding to the indicated receptors.
†Adapted, with permission, from Baldessarini et al.[8]

evidence presented in published systematic reviews that compared modern and conventional antipsychotic drugs[22–30] (Table 3; a longer version of the table is available online at www.cmaj.ca/cgi/content/full/172/13/1703/DC1). Notable limitations of the findings in many trials included in these reviews are possibly unrepresentative patient samples, relatively brief treatment, high dropout rates, unbalanced dose comparisons, modest clinical effects or outcome measures of sometimes dubious clinical relevance.[23,26,31,32] Of particular concern in some clinical trials is the use of relatively high doses of risperidone and standard comparators such as haloperidol, and low doses of quetiapine. High doses can decrease tolerability, and low doses can limit efficacy.[22–24,33]

Geddes and associates[22] found little advantage in measures of efficacy (improved symptom ratings) or tolerability (dropout rates) of modern antipsychotic agents over moderate daily doses of conventional agents, equivalent to 12 mg or less of haloperidol or 600 mg or less of chlorpromazine, whereas higher doses of comparators were poorly tolerated. Davis and colleagues[27] found that some modern antipsychotic drugs (e.g., amisulpride, clozapine, olanzapine, risperidone) but not others (e.g., aripiprazole, quetiapine, ziprasidone) had at least minor efficacy advantages over some older comparators, but they did not find that the dose of conventional antipsychotic drugs influenced outcomes. Leucht and colleagues[23] found that the superiority of modern drugs to older ones was variable and limited in terms of treatment dropouts due to inadequate benefits or poor tolerability. For example, quetiapine (at a dose of about 450 mg/d) was associated with 17% fewer dropouts due to

Table 3: Systematic reviews of antipsychotic agents (abridged)*

Trial	Focus of review	Study design and diagnoses	Main results
Leucht et al, 1999[23] *N* = 21 *n* = 7245	Compare efficacy and extrapyramidal symptoms: MAs (OLZ, QTP, RSP) v. HAL	RCTs (3–12 wk); schizophrenia or related disorders Comparator: HAL (8–20 mg/d)	Less antiparkinson drug use with MAs. Minor benefits in global efficacy and negative symptoms with OLZ and RSP. Fewer dropouts for treatment failure with RSP, or for adverse effects with QTP and OLZ
Geddes et al, 2000[22] *N* = 52 *n* = 12 649	Compare efficacy and dropout rates: MAs (CLZ, OLZ, QTP, RSP) v. CAs	RCTs (3–104 wk; median 6.5 wk); schizophrenia or related disorders	Superior symptom improvement with CLZ (moderate) and less with OLZ (small). No differences in dropout rates
Chakos et al, 2001[28] *N* = 12 *n* = 1916	Compare efficacy: MAs (CLZ, OLZ, RSP) v. CAs or other MAs	RCTs (6–104 wk; median 8 wk), treatment-resistant schizophrenia or schizoaffective disorder	Response rates higher with CLZ and OLZ than with CAs
Wahlbeck et al, 2001[26] *N* = 163 *n* = 18 585	Compare dropout rates: MAs v. CAs v. placebo	RCTs for schizophrenia (Cochrane database)	MAs associated with fewer dropouts only when CLZ included
Leucht et al, 2003[24] *N* = 31 *n* = 2320	Compare EPS risk: MAs v. low-potency CAs	RCTs (4–52 wk; median 6 wk), CPZ or other low-potency CAs as comparators for schizophrenia or related disorders	EPS less frequent with CLZ and OLZ. No differences in antiparkinson drug use
Leucht et al, 2003[25] *N* = 11 *n* = 2,032	Compare relapse, treatment failure and dropout rates due to adverse events: MAs v. HAL or other CAs	RCTs (22–130 wk, median 52 wk); schizophrenia or related disorders	Relapse and treatment failure rates reduced with RSP. Marginal difference in treatment failures but not relapses with OLZ. Rate of relapse and treatment failure not different for AMS or CLZ. No superiority for any MA in dropouts due to adverse events.
Davis et al, 2003[27] *N* = 124 *n* = 18 272	Compare efficacy: MAs (AMS, APZ, CLZ, OLZ, QTP, RSP, ZPS) v. CAs	RCTs (16/124 studies were ≥ 26 wk), schizophrenia or schizoaffective	By order of effect size, differences in symptom improvement favoured CLZ > AMS > RSP > OLZ. No advantages for APZ, QTP or ZPS
Correll et al, 2004[29] *N* = 11 *n* = 3248	Assess TD risk: MAs v. HAL	Follow-up studies (≥ 1 yr) in schizophrenia-like disorders	TD less frequent with MAs than with CAs

Note: AMS = amisulpiride, APZ = aripiprazole, CA = conventional antipsychotic agent, CLZ = clozapine, HAL = haloperidol, MA = modern (atypical) antipsychotic agent, OLZ = olanzapine, QTP = quetiapine, RSP = risperidone, ZPS = ziprasidone, EPS = extrapyramidal symptoms, *N* = trials, *n* = subjects, RCTs = randomized controlled trials, TD = tardive dyskinesia.
*A longer, more detailed version of this table appears online at www.cmaj.ca/cgi/content/full/172/13/1703/DC1.

adverse effects than various antipsychotic comparators (at haloperidol-equivalent doses of 8–12 mg/d); olanzapine (11–16 mg/d) yielded only 9% fewer dropouts due to treatment failure and 6% fewer due to adverse effects than haloperidol (12–18 mg/d), and risperidone lacked any advantage. These systematic reviews indicate that modern antipsychotic agents are not consistently superior to conventional drugs in efficacy or tolerability and that reported advantages are variable and often minor. The newest antipsychotic agents, ziprasidone and aripiprazole, have undergone fewer comparison trials, and their efficacy compared with that of other antipsychotic drugs remains uncertain.[34–36]

The effects of antipsychotic drugs on negative symptoms of emotional withdrawal and lack of motivation are especially difficult to ascertain because of challenges in rating such features and because of their interactions with depressed mood and reduced motility, both of which can be worsened by antipsychotic drugs.[37] In a large pooled comparison of a modern and a conventional antipsychotic agent, involving nearly 2000 subjects given treatment for 6 weeks,[38] the advantage (as measured by Cohen's effect size statistic) of olanzapine over haloperidol for negative symptoms was 0.2. Assuming a normal distribution of symptom response, this effect size suggests that 58% of patients taking olanzapine had greater improvement of negative symptoms compared with the mean level of improvement with haloperidol, but it also indicates that 42% did less well with olanzapine.[39] Relative efficacy of other modern antipsychotic agents versus older drugs has been similar or even smaller.[22] Such findings do not support the hope that modern agents would represent a major advance in the clinical management of negative symptoms.

Impaired cognition is common among patients with chronic psychotic illnesses, but it is also particularly sensitive to dosage of antipsychotic agents and may be worsened by concurrent administration of antiparkinson-anticholinergic drugs. Many studies have compared a newer antipsychotic agent with high doses of haloperidol given with anticholinergics, as needed.[40] For example, olanzapine (at a moderate average daily dose of 9.7 mg) was rated superior in several cognitive measures to high daily doses of haloperidol (average dose 27 mg),[41] but less so when compared with lower doses of haloperidol (5.5 mg).[42] Similarly, a 2-year randomized trial found no difference in cognitive improvements between risperidone (average dose 6 mg/d) and a moderate daily dose of haloperidol (average dose 5 mg/d).[43] Such studies do not indicate important advantages of modern over conventional antipsychotics with respect to cognitive function, and any between-drug differences appear to pale in comparison to the often severe cognitive deficits of schizophrenia.[42]

Positive effects on rates of relapse or readmission to hospital, as well as improvements in occupational and social functioning, quality of life and subjective well-being have been assessed much less consistently than have symptom ratings in most trials comparing treatments of psychotic disorders, even though such outcomes are important from clinical and public health perspectives and may not be predicted well by symptom improvement. In a long-term trial comparing risperidone and haloperidol in patients with chronic psychotic disorders, psychotic symptoms changed little (4.9% improvement and 3.9% worsening respectively), whereas the Kaplan–Meier estimates of relapse risk at the end of the study (34% v. 60% respectively) strongly favoured the modern drug.[44] This advantage of risperidone over haloperidol with respect to 1-year relapse risk was replicated in a study of first-episode psychosis (42% v. 55%) despite near identical improvements in symptom measures with low doses (about 3 mg/d) of both agents.[45] In contrast, a 12-month study found little difference between treatment with moderate doses of olanzapine (11–16 mg/d) and treatment with haloperidol (11–14 mg/d) combined with benztropine to limit extrapyramidal symptoms in outcomes including psychotic symptoms, negative symptoms, risk of extrapyramidal symptoms or tardive dyskinesia, quality of life and dropout rates.[20] Including an antiparkinson agent with moderate doses of haloperidol may have accounted for the lack of difference observed in this trial.[46]

A striking exception to the inconsistent but generally modest differences between use of a modern antipsychotic drug and appropriately managed treatment with an older drug is clozapine. Patented in 1960, clozapine has shown consistent and substantial superiority to several standard antipsychotic agents in a large number of head-to-head comparisons, with even more striking differences (e.g., in relapse rates and treatment compliance) occurring with prolonged treatment.[22,27,28,47] Superiority has been less consistent in comparison with other modern antipsychotic agents,[34] except that treatment adherence has been consistently greater with clozapine (60%) than with other modern (41%) or conventional (37%) antipsychotic drugs, perhaps because of the unusually close medical monitoring required for the safe use of clozapine.[48] Clozapine remains the drug of choice for treating refractory schizophrenia.[49] It also has been associated with reduced or delayed risk of suicide attempts, which led to the precedent-setting approval by the US Food and Drug Administration (FDA) for this effect in 2003.[50,51] In a pivotal 18-month comparison of clozapine and olanzapine among 450 patients with schizophrenia who were at relatively high risk of suicide but not necessarily unresponsive to treatment, the risk of suicide attempts and interventions to prevent suicide was moderately lower in the clozapine group (relative risk [RR] 1.32, 95% confidence interval [CI] 1.03–1.72).[50,51]

Tolerability and safety of modern antipsychotic agents

The validity of the claim that modern antipsychotic agents carry lesser risks of adverse effects than conventional antipsychotic drugs is challenged by findings from randomized studies that have shown similar rates of treatment dis-

continuation due to adverse events. The much promoted advantage of reduced risk of extrapyramidal symptoms with modern antipsychotic drugs needs to be balanced against other adverse effects.[22,24–26]

Adverse neurologic effects

The risk of extrapyramidal symptoms varies with specific agents, doses and particular neurologic syndromes. The superiority of the modern agents is clearest for reducing the risk of acute dystonia and late parkinsonian bradykinesia (Table 3). Not surprisingly, in clinical trials, the largest differences in risk have been demonstrated in comparisons between moderate doses of modern antipsychotic drugs and large doses of potent conventional antipsychotic agents without use of a prophylactic anticholinergic. When compared with low-potency antipsychotic drugs (e.g., chlorpromazine) or low to moderate doses of high-potency agents (e.g., haloperidol), or when high-potency agents are combined with anticholinergic drugs at regular doses, the advantage of modern agents of reduced extrapyramidal symptoms is lessened or eliminated.[24,46] Clozapine and possibly quetiapine appear to be relatively well tolerated by patients with Parkinson's disease who become psychotic with treatment. Risperidone and olanzapine are not well tolerated, and other modern agents have not been adequately investigated.[52]

Potential superiority of modern antipsychotics is less clear for acute or late dyskinesias, akathisia or neuroleptic malignant syndrome.[53–55] Regarding tardive dyskinesia, the 1-year incidence was 17 times lower with olanzapine than with haloperidol, each at a dose of about 14 mg/d (0.5% v. 7.4% respectively), but it was not avoided altogether.[54] The annualized risk in a randomized trial comparing risperidone (4.9 mg/d) and haloperidol (11.7 mg/d) with a follow-up of at least 1 year was 0.6% and 4.1% respectively. There are no blinded, randomized, long-term follow-up trials comparing other modern agents.[29,54]

Akathisia, marked by restlessness and anxious agitation, has been associated with virtually all antipsychotic agents, including clozapine.[56,57] This clinically distressing idiopathic syndrome is often misdiagnosed as psychotic agitation, typically persists as long as antipsychotic treatment continues and invites mistreatment with more antipsychotic therapy. Lack of an association with antidopaminergic potency suggests that D_2-receptor blockade does not explain akathisia, whereas beneficial effects of lipophilic, centrally active β-adrenoceptor antagonists (e.g., propranolol) suggest adrenergic involvement.[58]

Neuroleptic malignant syndrome is an uncommon, potentially life-threatening cerebrotoxic delirium, with variable fever, autonomic instability, and muscle rigidity with release of circulating creatine kinase and myoglobinuria.[59] It is important to emphasize that incomplete forms of neuroleptic malignant syndrome may occur: for example, in patients who are taking clozapine, the syndrome may present with less pronounced muscle rigidity.[60,61]

Endocrine and metabolic effects

Weight gain is a common adverse effect of several modern and some conventional antipsychotic drugs. In a review of the literature, Allison and coauthors[62] found the following mean increases in weight at 10 weeks of treatment: clozapine 4.45 kg, olanzapine 4.15 kg, chlorpromazine 2.58 kg, quetiapine 2.18 kg (at 6 weeks), risperidone 2.10 kg, haloperidol 1.08 kg and ziprasidone 0.04 kg. Weight gain associated with olanzapine tends to plateau over 8–12 months.[63] Weight gain is often considered to be clinically significant in antipsychotic drug trials at increases of at least 7%. In a systematic review, Taylor and McAskill[64] found the risk of such increases associated with olanzapine, quetiapine and risperidone to be 14%–27% at 6–8 weeks and as high as 40% by 3.5 years. The rates of increases of 10% or more associated with clozapine, olanzapine and risperidone were, respectively, 27%–60% at 3–12 months, 15% at 8 weeks and 6% at 8 weeks.[64] Lack of direct long-term comparisons precludes more reliable estimates of the rate and severity of weight gain with specific antipsychotic agents. However, the available data suggest that the risk of weight gain is greatest with clozapine and olanzapine, probably intermediate with quetiapine and low-potency conventional antipsychotic drugs, less with high-potency antipsychotic drugs including risperidone, and minimal with aripiprazole, molindone and ziprasidone. Many patients experience moderate weight gain, but some experience rapid and potentially massive increases that are very difficult to control.[65] Children are at particularly high risk of weight gain.[66] Mechanisms involved in weight gain and associated adverse metabolic changes probably include sedation and inactivity, perhaps more specific effects of central blockade of H_1 and 5-HT_{2C} receptors, as well as specific factors associated with the psychiatric disorder.[8,67,68]

Hyperlipidemia and hyperglycemia with resultant type 2 diabetes mellitus have been associated with modern antipsychotic agents. Their rates, although not well quantified, probably vary among specific antipsychotic drugs. Using a general practice research database in the United Kingdom, Koro and colleagues[69,70] estimated the risk of hyperlipidemia and diabetes associated with olanzapine to be 3.4 (95% CI 1.8–6.4) and 4.2 (95% CI 1.5–12.2) times the risk associated with conventional antipsychotic agents, and 4.6 (95% CI 2.4–8.9) and 5.8 (95% CI 2.0–16.7) times the risk associated with no antipsychotic use. The risk associated with risperidone was much lower, at 0.81 (95% CI 0.4–1.5) and 1.6 (95% CI 0.7–3.8) times the risk of conventional antipsychotic agents, and 1.1 (95% CI 0.6–2.1) and 2.2 (95% CI 0.9–5.2) times the risk associated with no antipsychotic use. In another study, Lambert and colleagues also found an increased risk of diabetes associated with olanzapine (odds ratio [OR] 1.36, 95% CI 1.20-1.53) compared with conventional antipsychotic drugs, but it was less than the risk reported by Koro and colleagues.[71]

They found a similar increase in risk associated with clozapine (OR 1.34, 95% CI 1.16-1.55). The risks associated with quetiapine (OR 1.2) and risperidone (OR 1.0) were not statistically different from those associated with conventional antipsychotic agents. Overall, the risk of disturbances in both glucose and lipid metabolism appears to be greatest with clozapine and olanzapine, possibly intermediate with quetiapine and the low-potency conventional agents chlorpromazine and thioridazine, and lowest with aripiprazole, risperidone and ziprasidone and with haloperidol and other high-potency conventional antipsychotic agents.[72–76] Risks of hyperlipidemia and hyperglycemia are associated with, but not necessarily dependent on, weight gain.[76,77] The health implications of long-term therapy with antipsychotic agents that increase the risk of medical morbidity are of growing concern and may well be more dangerous than the extrapyramidal symptoms typically associated with older antipsychotic agents.[8,78,79]

Moderate hyperprolactinemia is common with conventional antipsychotic drugs. Among the modern antipsychotic agents, the effect is seen only with risperidone, which can elevate prolactin levels at least as much as haloperidol can at comparable doses.[80,81] The mean reported prevalence of hyperprolactinemia among patients taking older antipsychotic agents or risperidone is 60% among women and 40% among men.[80] The rate of related complications, such as amenorrhea, galactorrhea, and erectile and ejaculatory dysfunction, is about 10%–15%. Aripiprazole, clozapine and quetiapine virtually lack this effect and can be useful for use in patients with prolactin-related adverse effects (amenorrhea, galactorrhea, gynecomastia or sexual dysfunction) or prolactin-dependent metastatic carcinoma of the breast.[81]

Cardiovascular effects

Several antipsychotic agents are associated with worsening of cardiovascular risk factors, including the previously described weight gain, hyperglycemia and hyperlipidemia. In addition to acute hypotensive effects (Table 4), elevated blood pressure has been reported in patients with weight gain due to antipsychotic use.[63] A post hoc analysis involving 113 patients with bipolar disorder taking olanzapine for several months revealed an increase of 13.1% (11 mm Hg) and 9.4% (5.9 mm Hg) in systolic and diastolic blood pressures respectively in those who had above-median changes in body mass index (BMI). Blood pressure was not changed in patients with below-median changes in BMI.[63]

Some antipsychotic drugs are associated with prolongation of ventricular repolarization, which is reflected as a prolongation of the QT interval on an electrocardiogram. Prolongation of the QT interval is associated with an increased risk of polymorphic ventricular tachycardia (torsades de pointes) and sudden cardiac death, especially when the QT interval corrected for rate (QTc) exceeds 500 ms.[82] The precise risks for prolonged QT interval are unknown for particular antipsychotic drugs but can occur with both older and modern agents. Among older agents, thioridazine and mesoridazine have been virtually abandoned as a result of this association.[83] Among modern agents, ziprasidone

Table 4: Benefits and risks of modern and conventional antipsychotic agents*

	Modern antipsychotic agents						Conventional antipsychotic agents by potency†		
Property	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone	High	Moderate	Low
Efficacy in terms of									
positive symptoms	++	++++	+++	++	+++	+++	+++	+++	+++
negative symptoms	+	++	+	+	+	+	+	+	+
relapse	++	++++	+++	?	+++	?‡	++	++	++
Adverse effects									
Anticholinergic	0	+++	+	0	0	0	0	++	+++
Cardiac repolarization	0	0	0	0	0	+	0	0	++
Hypotension	+	+++	++	++	+++	+	+	++	+++
Hyperprolactinemia	0	0	+	0	++	+	++	++	++
Type 2 diabetes mellitus	+	++	++	+	+	+	+	+	+
Sexual dysfunction	+	++	++	+	++	+	++	++	+++
Weight gain	0	+++	+++	++	+	0	0	+	++
EPS§	+	0	+	0	++	+	++++	+++	++
NMS	?	+	+	+	+	+	+++	++	+

Note: EPS = extrapyramidal signs or symptoms (dystonia, bradykinesia tremor, akathisia, dyskinesia), NMS = neuroleptic malignant syndrome (fever, delirium, unstable vital signs, variable rigidity).
*Benefit or risk: ++++ = very high, +++ = high, ++ = moderate, + = low, 0 = negligible, ? = poorly defined.
†Examples of high-potency conventional agents are flupenthixol, fluphenazine, haloperidol, trifluoperazine; moderate-potency agents include loxapine and zuclopenthixol; and low-potency agents include chlorpromazine, methotrimeprazine and thioridazine.
‡The risk of relapse was reduced when compared with placebo over 1 year. No long-term data are available for comparison with other antipsychotic agents.
§Akathisia (anxious restlessness) can occur with modern antipsychotic agents.

may be dangerous when combined with other drugs that result in prolonged QT intervals,[84] but when used alone it has not been associated with an increased risk of cardiac arrhythmia or death.[85] The effects on the QT interval are likely to be more pronounced when antipsychotic drugs are used in combination with other drugs that prolong the QT interval. The list of such drugs is extensive, although common agents include class I and III antiarrhythmic drugs, tricyclic antidepressants and some antibiotics.

Of great concern are findings associating modern antipsychotic drugs with increased risks of death and cerebral ischemia or stroke among elderly patients receiving therapy for psychotic disorders or the agitation of dementia. On the basis of findings from 17 placebo-controlled trials of modern antipsychotic drugs (aripiprazole, olanzapine, quetiapine and risperidone) involving a total of 5106 elderly patients with dementia-related psychosis, the US FDA issued a warning of a 1.6- to 1.7-fold increase in the risk of death associated with *all* modern antipsychotics, including clozapine and ziprasidone.[86–88] Collectively, the mean rate of death was 4.5% with modern antipsychotic drugs and 2.6% with placebo over 10 weeks. The attributable risk of death in this population with conventional antipsychotic drugs remains unknown. Regarding stroke or transient cerebral ischemia, the incidence in 4 placebo-controlled trials was 3.3% with risperidone versus 1.1% with placebo (RR 3.30, 95% CI 1.43–7.70).[89] In 5 other trials, the risk of cerebrovascular events was 1.3% with olanzapine and 0.4% with placebo (RR 3.04, 95% CI 0.70–13.3; $p = 0.043$ when controlling for sex, age and type of dementia).[90] However, a large retrospective analysis found negligible differences between 14 865 elderly patients taking older antipsychotic drugs and 13 503 taking risperidone (RR 1.04, 95% CI 0.82–1.31), 3459 taking olanzapine (RR 0.91, 95% CI 0.62–1.32) or 883 taking quetiapine (RR 0.78, 95% CI 0.38–1.57).[2] Without untreated control groups, these findings are inconclusive about the potential risks of older antipsychotic agents, and comparisons with other modern antipsychotic agents are not available.

Clozapine

Despite its considerable advantages in treating psychosis, clozapine's value is limited by potentially life-threatening agranulocytosis, which has an incidence of about 1% without close monitoring of leukocyte counts, especially during the initial months of treatment.[91] In addition, clozapine has a dose-dependent risk of epileptic seizures (about 5% at a daily dose of 600 mg or more);[91] potentially massive weight gain;[92] possible cardiac damage, including early myocarditis (≤ 19 per 10 000) or late cardiomyopathy (≤ 10 per 10 000);[93,94] cerebral intoxication such as that seen with neuroleptic malignant syndrome, with delirium and fever but not muscle rigidity or elevated creatine kinase levels;[60] and severe depression of intestinal motility.[8,95]

Conclusions

Modern antipsychotic drugs (Table 1) offer useful therapeutic options, and the risk of some extrapyramidal symptoms is generally lower with these drugs than with older antipsychotic drugs (Table 3, Table 4). As a group, modern antipsychotic drugs vary greatly in their pharmacology (Table 2) and in their risks of specific adverse effects (Table 4). With the exception of clozapine, they do not represent major gains in effectiveness or tolerability (Table 4). Some present potentially important adverse effects associated with weight gain, including diabetes, hyperlipidemia and hypertension. As a group, they are much more expensive than older antipsychotic drugs, some of which are available as generic drugs (Table 1). It seems reasonable to consider an antipsychotic drug from either group, conventional or modern, for the treatment of psychotic disorders and to inform patients of the relative benefits, risks and costs associated with specific choices.

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Clinical trial registration

CMAJ will consider clinical trials for publication only if they have been registered in a publicly accessible clinical trials registry before the enrolment of the first patient. This policy applies to trials that start recruiting on or after July 1, 2005. For trials that began enrolment before this date, registration is required by Sept. 13, 2005. The criteria for acceptable registration are described in *CMAJ* (2005;172[13]:1700-2).