Therapeutic Reviews

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Antipsychotics *AHFS 28:16.08.04*

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Indications: Licensed indications vary between products; consult the manufacturer's Product Insert for details. Uses include acute psychotic symptoms, mania and bipolar disorders, schizophrenia, agitation, delirium, nausea and vomiting, intractable hiccup, treatment-resistant depression.[1]

Neurophysiology of Dopamine

Dopamine has a central role in arousal, motivation, attention, the extrapyramidal motor system and other pathways (Table 1). Although the exact etiology is uncertain, dopamine dysregulation plays a role in a number of symptoms, e.g., nausea, hallucinations, and dopamine antagonist drugs such as antipsychotics can help palliate these. An appreciation of the neurophysiology of dopamine facilitates a fuller understanding of the numerous therapeutic uses and undesirable effects of antipsychotics.

Psychotic symptoms arise from opposing dopamine imbalances:

- "positive" symptoms (delusions and hallucinations) result from dopamine *excess* in the mesolimbic system
- "negative" symptoms (apathy, anhedonia and cognitive blunting) result from dopamine *deficit* in the mesocortical system.

Arousal, motivation and attention are regulated by a two-way loop between the prefrontal/limbic cortex and the thalamus. The prefrontal/limbic cortex identifies situations requiring attention and the thalamus is directed to allow relevant information to pass through to the cerebral cortex while filtering out the rest. This thalamic sensory filter is formed by GABAergic neurons, which are switched off by dopamine to allow salient information through. In psychosis, dopamine overactivity leads to excessive information throughput, resulting in hallucinations and delusions (the "salience hypothesis"). D_2 antagonist antipsychotics help to correct this overactivity, and improve these symptoms.[2–5] Conversely, D_2 antagonists augment dopaminergic underactivity in the mesocortical system, leading to, or exacerbating, "negative" symptoms.[2,4,5]

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Table 1
Dopaminergic Pathways

Pathway	Function	Symptoms of Dysregulation
Mesolimbic Midbrain reticular formation → limbic cortex	Pleasure, motivation and reward[a]	↑Dopamine: "positive" symptoms of psychosis (delusions, hallucinations)
Mesocortical system Midbrain reticular formation → prefrontal cortex	Affect, executive function, concentration	↓Dopamine: depression; "negative" symptoms of psychosis (apathy, anhedonia and cognitive blunting)
Nigrostriatal system Substantia nigra → corpus striatum	Extrapyramidal motor system	↓Dopamine: Parkinson's disease, drug-induced parkinsonism, akathisia, dystonia, restless legs ↑Dopamine: dyskinesia
Tuberoinfundibular system	Dopaminergic inhibition of prolactin secretion	↓Dopamine: hyperprolactinemia
Thalamic dopamine pathway[a] Multiple origins → thalamus	Sleep and arousal through sensory gating	
Area postrema	Emetogenesis	↑Dopamine: nausea and vomiting

[a]Both the mesolimbic and thalamic dopamine pathways affect thalamic sensory gating. Mesolimbic dysregulation is best characterized in the formation of "positive" psychotic symptoms (see text).

D_2 antagonism can also disrupt other pathways unaffected by psychosis:
- nigrostriatal system, part of the extrapyramidal motor system:
  - ➢ D_2 antagonists initially cause underactivity, similar to Parkinson's disease → acute extrapyramidal symptoms
  - ➢ subsequent adaptation to D_2 antagonism leads to D_2 receptor upregulation → tardive dyskinesia
- tuberoinfundibular system; D_2 antagonists cause hyperprolactinemia → sexual dysfunction.

The newer "atypical" antipsychotics have been developed in an attempt to overcome some of the above limitations of "typical" D_2 antagonists.

Pharmacology

Conventionally, antipsychotics are divided into two classes:
- typical:
  - ➢ phenothiazines: chlorpromazine, levomepromazine (not USA), perphenazine, prochlorperazine, promazine, trifluoperazine
  - ➢ butyrophenones: haloperidol
- atypical: aripiprazole, clozapine, olanzapine, quetiapine, risperidone.

However, there is much variation within, and overlap between, these classes. Although all antipsychotics are characterized by D_2 antagonism, differences in receptor profile result in clinical differences between them (Table 2).[6] Antipsychotics are variably associated with antagonistic effects at the following receptors:

Table 2
Receptor Affinities for Selected Antipsychotics[6–9]

	D_2	$5HT_{2A}$	$5HT_{2C}$	$5HT_3$	H_1	α_1	α_2	ACh_M
Aripiprazole	+++PA	+++	+++	-	+++	+++	++	-
Chlorpromazine	+++	+++	++	-	+++	+++	+	++
Clozapine	+	+++	++	+	+++	+	+	+++
Haloperidol	+++	+	-	-	-	++	-	-
Levomepromazine (not USA)	++	+++			+++	+++	+	++
Perphenazine	+++	+++	+		+++	++	+	-
Prochlorperazine	+++	++	+	-	++	++	-	+
Olanzapine	++	+++	+	+	+	++	+	++
Quetiapine	+	+	+	-	++	+	++	-
Risperidone	+++	+++	++	-	++	+	+++	-

Affinity: +++ high, ++ moderate, + low, (+) borderline, - negligible or none; blank = no data. PA = partial agonist.

- muscarinic, causing dry mouth, constipation, etc.
- adrenergic, causing postural hypotension
- histaminic, causing drowsiness.

In contrast, the D_2-specific action of haloperidol avoids such problems, but increases the risk of extrapyramidal effects.

Atypical antipsychotics carry a lower risk of extrapyramidal effects and improved efficacy for negative symptoms. This relates to:[2,10,11]

- $5HT_2$ receptor antagonism
- D_2 partial agonism
- lower affinity and shorter duration D_2 antagonism.

$5HT_2$ receptors inhibit the nigrostriatal and mesocortical systems. Thus, $5HT_2$ antagonist antipsychotics increase activity in these pathways, countering the extrapyramidal impact of D_2 antagonism and improving "negative" symptoms.[12] "Negative" symptoms overlap with depressive symptoms and can respond to antidepressants.[13] Conversely some $5HT_2$ antagonist antipsychotics are beneficial in refractory depression (e.g., olanzapine).[14,15] It is noteworthy that increased prefrontal dopamine release through $5HT_2$ antagonism is also an important action of some antidepressants, e.g., mirtazapine.

An antipsychotic that acts as a D_2 partial agonist will function as a D_2 antagonist in the presence of excessive dopamine (e.g., as in the mesolimbic system in psychosis), because partial activation of the D_2 receptor will reduce overall transmission. However, when there is dopamine depletion, the partial D_2 receptor activation is sufficient to increase overall transmission, and it functions as a D_2 agonist, e.g., in the nigrostriatal and mesocortical systems. In consequence, a D_2 partial agonist antipsychotic can potentially improve both "positive" and "negative" symptoms and limit undesirable extrapyramidal effects.

However, the extent to which atypical antipsychotics succeed *in practice* in reducing extrapyramidal effects and negative symptoms is unclear. The relatively lower doses of atypicals used in RCTs with typicals may partly explain some of the observed differences. Further, the properties purported to account for such differences also are shared by some typical antipsychotics, e.g., $5HT_2$ antagonism. On the other hand, the higher incidence of other undesirable effects (particularly metabolic) with atypicals limits improvement in overall tolerability.

Direct comparisons suggest that acute extrapyramidal effects would be avoided in one patient for every 3–6 patients treated with an atypical rather than a typical antipsychotic.[16,17] However, the difference is greatest relative to haloperidol. Further, in an RCT, although extrapyramidal effects accounted for more discontinuations of perphenazine compared with several atypicals (8% vs. 2–4%), overall discontinuation rates for undesirable effects or lack of efficacy were comparable.[18] All treatment groups experienced some degree of involuntary movement (13–17%), akathisia (5–9%) or extrapyramidal signs (4–8%). Most studies are too short to evaluate the risk of tardive dyskinesia. Available data suggest a five times lower risk with atypicals compared with haloperidol in the first year of use, although haloperidol doses were relatively higher.[19] Among atypicals, risperidone carries the highest risk of extrapyramidal effects, and clozapine and quetiapine the lowest.[20]

Acquisition costs for atypicals are higher than for typicals. Suggested reductions in costs from the long-term use of atypicals may be less relevant in palliative care if drugs are used at lower doses and for shorter periods.[21]

Pharmacokinetic details of selected antipsychotics are summarized in Table 3.

Cautions

For full list, see manufacturer's Package Insert.

Stroke Risk

Meta-analysis of RCTs in the elderly with dementia has shown that the risk of stroke with olanzapine and risperidone is 2–3 times higher compared with placebo,[24–27] with a doubling of all-cause mortality with olanzapine.[25] The mechanism of this association is not known, but it is regarded as a class effect. Subsequent findings indicate an increased risk in all elderly patients for both typicals and atypicals,[20,28–30]

Table 3
Pharmacokinetic Details for Selected Antipsychotics[22,23]

	Oral Bioavailability (%)	Time to Peak Plasma Concentration	Half-Life (h)	Metabolism (Predominant P450 Isoenzyme)
Chlorpromazine	10–25	2–4 h (PO)	30	CYP2D6
Clozapine	50–60	2 h	12	CYP1A2, CYP3A4
Haloperidol	60–70	2–6 h (PO) 10–20 min (SC)	13–35	Multiple
Levomepromazine (not USA)	40	1–3 h (PO) 30–90 min (SC)	15–30	Multiple[a]
Olanzapine	60	5–8 h	34[b] (52[c])	CYP1A2, CYP2D6
Prochlorperazine	6 14 (buccal)	4 h (PO) 4–8 h (buccal); shorter with multiple doses	15–20	Multiple
Quetiapine	100	1.5 h	7[d] (10–14[c]) (12[e])	CYP3A4
Risperidone	99	1–2 h	24[f,g]	CYP2D6[h]

[a]P450 isoenzymes not fully characterised; some metabolites are active.
[b]Unaffected by hepatic or renal impairment.
[c]In the elderly.
[d]Clearance reduced by both renal and hepatic impairment.
[e]Of active metabolite.
[f]For risperidone + active 9-hydroxy metabolite.
[g]Clearance reduced by renal impairment: see Product Monograph.
[h]Activity of 9-hydroxyrisperidone, the predominant CYP2D6 metabolite, is comparable to risperidone; thus overall clinical effect is not altered by CYP2D6 polymorphisms or inhibitors.

greatest in those with dementia,[31] within the first month of starting treatment, and with higher doses. The relative risk with individual drugs has not yet been determined.

Epilepsy

Similar to many other psychotropic medications, antipsychotics cause a dose-dependent reduction in seizure threshold. The risk for individual agents approximates to the degree of sedation: chlorpromazine and clozapine carry a higher risk and haloperidol a lower risk. To minimize the risk, use the lowest risk antipsychotic (e.g., haloperidol) at the lowest effective dose. In palliative care, depot formulations are best avoided because they cannot be withdrawn quickly if problems occur.

Parkinsonism and Parkinson's Disease

All antipsychotics, through D_2 antagonism, can cause parkinsonism or worsen existing parkinsonism of any etiology. The risk is lower with clozapine and quetiapine. In patients with parkinsonism, alternatives to antipsychotics should be used where possible, e.g., for agitation, consider trazodone or a benzodiazepine, for nausea and vomiting consider:

- domperidone (available as a suppository)
- ondansetron
- scopolamine (hyoscine) *hydrobromide*, but may cause delirium.

Nonetheless, at the end of life, despite being D_2 antagonists, it may be necessary to prescribe small doses of chlorpromazine, olanzapine or quetiapine if all else fails.

Where delirium or psychotic symptoms occur in the context of Parkinson's disease or Lewy body dementia:

- look for potentially reversible causes of delirium, e.g., sepsis
- consider a trial reduction of antiparkinsonian medication:
  - ➢ reduce dopamine receptor agonists and antimuscarinic agents initially
  - ➢ dopamine precursors, e.g., levodopa, are less likely to cause psychosis.[32]

If the above measures are unhelpful, commence quetiapine 12.5–25 mg/24 h; if not tolerated, seek specialist advice. Options include switching to clozapine.[32]

Drug Interactions

For full list, see manufacturer's Package Insert.

Several pharmacodynamic interactions (additive sedation, hypotension and QT prolongation; reduced effect of antiparkinsonian medication) can be predicted from the receptor profile of antipsychotics.

Potentially serious interactions may result from induction or inhibition of hepatic metabolism. CYP3A4 inhibitors (e.g., aprepitant, cimetidine, macrolide antibiotics, ketoconazole) can significantly increase plasma levels of aripiprazole, pimozide and quetiapine. Carbamazepine and protease inhibitors exhibit varied interactions.

Antipsychotics are one of several classes of drugs that can prolong the QT interval, and at least theoretically increase the risk of cardiac tachyarrthymias, including potentially fatal *torsade de pointes*. Generally, concurrent prescribing of two drugs which can significantly prolong the QT interval should be avoided (see www.azcert.org).

Undesirable Effects

For full list, see manufacturer's Package Insert.

A summary is given in Box A.

Neuroleptic (Antipsychotic) Malignant Syndrome

Neuroleptic (antipsychotic) malignant syndrome (NMS) is a potentially life-threatening reaction that occurs in <1% of those prescribed an antipsychotic (Box B).[37,38] This idiosyncratic syndrome is associated with all antipsychotics.[39]

Most cases of NMS occur within two weeks of starting treatment or a dose increase. It is a hypodopaminergic state; bradykinesia progresses to immobilization, akinesia and stupor, accompanied by lead-pipe rigidity, fever, and autonomic instability.

Symptoms indistinguishable from NMS have been reported in patients with Parkinson's disease when long-term treatment with levodopa and bromocriptine has been abruptly discontinued.[40–42] This has led

Box A. Undesirable Effects of Antipsychotics

Extrapyramidal syndromes

Parkinsonism, akathisia, dystonia, tardive dyskinesia.[33]

Metabolic effects[20,34]

More common with typicals and risperidone

Hyperprolactinemia resulting in amenorrhea, galactorrhea, gynecomastia, sexual dysfunction, osteoporosis.

More common with atypicals, particularly olanzapine and clozapine

Weight gain.

Dyslipidemia, possibly associated with weight gain.

Type 2 diabetes mellitus, both new onset and exacerbation of pre-existing disease; risk independent of weight gain.

Cardiovascular effects

QT prolongation: dose-related, affected by presence of other risk factors, highest risk with thioridazine (withdrawn) and ziprasidone.[20,35]

Venous thromboembolism; risk possibly highest with atypicals.[36]

Stroke and increased risk of death in elderly patients (see Cautions).

Postural hypotension (α-adrenergic antagonism), particularly phenothiazines and clozapine; also seen with quetiapine and risperidone.

Miscellaneous[20]

Reduced seizure threshold (see Cautions).

Antimuscarinic effects; more with phenothiazines and clozapine.

Neuroleptic (antipsychotic) malignant syndrome (see below).

Agranulocytosis is seen in about 1% of patients taking clozapine, generally after 3–6 months.

Box B. Clinical Features of Neuroleptic (Antipsychotic) Malignant Syndrome

Essential
Severe muscle rigidity
Pyrexia ± sweating

Additional
Muteness γ stupor
Tachycardia and elevated/labile blood pressure
Leukocytosis
Raised plasma creatine phosphokinase ± other evidence of muscle injury, e.g., myoglobinuria

to the suggestion that the syndrome would be better called *acute dopamine depletion syndrome*.[40]

Death occurs in up to 20% of cases, mostly as a result of respiratory failure. The use of a dopamine agonist, e.g., bromocriptine, halves the mortality.[43] Subsequent prescription of an antipsychotic carries a 30–50% risk of recurrence.[44]

NMS is self-limiting if the causal antipsychotic drug is discontinued (and an alternative antipsychotic *not* prescribed). Generally it resolves in 1–2 weeks unless caused by a depot antipsychotic, when it takes 4–6 weeks. Antipsychotics are *not* removed by hemodialysis. Specific measures include:
- discontinuation of the causal drug
- prescription of a muscle relaxant, e.g., a benzodiazepine
- in severe cases, prescription of bromocriptine.[43]

General supportive measures may need to extend to artificial hydration and nutrition. Complications such as hypoxia, acidosis and renal failure require appropriate acute management.

Use of Antipsychotics in Palliative Care

For greater detail about doses, see the individual drug monographs in the Hospice and Palliative Care Formulary USA[45] or the Palliative Care Formulary (Canadian edition),[46] or visit www.palliativedrugs.com.

Nausea and vomiting

The D_2 antagonism of all antipsychotics is likely to provide anti-emetic activity in the area postrema (chemoreceptor trigger zone). Where specific action at this site is required (e.g., most chemical causes of nausea), a selective dopaminergic agent such as haloperidol is used,[47] although studies in palliative care patients are lacking.[48] However, most antipsychotics have moderate or high affinity at several receptors, some of which are involved in the transduction of emetic signals.[49] Thus, most antipsychotics are, to a variable extent, broad-spectrum anti-emetics. Levomepromazine (not available in the USA) and olanzapine are the most attractive choices (and haloperidol is the least) in this respect.[50,51]

Delirium

Treatment of underlying causes, non-drug management (e.g., orientation strategies, correction of sensory deprivation) and prevention of complications are central to delirium management.

When medication is required, antipsychotics are often used, e.g., haloperidol, although evidence is limited and comparative studies with other psychotropics are lacking.[52–54] When antipsychotics alone are insufficient, or when sedation also is required, e.g., for the initial management of a hyperactive, frightened patient, benzodiazepines or trazodone can be added.

Benzodiazepines can paradoxically worsen agitation, but are preferred for delirium related to alcohol withdrawal, neuroleptic malignant syndrome or Parkinson's disease. The use of cholinergics has been reported, but rivastigmine increased mortality in an RCT.[55] Hallucinations in delirium respond to antipsychotics in hours–days, whereas seemingly identical phenomena in a psychosis may not resolve for 1–2 weeks.

Agitation and challenging behaviors in dementia

Patients with dementia may become agitated for many reasons, including an appropriate response to a distressing situation. Possible precipitants should be treated or modified:

- intercurrent infections
- pain and/or other distressing symptoms
- environmental factors.

When no reversible cause is found and agitation is mild, assurance that such behaviors are often self-limiting may suffice. Training in non-drug management of behavioral disturbances reduces the need for psychotropic medication.[56]

The first-line use of antipsychotics for behavioral disturbance in dementia is inappropriate and actively discouraged.[57–60] In addition to safety concerns (increased risk of stroke and overall mortality, see above), evidence of benefit compared with non-drug measures is limited. A recent large RCT for agitation or psychosis in patients with dementia found both atypicals and typicals to be no better than placebo in all but a few secondary outcomes.[61] Taken together with other studies, the efficacy of antipsychotics in dementia is at best modest, and should be used only where other measures have failed.[62,63]

The use of alternative drugs, i.e., antidepressants, benzodiazepines, antiepileptics and cholinesterase inhibitors, has been proposed. However, evidence is generally more limited than for antipsychotics, and insufficient to allow clear evidence-based recommendations of one class over another.[62,64] Further, larger studies have not replicated the earlier benefit reported for trazodone.[62]

Even so, the serious consequences of not treating severe agitation or psychosis in dementia also are recognized.[62] Where drug treatment is required, clinicians should be guided by the individual patient's symptoms and co-morbidities, and the clinicians' familiarity with the agents available. Options include:

- haloperidol
- atypicals, e.g., olanzapine, quetiapine, risperidone
- cholinesterase inhibitors (benefit is marginal, but may be better tolerated).[64]

Whichever drug is selected, use the lowest effective dose for the shortest possible time; attempt dose reduction every 2–3 months; many patients do not deteriorate when medication is withdrawn.[63–65]

Intractable hiccup

Chlorpromazine or haloperidol are used when more specific treatment, e.g., simethicone (an anti-foaming agent) ± metoclopramide for gastric distension, or baclofen are ineffective.[66]

Refractory depression

Certain antipsychotics have been used as adjuncts for depression refractory to conventional antidepressants, particularly when switching antidepressants has been unsuccessful. Generally, either quetiapine or olanzapine is added to an SSRI.[15,67,68]

Pain

Dopamine is implicated in pain processing[69] and, in the past, antipsychotics were sometimes used as part of an analgesic cocktail. However, RCTs yield conflicting results.[70] Although no longer used as analgesics themselves, antipsychotics are helpful for treating the undesirable effects of analgesics, particularly nausea and delirium.[71]

Table 4
Equivalent Doses of Typical Antipsychotics[72]

Drug	Dose (mg)
Chlorpromazine	100
Promazine	100
Perphenazine	8
Trifluoperazine	5
Haloperidol	3

Switching Antipsychotics

Equivalent doses of typicals have been estimated, predominantly from surveys of psychiatric practice, and provide a starting point if switching from one to another (Table 4).[72] However, the dose of atypicals is less variable and thus their starting dose is unaffected by the dose of previous antipsychotics.

Abbreviations/Key

$5HT_{2A}$, $5HT_{2C}$, $5HT_3$	5 Hydroxytryptamine-2A, -2C and -3 receptors
α_1, α_2	Alpha-1 and -2 receptors
ACh_M	Anticholinergic (muscaric) receptor
CYP	Cytochrome P450
D_2	Dopamine-2 receptor
H_1	Histamine-1 receptor
PO	Per os, by mouth
RCT	Randomized controlled trial
SC	Subcutaneous
SSRI	Selective serotonin reuptake inhibitor

References

1. Mahmoud RA, Pandina GJ, Turkoz I, et al. Risperidone for treatment-refractory major depressive disorder: a randomized trial. Ann Intern Med 2007;147:593–602.

2. Stahl SM. Antipsychotic agents. In: Stahl's essential psychopharmacology: Neuroscientific basis and practical applications, 3rd ed. New York: Cambridge University Press, 2008:327–451.

3. Boutrel B, Koob GF. What keeps us awake: the neuropharmacology of stimulants and wakefulness-promoting medications. Sleep 2004;27:1181–1194.

4. Alves Fda S, Figee M, Vamelsvoort T, Veltman D, de Haan L. The revised dopamine hypothesis of schizophrenia: evidence from pharmacological MRI studies with atypical antipsychotic medication. Psychopharmacol Bull 2008;41:121–132.

5. Stahl SM. Psychosis and schizophrenia. In: Stahl's essential psychopharmacology: Neuroscientific basis and practical applications, 3rd ed. New York: Cambridge University Press, 2008:247–325.

6. Jindal RD, Keshavan MS. Classifying antipsychotic agents: need for new terminology. CNS Drugs 2008;22:1047–1059.

7. Lal S, Nair NP, Cecyre D, Quirion R. Levomepromazine receptor binding profile in human brain–implications for treatment-resistant schizophrenia. Acta Psychiatr Scand 1993;87:380–383.

8. National Institute of Mental Health (NIMH). NIMH's psychoactive drug screening program. 2006. University of North Carolina. Available from http://pdsp.med.unc.edu/indexR.html.

9. Shiloh R, Stryjer R, Weizman A, Nutt D, et al. Antipsychotic drugs. In: Atlas of psychiatric pharmacotherapy, 2nd ed. London: Taylor & Francis, 2006:90–105.

10. Kapur S, Mamo D. Half a century of antipsychotics and still a central role for dopamine D2 receptors. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1081–1090.

11. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. CNS Drugs 2004;18:251–267.

12. Meltzer HY. What's atypical about atypical antipsychotic drugs? Curr Opin Pharmacol 2004;4:53–57.

13. Rummel C, Kissling W, Leucht S. Antidepressants for the negative symptoms of schizophrenia. Cochrane Database Syst Rev 2006;3. CD005581.

14. Millan MJ, Gobert A, Rivet JM, A, et al. Mirtazapine enhances frontocortical dopaminergic and corticolimbic adrenergic, but not serotonergic, transmission by blockade of alpha2-adrenergic and serotonin2C receptors: a comparison with citalopram. Eur J Neurosci 2000;12:1079–1095.

15. Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. CNS Drugs 2010;24:131–161.

16. Wahlbeck K, Cheine M, Essali MA. Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst Rev 2000;2. CD000059.

17. Hunter RH, Joy CB, Kennedy E, Gilbody SM, Song F. Risperidone versus typical antipsychotic medication for schizophrenia. Cochrane Database Syst Rev 2003;2. CD000440.

18. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–1223.

19. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 2004;161:414–425.

20. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. CNS Drugs 2007;21:911–936.

21. Davies A, Langley PC, Keks NA, et al. Risperidone versus haloperidol: II. cost-effectiveness. Clin Ther 1998; 20:196–213.

22. Eiermann B, Engel G, Johansson I, Zanger UM, Bertilsson L. The involvement of CYP1A2 and CYP3A4 in the metabolism of clozapine. Br J Clin Pharmacol 1997;44:439–446.

23. Finn A, Collins J, Voyksner R, Lindley C. Bioavailability and metabolism of prochlorperazine administered via the buccal and oral delivery route. J Clin Pharmacol 2005;45:1383–1390.

24. Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. CMAJ 2002;167:1269–1270.

25. Wooltorton E. Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials. CMAJ 2004;170:1395.

26. Bullock R. Treatment of behavioural and psychiatric symptoms in dementia: implications of recent safety warnings. Curr Med Res Opin 2005;21:1–10.

27. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943.

28. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353:2335–2341.

29. Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 2007;146:775–786.

30. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009;360:225–235.

31. Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ 2008;337:a1227.

32. Weintraub D, Hurtig HI. Presentation and management of psychosis in Parkinson's disease and dementia with Lewy bodies. Am J Psychiatry 2007;164:1491–1498.

33. Twycross R, Wilcock A. Drug induced movement disorders. In: Hospice and palliative care formulary USA, 2nd ed. Nottingham: palliativedrugs.com, 2008: 547–550.

34. Yood MU, DeLorenze G, Quesenberry CP Jr, et al. The incidence of diabetes in atypical antipsychotic users differs according to agent–results from a multisite epidemiologic study. Pharmacoepidemiol Drug Saf 2009;18:791–799.

35. Twycross R, Wilcock A. Prolongation of the QT interval in palliative care. In: Hospice and palliative care formulary USA, 2nd ed. Nottingham: palliativedrugs.com, 2008: 531–536.

36. Liperoti R, Pedone C, Lapane KL, et al. Venous thromboembolism among elderly patients treated with atypical and conventional antipsychotic agents. Arch Intern Med 2005;165:2677–2682.

37. Caroff S, Mann S. Neuroleptic malignant syndrome. Med Clin North Am 1993;77:185–202.

38. Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. Br J Anaesth 2000;85:129–135.

39. Isbister GK, Dawson AH, Whyte IM. Comment: neuroleptic malignant syndrome associated with risperidone and fluvoxamine. Ann Pharmacother 2002;36: 1293. Author reply 1294.

40. Keyser DL, Rodnitzky RL. Neuroleptic malignant syndrome in Parkinson's disease after withdrawal or alteration of dopaminergic therapy. Arch Intern Med 1991;151:794–796.

41. Mann SC, Caroff SN. Pathogenesis of neuroleptic malignant syndrome. Psychiatr Ann 1991;21:175–180.

42. Ong KC, Chew EL, Ong YY. Neuroleptic malignant syndrome without neuroleptics. Singapore Med J 2001; 42:85–88.

43. Sakkas P, Davis JM, Hua J. Pharmacotherapy of neuroleptic malignant syndrome. Psychiatr Ann 1991; 21:157–164.

44. Wells AJ, Sommi RW, Crismon ML. Neuroleptic rechallenges after neuroleptic malignant syndrome: case report and literature review. Drug Intell Clin Pharm 1988;22:475–479.

45. Twycross R, Wilcock A. Hospice and palliative care formulary USA, 2nd ed. Nottingham: palliativedrugs.com, 2008.

46. Twycross R, Wilcock A, Dean M, Kennedy B. Canadian palliative care formulary. Nottingham: palliativedrugs.com, 2010.

47. Büttner M, Walder B, von Elm E, Tramèr MR. Is low-dose haloperidol a useful antiemetic? A meta-analysis of published and unpublished randomized trials. Anesthesiology 2004;101:1454–1463.

48. Perkins P, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Database Syst Rev 2009;2. CD006271.

49. Twycross R, Wilcock A. Antiemetics. In: Hospice and palliative care formulary USA, 2nd ed. Nottingham: palliativedrugs.com, 2010:185–190.

50. Passik SD, Navari RM, Jung SH, et al. A phase I trial of olanzapine (Zyprexa) for the prevention of delayed emesis in cancer patients: a Hoosier Oncology Group study. Cancer Invest 2004;22:383–388.

51. Navari RM, Einhorn LH, Passik SD, et al. A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier Oncology Group study. Support Care Cancer 2005;13:529–534.

52. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. Nat Rev Neurol 2009;5:210–220.

53. Caraceni A, Simonetti F. Palliating delirium in patients with cancer. Lancet Oncol 2009;10:164–172.

54. Attard A, Ranjith G, Taylor D. Delirium and its treatment. CNS Drugs 2008;22:631–644.

55. van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet 2010;376:1829–1837.

56. Fossey J, Ballard C, Juszczak E, et al. (2006) Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. BMJ 2006;332:756–761.

57. Committee on Safety of Medicines. Antipsychotic drugs and stroke. 2004. Available from: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON1004298.

58. Mowat D, Fowlie D, MacEwan T. CSM warning on atypical psychotics and stroke may be detrimental for dementia. BMJ 2004;328:1262.

59. Health Canada. Increased mortality associated with the use of atypical antipsychotic drugs in elderly patients with dementia. Notice to healthcare professionals. 2005. Available from www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2005/atyp-antipsycho_hpc-cps-eng.php.

60. US Food and Drug Administration. Alert. Information on antipsychotics (6/16/2008). 2008. Available from www.fda.gov/Drugs,

61. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525–1538.

62. Jeste DV, Blazer D, Casey D, et al. ACNP White Paper: Update on use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology 2008; 33:957–970.

63. Ballard CG, Gauthier S, Cummings JL, et al. Management of agitation and aggression associated with Alzheimer disease. Nat Rev Neurol 2009;5:245–255.

64. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 2005;293:596–608.

65. Lee PE, Gill SS, Freedman M, et al. Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. BMJ 2004;329:75.

66. Twycross R, Wilcock A, Toller CS. Symptom management in advanced cancer, 4th ed. Nottingham: palliativedrugs.com, 2009. 174–177.

67. National Institute for Health and Clinical Excellence (NICE). Clinical guideline 90. Depression. London: NICE, 2009. Available from www.nice.org.uk.

68. Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. J Psychopharmacol 2008;22:343–396.

69. Wood PB. Mesolimbic dopaminergic mechanisms and pain control. Pain 2006;120:230–234.

70. Seidel S, Aigner M, Ossege M, et al. Antipsychotics for acute and chronic pain in adults. Cochrane Database Syst Rev 2008;4: CD004844.

71. Coyle N, Breitbart W, Weaver S, Portenoy R. Delirium as a contributing factor to 'crescendo' pain: three case reports. J Pain Symptom Manage 1994;9:44–47.

72. Foster P. Neuroleptic equivalence. Pharmaceutical J 1989;243:431–432.