

Therapeutics Initiative

Better prescribing. Better health.

How well do you know your dopamine antagonists?

Most Therapeutics Letters analyze evidence to draw conclusions about average drug effects in defined groups of people. This Letter takes a clinical pharmacological approach to review **how individuals may be harmed by dopamine (DA) receptor antagonists**. Using these drugs safely requires that clinicians and patients appreciate their important adverse effects, which are not always well understood.¹ The online version links to **videos of patient experiences** that illustrate problems arising from dopamine blockade. Patients provided informed consent in the hope that health professionals and students can better appreciate potential harms, after watching and hearing about their experiences.

Dopamine receptor antagonists are widely prescribed in Canada. They include all antipsychotic drugs, the common anti-emetics metoclopramide and prochlorperazine, and domperidone (used to promote lactation or stomach emptying). Haloperidol, methotrimeprazine, and olanzapine are also used to control nausea in palliative care.

Excessive prescribing of antipsychotics

Deprescribing initiatives have reduced inappropriate use of antipsychotics for people with dementia living in long-term care;² yet over 25% of BC long-term care residents still received them in 2021.³ We know little about avoidable prescriptions in outpatients, but during 2021 over 172,000 community living British Columbians were dispensed at least one DA antagonist: 3.3% of BC's population, versus 2.7% in 2011.⁴ (Table)

Drug class	Examples	Patients*
All antipsychotics		172,080
Older drugs	Methotrimeprazine	10,340
many fewer:	Haloperidol	8,240
chlorpromazine, fluphenazine,	Loxapine	6,320
flupentixol, perphenazine,	Clozapine (weak antagonist)	4,360
pimozide, trifluoperazine	Zuclopenthixol	1,700
Newer drugs	Quetiapine	94,540
many fewer:	Risperidone	26,720
asenapine, ziprasidone	Aripiprazole (partial D2 agonist)	22,760
	Olanzapine	16,900
	Paliperidone (9-hydroxyrisperidone)	6,020
	Brexipiprazole (partial D2 agonist)	2,920
	Lurasidone	2,000
Other DA antagonists		
for lactation, nausea, or gastro paresis	Domperidone (low CNS penetration)	33,040
	Metoclopramide	31,480
	Prochlorperazine	4,860

* Outpatients dispensed DA antagonists in 2021.⁴

PharmaNet statistics exclude First Nations Benefit plan and Military/RCMP (federally insured).



Dopamine's role in the brain

Dopamine (DA) is a predominant neurotransmitter in brain, influencing arousal, motivation and reward, emotion, cognition, memory, motor control, and regulation of prolactin release from the anterior pituitary. Five distinct receptor types are now grouped into two families: D1-like and D2-like DA receptors.⁵

Profound effects of DA blockade

In 1952 French Army surgeon Henri Laborit described a calming effect of chlorpromazine, a recently synthesized drug related to the first antihistamines. It was soon found to reduce "positive symptoms" of schizophrenia such as hallucinations and disturbing behaviour. Availability of a drug that spared psychotic patients from straitjackets, frontal lobotomy, ECT, or insulin coma jump-started the science of psychopharmacology.⁶⁻⁷

With new pharmacological techniques, it was recognized in the 1950's that these beneficial effects were in some way related to dopamine. Appreciation that dopamine is a neurotransmitter led to discovery of its deficiency in Parkinson's disease, and breakthrough treatment with the oral DA precursor L-DOPA.⁸ The "*dopamine hypothesis of schizophrenia*" arose from the observation that drugs which block D2 dopamine receptors *in vitro* were associated with improvements in symptoms of psychosis. This working hypothesis continues to evolve in complexity, but has been criticized for the lack of supporting evidence.⁹⁻¹¹

But chlorpromazine and subsequent competitors also caused serious adverse effects. Patients experienced a range of symptoms and movement disorders collectively termed "*extrapyramidal symptoms*" (EPS), probably due to dopamine blockade. Videos embedded in the online version show patients affected by quetiapine, metoclopramide, and prochlorperazine.

- **Drug-induced Parkinsonism** includes decreased or slowed movements, rigidity, tremor, unsteadiness, and loss of facial expression. (videos 1, 2)
- **Akathisia** refers to intense internal restlessness or a constant desire to move. To diagnose “restless leg syndrome”, drug-induced akathisia must be excluded.¹²⁻¹³ (video 3)
- **Acute dystonic reaction** is a sudden, involuntary, and often painful muscle spasm that can affect the neck, eyes, back (causing painful posturing), or vocal cords (making it hard to breathe). (video 4)
- **Dyskinesia**, whether early or later onset (*tardive dyskinesia*, TD) is of special concern, because it is so hard to treat and can be permanent. TD consists of repetitive, involuntary movements that can be associated with cognitive decline.¹⁴ (videos 5, 6, 7)

Drugs from other classes that target the brain, including many antidepressants and domperidone (a DA antagonist with poor brain penetration) can cause similar symptoms and signs.¹⁵⁻¹⁹

Withdrawal symptoms, including psychosis, were recognized later as a consequence of stopping long-term antipsychotic treatment.²⁰⁻²¹ Antipsychotic drugs have other important adverse effects: cognitive (including sedation and apathy), gynecomastia/galactorrhea, weight gain, type 2 diabetes, increased cardiovascular disease, and increased mortality in nursing home patients.²²

Are “atypical antipsychotics” different?

Clozapine, the original putative “atypical antipsychotic”, causes fewer EPS, but other toxicities limit use to the most treatment refractory patients. Olanzapine, quetiapine, risperidone, and many later competitors

References

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were promoted as “atypical” or “second generation”.²³ These marketing terms imply mediation of effects through mechanisms different from DA blockade.²⁴ But while some patients tolerate one drug better than another, newer drugs retain the potential to cause serious neurological, metabolic, and other problems.²⁵⁻²⁷

Avoiding serious neurological harms

EPS are dose-related, but also occur at low doses and with short or even single exposures. (videos 3, 4, 5) Avoidance starts by prescribing DA antagonists only when essential, at the lowest effective dose, and shortest duration. Cautious time-limited prescribing is appropriate for people with psychotic disorders including schizophrenia, psychotic depression, or bipolar mania, and for some long-term care residents only after non-drug interventions are exhausted.²⁸ The same considerations apply for control of nausea, to promote stomach emptying, or to enhance breast feeding.

Conclusions

- Learn and teach the symptoms and signs of dopamine blockade. Exclude causation by DA antagonists before applying terms like “flat affect” or “restless legs” to patients.
- During treatment, re-examine patients frequently. Look and listen for EPS including drug-induced Parkinsonism, akathisia, and movement disorders.
- When renewing or dispensing a prescription, also reassess dose and duration of treatment.
- Videos embedded online at www.ti.ubc.ca/letter139 may help health professionals and students understand potential harms of DA receptor blockade.

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