Clinical Handbook of Psychotropic Drugs

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(Editors)

25

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HOW TO USE THIS BOOK

The *Clinical Handbook of Psychotropic Drugs* uses color coding and icons for intuitive navigation:

- Blue sections contain general information on drugs / treatments and their availability.
- Green sections cover drug action and dosing.
- Red sections outline warnings and precautions.
- Orange sections detail patient-related information, such as considerations for special populations, nursing and patient advice.

This page provides a summary of the colors and icons used.

At the end of each chapter, additional useful sources of information are listed as


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Clinical Handbook of Psychotropic Drugs

25th edition

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The authors and publisher have made every effort to ensure that drug selections and dosages suggested in this text are in accord with current recommendations and practice at the time of publication. However, due to changing government regulations, continuing research, and changing information concerning drug therapy and reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage, or for added precautions. The authors and publisher disclaim any responsibility for any consequences which may follow from the use of information presented in this book.

INTRODUCTION

The *Clinical Handbook of Psychotropic Drugs* is a user-friendly and practical resource guide for health care practitioners working in any setting where psychotropic drugs are utilized. Its content is derived from various forms of published literature (including randomized controlled trials, scientific data such as pharmacokinetic trials, cohort trials, case series, and case reports) as well as from leading clinical experts. The handbook is continually updated as the scientific literature evolves, so we can provide current evidence-based and clinically relevant information to optimize patient care. New sections, periodically added, reflect changes in therapy and in current practice.

For this 25th edition, we have again revised and updated the book throughout and added a number of new treatments and formulations. In the antidepressants chapter, we have added a new section on the NMDA receptor antagonist/CYP2D6 inhibitor combination product (dextromethorphan/bupropion), and the dementia chapter has a new section on lecanemab, a new fast-track FDA-approved treatment for Alzheimer's disease. The revised clozapine monitoring tables in the antipsychotics chapter now also contain monitoring requirements for patients with or without non-benign ethnic neutropenia. In the chapter on substance use disorder, we have added a rapid micro-induction method for buprenorphine that allows treatment to start without waiting for the patient to be in withdrawal.

As in previous editions, charts and tables of comparisons are employed to enable the reader to have quick access to information.

Both American and Canadian trade names are used in the text. Though plasma levels are given in SI units, conversion rates to Imperial US units are available in the text.

Given that changes may occur in a medication's indications, and differences are seen among countries, specific "indications" listed in this text as "approved" should be viewed in conjunction with product monographs approved in your jurisdiction of interest.

Dose comparisons and plasma levels are based on scientific data. However, it is important to note that some patients will respond to doses outside the reported ranges. Age, sex, and the medical condition of the patient must always be taken into consideration when prescribing any psychotropic agent.

Patient Information Sheets for most drug categories are provided as printable pdf files to facilitate education/counselling of patients receiving these medications. For details, please see p. 474.

For those who like the convenience of electronic resources, the *Clinical Handbook of Psychotropic Drugs* is also available as an online version that provides even quicker access to all the information in the handbook, with some added extras: (1) An auto-completion powered search function, (2) browse features for generic names, trade names, indications, and interacting agents, (3) column-selector enhancement of comparison charts (dosages, side effects, pharmacokinetics, interactions, etc.) that allows you to choose which information is displayed, and (4) hundreds of additional references. Further details on this can be found at https://chpd.hogrefe.com/

On behalf of the editors, I would like to express my abundant gratitude to each of the contributors. The *Clinical Handbook of Psychotropic Drugs* would not be possible if it were not for their collective expertise, investment of time, and commitment to patient care. Over the years, many readers have asked challenging questions and provided useful feedback regarding the content and format of the handbook. This input is critical to keeping this handbook current, accurate, and relevant. Please feel free to e-mail me at the address below with your comments and questions.

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TABLE OF CONTENTS

ANTIDEPRESSANTS

Classification

- Antidepressants can be classified as follows:

Pharmacological Class	Examples	Page
Cyclic Antidepressants (*)		
Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	See p. 3
Norepinephrine Dopamine Reuptake Inhibitor (NDRI)	Bupropion	See p. 19
Selective Serotonin-Norepinephrine Reuptake Inhibitor (SNRIs)	Desvenlafaxine, duloxetine, levomilnacipran, venlafaxine	See p. 25
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NMDA Receptor Antagonist	Esketamine	See p. 80
NMDA Receptor Antagonist/CYP2D6 Inhibitor	Dextromethorphan/bupropion	See p. 84

(*) Cyclic antidepressants are currently classified according to their effect on brain neurotransmitters. These neurotransmitter effects determine the antidepressants' spectrum of activity and adverse effects (see table p. 89),

General Comments

- Antidepressants are associated with a small (2–3%) risk of hostility or suicidal ideation and associated behaviors in children, adolescents, and young adults (aged up to 24 years). Risk for suicide should be closely assessed and monitored during the initial weeks of antidepressant therapy
- In patients presenting with depression and a high risk of suicide, treatment selection should consider safety in overdose (i.e., consider using newer antidepressant agents rather than nonselective cyclic and MAOI antidepressants). Prescription quantities should be consistent with safe patient care
- Some antidepressants are associated with restlessness or psychomotor agitation prior to seeing any change in core symptoms of depression. On average, all antidepressants are equally efficacious at reducing symptoms of depression though some randomized double-blind, controlled trials and systematic reviews suggest otherwise. Overall effects of antidepressants are modest when the effects of publication bias are considered. Compared to placebo, the effect size of antidepressant treatment is reported as 0.31
- Based on the most comprehensive network meta-analysis and systematic review thus far involving 21 antidepressants, only agomelatine, escitalopram, and vortioxetine demonstrated superior efficacy combined with better acceptability/tolerability when used as initial treatment for Major depressive disorder (MDD).[1] However, the authors make it clear that there are important limitations to these results – they may only help inform as to initial treatment choice, they do not reflect longer term tolerability or benefit with respect to functionality, and they do not account for individual factors which are typically used to help guide treatment selection in clinical practice

Reversible Inhibitor of MAO-A (RIMA)

Product Availability*

Generic Name	Neuroscience-based Nomenclature• (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths
Moclobemide[C]	Serotonin, norepinephrine, dopamine/Enzyme inhibitor	Manerix	Tablets: 100 mg, 150 mg, 300 mg

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com), [A] Generic preparations may be available, [C] Not marketed in the USA

Indications‡ (👍 approved)

- 👍 Major depressive disorder (MDD)
- 👍 Dysthymia, chronic
- Seasonal affective disorder (SAD), chronic fatigue syndrome, and obsessive-compulsive disorder (OCD) – weak evidence suggests efficacy
- Borderline personality disorder – suggested to modulate impulsivity/aggression and affective instability
- Social anxiety disorder

General Comments

- In patients presenting with depression and a high risk of suicide, treatment selection should consider safety in overdose (i.e., consider using newer antidepressant agents rather than nonselective cyclic and MAOI antidepressants). Prescription quantities should be consistent with safe patient care
- Increases REM sleep

Pharmacology

- Short-acting reversible inhibitor of the enzyme MAO-A; inhibits the metabolism of serotonin, norepinephrine, and dopamine
- Chronic dosing over 400 mg daily will inhibit 20–30% of MAO-B in platelets
- Inhibition reverses within 24 h
- Combining moclobemide with TCAs or lithium may increase antidepressant effect

Dosing

- Starting dose: 300 mg daily in divided doses; further dose increases should wait at least 1 week; bioavailability increases over the first week. Usual dose range: 300–600 mg daily; some patients respond to 150 mg daily, but most require doses above 450 mg/day
- Moclobemide should be taken after meals to minimize tyramine-related effects (e.g., headache)
- Preliminary data suggests that once daily dosing is as effective as divided dosing
- Dosing is not affected by age
- Hepatic disease: Decreases clearance [Management: Decrease dose by one third to one half in patients with severe hepatic impairment]
- Renal disease: Use with caution, does not affect dosing

Pharmacokinetics

- See p. 96
- Rapidly absorbed from the gut with a high first-pass effect; absorption increases from 50% with first dose to approximately 90% after 2 weeks
- Relatively lipophilic, but highly water soluble at low pH
- Low plasma-protein binding, approximately 50%, primarily albumin
- Peak effect occurs between 0.7 and 1.1 h in the absence and presence of food, respectively
- Plasma levels increase in proportion to dose; blockade of MAO-A correlates with plasma concentrations
- Extensively metabolized by oxidation; partial metabolism primarily via CYP2C19 and 2D6

‡ Indications listed here do not necessarily apply to all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration, Health Canada Drug Product Database) for the most current availability information and indications

Frequency of Adverse Reactions to Antidepressants at Therapeutic Doses

Reaction	SSRIs						NDRI	SNRIs				SARIs	
	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Bupropion	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine	Nefazodone	Trazodone
CNS Effects [–]													
Drowsiness, sedation	> 10%	> 2%	> 10%	> 10%	> 10%	> 10%	> 2%	> 10%	> 10%	–	> 10%	> 30%	> 30%
Insomnia	> 10%	> 10%	> 10%[a]	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 5%	> 10%[a]	> 2%	> 2%
Excitement, hypomania[*]	> 2%	< 2%	> 2%	> 10%	> 2%	> 10%	> 10%[b]	> 3%	> 2%	–	> 10%[b]	> 2%	–[b]
Disorientation/confusion	< 2%	< 2%	> 10%	> 2%	< 2%	< 2%	> 2%	< 2%	–	–	> 2%	> 10%	< 2%
Headache	> 10%	< 2%	> 10%	> 10%	> 10%	> 10%	> 10%	> 3%	> 10%	> 10%	> 10%	> 30%	> 2%
Asthenia, fatigue	> 10%	> 2%	> 10%	> 10%	> 10%	> 2%	> 2%	> 10%	> 10%	–	> 10%	> 10%	> 10%
Anticholinergic Effects													
Dry mouth	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 5%	> 10%	> 10%	> 10%
Blurred vision	> 2%	< 2%	> 2%	> 2%	> 2%	> 2%	> 10%	> 3%	> 2%	< 2%	> 2%	> 10%	> 2%[c]
Constipation	> 2%	> 2%	> 2%	> 10%	> 10%	> 2%	> 10%	> 10%	> 10%	< 10%	> 10%	> 10%	> 2%
Sweating	> 10%	> 2%	> 2%	> 10%	> 10%	> 2%	> 10%	> 10%	> 10%	< 10%	> 10%	> 2%	–
Delayed micturition[**]	> 2%	–	> 2%	> 2%	> 2%	< 2%	> 2%	< 2%	< 2%	> 2%[d]	< 2%	< 2%	< 2%
Extrapyramidal Effects													
Unspecified	> 2%	< 2%	< 2%	> 2%[e]	> 2%	> 2%	< 2%	?	< 2%	< 2%	> 2%	< 2%	> 2%[e]
Tremor	> 2%	< 2%	> 10%	> 10%	> 10%	> 10%	> 10%	> 2%	> 2%	< 2%	> 2%	< 2%	> 2%
Cardiovascular Effects													
Orthostatic hypotension/dizziness	> 2%	> 2%	> 10%	> 2%	> 10%	> 10%	> 2%[f]	> 10%[f]	> 10%[f]	> 10%	> 10%[f]	> 10%	> 10%[g]
Tachycardia, palpitations	> 2%[h]	> 2%[h]	< 2%[h]	< 2%[h]	> 2%[h]	> 2%[h]	> 2%	> 3%	> 2%	> 2%	> 2%[i]	< 2%[h]	> 2%
ECG changes[***]	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	–	< 2%	< 2%[i]	< 2%	> 2%
Cardiac arrhythmia	< 2%	< 2%	< 2%[k]	< 2%	< 2%	< 2%	< 2%	< 2%	–	< 2%	< 2%	< 2%	> 2%[l]
GI distress	> 10%	> 10%	> 10%	> 30%	> 10%	> 30%	> 10%	> 30%	> 10%	> 20%	> 30%	> 10%	> 10%
Dermatitis, rash	< 2%	> 2%	> 2%	> 2%	< 2%	> 2%	> 2%	< 2%	> 2%	< 2%	> 2%	< 2%	< 2%
Weight gain (over 6 kg) [#]	> 2%	< 2%	> 2%[m]	> 2%[m]	> 10%[m]	≥ 2%[m]	< 2%[m]	?	> 2%	–	> 2%[m]	> 2%	> 2%
Sexual disturbances	> 30%	> 10%	> 30%[n]	> 30%	> 30%[n]	> 30%[n]	< 2%[n][o]	> 3%	> 30%	< 10%	> 30%[n]	> 2%	< 2%[n]
Seizures [##]	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%[p]	< 2%	< 2%	< 1%	< 2%	< 2%	< 2%

[–] None reported in literature perused, [*] More likely in bipolar patients, [**] Primarily in the elderly, [***] ECG abnormalities usually without cardiac injury, [#] With chronic treatment, [##] In nonepileptic patients; risk increased with elevated plasma levels
[a] Especially if given in the evening, [b] Less likely to precipitate mania, [c] Found to lower intraocular pressure, [d] Dose-related [e] Tardive dyskinesia reported (rarely), [f] Hypertension reported; may be more common in patients with pre-existing hypertension, [g] Less frequent if drugs given after meals, [h] Decreased heart rate reported, [i] Increased risk with higher doses, [k] Slowing of sinus node and atrial dysrhythmia, [l] Patients with pre-existing cardiac disease have a 10% incidence of premature ventricular contractions, [m] Weight loss reported initially, [n] Priapism reported, [o] Improved sexual functioning, [p] Higher incidence if doses used above 450 mg/day of bupropion or in patients with bulimia

Switching Antidepressants

Antidepressant Nonresponse

- Ascertain that diagnosis is correct and that patient is compliant with therapy
- Ensure dosage prescribed is therapeutic; measure plasma level; ensure there has been an adequate trial period, i.e., up to 6 weeks at a reasonable dose
- Regular, systematic assessment of the patient's response to drug therapy, with the use of measurement tools for symptoms, adverse effects, and patient adherence is useful to guide future clinical decisions

Factors Complicating Response

- Concurrent medical or psychiatric illness, e.g., hypothyroidism, OCD
- Personality disorders lead to poor outcome; however, depression may evoke personality problems that may disappear when the depression is alleviated
- Drug abuse may make management difficult (e.g., cocaine); see CANMAT recommendations
- Psychosocial factors may affect response
- Low folate levels associated with lack of remission, response and relapse
- Concurrent prescription drugs may interfere with efficacy (e.g., calcium channel blockers)
- Metabolic inducers (e.g., carbamazepine) or inhibitors (e.g., erythromycin) will affect plasma level of antidepressant
- Genetic variants

Switching Antidepressants

- Switching from one SSRI to another can enhance response in previously nonresponsive patients
- 20–25% remission rate when switching from SSRI to another class of antidepressant or a different SSRI after failure of first SSRI (STAR*D studies)
- Switching between tricyclic agents is of questionable benefit
- One study found significantly higher response rates when switching from imipramine to sertraline than vice versa and better tolerability
- Two studies have demonstrated that switching imipramine nonresponders to phenelzine was superior to switching phenelzine nonresponders to imipramine
- Use caution when switching to or from irreversible MAOIs (see Switching Antidepressants, pp. 97–99)

Advantages of Switching

- Minimizes polypharmacy
- Decreased risk of drug interactions
- Second agent may be better tolerated
- Improved compliance
- Less costly

Disadvantages of Switching

- Loss of partial efficacy of first agent
- Time required to taper first agent or need for a washout (risk of relapse)
- Delayed onset of action

Switching Strategies

Switching from		Switching to	Switching Method[a]
SSRI (not fluoxetine)	→	SSRI (including fluoxetine)	Direct switch, **OR** taper, stop, and switch
	→	NDRI, SPARI, clomipramine	Taper, stop, and switch
	→	SNRI	Taper, stop, and switch, **OR** cross-taper
	→	SARI, SMS, NaSSA, nonselective cyclics (not clomipramine)	Cross-taper
	→	RIMA, Irreversible MAOI, MAO-B	Taper, stop, washout (1 week), and switch

Antipsychotic Doses and Pharmacokinetics (Oral and Short-Acting Injections)

FIRST-GENERATION AGENTS (FGAs)										
Drug	**Oral CPZ Equivalents (mg)[1]**	**Monograph Doses for Psychosis**	**Bioavailability**	**Protein Binding**	**Peak Plasma Level (h) (T_{max})**	**Elimination Half-Life (h)**	**Metabolizing Enzymes[2] / Transporters (CYP450; other)**	**Enzyme Inhibition[3] / Transporters (CYP450; other)**	**% D_2 Receptor Occupancy[4] (dose & plasma level)**	**% 5-HT_{2A} Occupancy (dose)**
Chlorpromazine (Largactil[C], Thorazine[B])	100	Oral: Start: 25–75 mg daily in 2–4 divided doses; increase by 20–50 mg twice weekly. Recommended maximum: 1 g/day. Give od or bid for maintenance with larger dose at at bedtime Short-acting IM: Start: 25 mg followed by 25–50 mg in 1 h if needed, then q 3–12 h prn. Can increase over several days. Recommended maximum (acute psychosis or mania): 400 mg q 4–6 h	Oral: 25–65%	95–99% (to albumin)	Oral: 0.51	Oral: 16–30	1A2[w], **2D6**[p], 3A4[w]; UGT1A4	1A2, **2D6**[p], 3A4[w], 2C9[w], 2C19, 2E1; P-gp	78–80% (100–200 mg; 10 nmol/L)	?
Flupenthixol[C] (Fluanxol)	2	Oral: Start: 1 mg tid; increase by 1 mg q 2–3 days if needed. Usual = 3–6 mg/day in divided doses; up to 12 mg/day used in some patients	30–70%	99%	3–8	26–36	?	2D6[w]	70–74% (5–10 mg; 2–5 nmol/L)	?
Fluphenazine HCL (Moditen[C], Prolixin[B])	2	Oral: Start: 2.5–10 mg daily in divided doses q 6–8 h. Maintenance: 1–5 mg/day. Doses greater than 20 mg = use with caution Short-acting IM or SC: Start: 1.25 mg; range 2.5–10 mg daily divided q 6–8 h. Doses greater than 10 mg = use with caution	1–50%	90–99%	Oral: 0.5 Short-acting IM: 1.5–2	Oral: 13–58 Short-acting IM: 13–58	1A2, 2D6; P-gp	1A2, **2D6**[p], 3A4[w], 2E1 2C8/9; P-gp	?	?
Haloperidol (Haldol)	2	Oral: Start: 1.5–3 mg divided bid or tid (elderly 0.25–1 mg od or divided bid) Maintenance: 4–12 mg divided od–tid Usual maximum = 20 mg/day 85–100 mg daily used rarely	40–80%	92% (to α_1-AGP)	0.5–3	12–36	1A2[w], 2D6[w], **3A4**[p]	**2D6**, 3A4; P-gp[w]	75–89% (4–6 mg; 6–13 nmol/L)	?
Haloperidol lactate		Short-acting IM: 2–5 mg (0.5–1 mg in the elderly) q 4–8 h prn; may repeat q 1 h if required Maximum: 20 mg/day (elderly ~5 mg/day)			Short-acting IM (lactate): 10–20 min					

Indications‡
(👍 approved)

	SECOND-GENERATION AGENTS		THIRD-GENERATION AGENTS			
	Carbamazepine	**Valproate**	**Gabapentin**	**Lamotrigine**	**Oxcarbazepine**	**Topiramate**
Acute mania	👍 + (second-line agent as combination therapy)	👍 + (first-line agent as mono- or combination therapy; also effective in case series of corticosteroid-induced mania)	not recommended	not recommended	+/– (third-line agent as combination therapy)	not recommended
Acute bipolar I depression	+ (third-line agent)	+ (second-line agent)	–	+ (first-line agent) (– evidence in combination with folic acid)	?	?
Maintenance of bipolar I disorder	👍 + (second-line agent)	+ (first-line agent)	+ (third-line adjunctive agent)	👍 + (first-line agent; limited efficacy in preventing mania)	+/–	?
Acute bipolar II depression	?	?	?	+ (second-line agent)	?	?
Maintenance of bipolar II disorder	+ (third-line agent)	+ (third-line agent)	?	+ (first-line agent	?	?
Rapid-cycling bipolar disorder	👍 +/–	+	?/–	– (bipolar I) + (bipolar II)	–	?/–
Mixed states	+	+	?	not recommended	+ (adjunctive drug)	–
Anticonvulsant	👍 Partial and generalized tonic-clonic seizures. Not effective for absence, myoclonic or atonic seizures	👍 Complex partial seizures with and without other seizure types (monotherapy or adjunctive) 👍 Simple and complex absence seizures (monotherapy or adjunctive) 👍 Adjunctive agent in adults with multiple seizure types	👍 Partial seizures with and without secondary generalization (adjunctive) 👍 Epilepsy not satisfactorily controlled by conventional therapy (adjunctive)	👍 Partial onset seizures and primary generalized tonic-clonic seizures (adjunctive) 👍 Partial-onset seizures (monotherapy) 👍 Generalized seizures associated with Lennox-Gastaut (adjunctive)	👍 Partial seizures (monotherapy or adjunctive)	👍 Partial onset or primary generalized tonic-clonic seizures (monotherapy) 👍 Partial onset seizures, primary generalized tonic-clonic seizures, seizures associated with Lennox-Gastaut (adjunctive)
Paroxysmal pain syndromes	👍 + (Trigeminal neuralgia); glossopharyngeal neuralgia in some patients ? Fibromyalgia	+ (diabetic neuropathy, postherpetic neuralgia)	👍 Postherpetic neuralgia + (neuropathic pain) ? Complex regional pain syndrome/ fibromyalgia	+/– (central pain); Cochrane review: ineffective in neuropathic pain and fibromyalgia	+/– (neuropathic pain, trigeminal neuralgia)	– (neuropathic pain); Cochrane review: no separation from placebo

‡ Indications listed here do not necessarily apply to all anticonvulsants or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration, Health Canada Drug Product Database) for the most current availability information and indications

Comparison of Anticonvulsants (cont.)

	Carbamazepine	Gabapentin	Lamotrigine	Oxcarbazepine	Topiramate	Valproate
Pharmacokinetics						
Bioavailability	75–85%	Approx. 60% (dose dependent; higher with qid dosing)	100%	> 95%	80%	78–90%
Peak plasma level	1–6 h	2–3 h	1–5 h (rate may be reduced by food)	1–3 h (parent) 4–12 h (active MHD metabolite) and 2–4 h at steady state	2–4 h (delayed by food)	Oral valproic acid: 1–4 h (may be delayed by food) Divalproex and extended-release: 3–8 h
Protein binding	75–90%	Minimal	55%	40% (MHD)	15–41%	60–95% (concentration dependent); increased by low-fat diets. Decreased in elderly, hepatic or renal impairment, concurrent use of highly protein bound drugs
Half-life	15–35 h (acute use); 10–20 h (chronic use) – stimulates own metabolism	5–7 h	33 h mean (acute use) 26 h mean (chronic use)	Parent: 1–5 h MHD metabolite: 7–20 h	19–23 h	5–20 h
Metabolizing enzymes	CYP1A2, 3A4$^{(m)}$, 2C8, 2C9; P-gp	Not metabolized – eliminated by renal excretion	Metabolized primarily by glucuronic acid conjugation; also by UGT1A4, 2B7	Rapidly metabolized by cytosolic enzymes to active metabolite MHD	P-gp; 70% eliminated unchanged in urine	CYP2C9; UGT1A6, 1A9, 2B7
Metabolism effects	Inducer of CYP1A2$^{(p)}$, 3A4$^{(p)}$, 2C8$^{(p)}$, 2C9$^{(p)}$, 2C19$^{(p)}$, 2B6$^{(p)}$, 3A4$^{(p)}$ and UGT1A4 Induces own metabolism (auto-induction) Inducer of P-gp	–	–	Moderate inducer of CYP3A4 Inhibitor of CYP2C19$^{(w)}$ and UGT1A4 (does not induce own metabolism)	Weak inhibitor of CYP2C19; weak inducer of 3A4	Inhibitor of CYP2D6$^{(w)}$, 2C9, 2C19; UGT2B7$^{(p)}$, 2B15, 3A4$^{(w)}$
Adverse Effects						
CNS	Sedation (11%), cognitive blunting, confusion (higher doses)	Sedation (19%), fatigue (11%), abnormal thinking, amnesia	Sedation (> 10%), asthenia, cognitive blunting, "spaced-out" feeling	Sedation (19%), lethargy	Sedation (6–15%), lethargy, fatigue (8–15%) Deficits in word finding, concentration, and memory (dose dependent, 1–11%)	Sedation (> 10%), lethargy, behavior changes/deterioration, cognitive blunting, encephalopathy
	Agitation, restlessness, irritability, insomnia May exacerbate schizophrenia on withdrawal	Nervousness, anxiety, hostility Rare switches to hypomania/mania Cases of depression	Agitation, activation, irritability, insomnia Switches to hypomania/mania		Anxiety, agitation, insomnia Increased panic attacks, worsening of depression or psychosis	Hyperactivity, aggression Case of delirium (following loading-dose strategy) Rare cases of psychosis

DRUGS FOR TREATMENT OF DEMENTIA

Classification

- Drugs for treatment of dementia can be classified as follows:

Chemical Class	Agent	Page
Cholinesterase inhibitors	Donepezil Rivastigmine Galantamine	See p. 339
Aminoadamantane	Memantine	See p. 346
Amyloid beta-directed antibody	Lecanemab	See p. 349

Cholinesterase Inhibitors

Product Availability*

Generic Name	Chemical Class	Neuroscience-based Nomenclature* (Pharmacological Target/Mode of Action)	Trade Name[A]	Dosage Forms and Strengths
Donepezil	Piperidine	Acetylcholine/Enzyme inhibitor	Aricept	Tablets: 5 mg, 10 mg, 23 mg[B] Orally disintegrating tablets: 5 mg, 10 mg
Galantamine (Galanthamine)	Phenanthrene alkaloid	Acetylcholine/Multimodal	Razadyne[B] Reminyl ER[C], Razadyne ER[B]	Tablets: 4 mg, 8 mg, 12 mg Liquid: 4 mg/mL Extended-release capsules: 8 mg, 16 mg, 24 mg
Rivastigmine	Carbamate	Acetylcholine/Enzyme inhibitor	Exelon Exelon Patch	Capsules: 1.5 mg, 3 mg, 4.5 mg, 6 mg Oral solution: 2 mg/mL Patch: 5 (4.6 mg/24 h), 10 (9.5 mg/24 h), 15 (13.3 mg/24 h)

* Refer to Health Canada's Drug Product Database or the FDA's Drugs@FDA for the most current availability information. • Developed by a taskforce consisting of representatives from the American College of Neuropsychopharmacology (ACNP), the Asian College of Neuropsychopharmacology (AsCNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the International Union of Basic and Clinical Pharmacology (IUPHAR) (see https://nbn2r.com),
[A] Generic preparations may be available, [B] Not marketed in Canada, [C] Not marketed in the USA

Indications‡ (👍 approved)

- 👍 Dementia of Alzheimer's type – mild, moderate (donepezil, galantamine, rivastigmine), and severe (donepezil, memantine, rivastigmine patch (USA)): Symptomatic treatment of mild to moderate disease; no proof of a beneficial effect on the underlying neurodegenerative process but some disease markers may be positively affected (e.g., hippocampal volume loss)
- 👍 Dementia of Parkinson's disease – mild to moderate (rivastigmine)
- 👍 Alzheimer's disease: Treatment of severe disease (donepezil, memantine)
- Galantamine in conjunction with memantine have shown efficacy for the treatment of cognitive impairment post traumatic brain injury
- Galantamine and donepezil suggested to improve cognition and behaviors and to stabilize or improve activities of daily living

‡ Indications listed here do not necessarily apply to all cholinesterase inhibitors or all countries. Please refer to a country's regulatory database (e.g., US Food and Drug Administration, Health Canada Drug Product Database) for the most current availability information and indications

Cholinesterase Inhibitors (cont.)

Use in Pregnancy◊

- Based on animal data, may cause fetal harm. Adequate, well-controlled human studies are lacking, and animal studies have shown risk to the fetus or are lacking as well

Breast Milk

- Not recommended for nursing women

Nursing Implications

- Advise patients to take the drug as directed; increasing the dose will increase adverse effects while skipping doses will decrease the benefit of the drug
- Advise patients not to stop the medication abruptly, as changes in behavior and/or concentration can occur
- Anticholinergic agents (including over-the-counter drugs, e.g., antinauseants) will reduce the effects of these drugs and should be avoided
- Rivastigmine patches should be kept sealed until use. Apply the first rivastigmine patch the day following the last oral dose. The location of the patch should be rotated and the patch applied to the upper or lower back, upper arm, or chest; if there is potential for the patient to remove the patch, apply it onto an inaccessible area. **Remove patch after 24 h, prior to applying the next dose** – fold it in half with the adhesive sides on the inside and dispose of in waste container; wash hands after handling
- Advise patient that rivastigmine patch may compromise driving ability
- Advise patient to stop taking rivastigmine and inform doctor if a rash develops
- The 23 mg donepezil tablet should not be split, crushed or chewed because this may increase the rate of absorption

Patient Instructions

- For detailed patient instructions on cognition enhancers, see the Patient Information Sheet (details p. 474)

Drug Interactions

- Clinically significant interactions are listed below
- For more interaction information on any given combination, also see the corresponding chapter for the second agent

DRUGS INTERACTING WITH DONEPEZIL

Class of Drug	Example	Interaction Effects
Antiarrhythmic	Quinidine	Inhibited metabolism of donepezil via CYP2D6
Antibiotic	Clarithromycin, erythromycin	Inhibited metabolism of donepezil via CYP2D6
Anticholinergic	Benztropine, diphenhydramine	Antagonism of effects
Anticonvulsant	Carbamazepine, phenytoin, phenobarbital	Increased metabolism of donepezil, resulting in decreased efficacy
Antidepressant	SSRI – fluoxetine, paroxetine	May increase plasma level of donepezil by inhibiting metabolism via CYP2D6. Fulminant hepatitis reported in combination with a high dose of sertraline Case reports of increased GI and CNS adverse effects as well as extrapyramidal symptoms with paroxetine and donepezil
	Nefazodone	Inhibited metabolism of donepezil via CYP3A4
Antifungal	Itraconazole, ketoconazole	Inhibited metabolism of donepezil via CYP3A4
Antipsychotic	Risperidone	Exacerbation of EPS; worsening of Parkinson's disease
Antitubercular drug	Rifampin	Increased metabolism of donepezil, resulting in decreased efficacy
β-blocker	Propranolol	May potentiate bradycardia; may increase risk of bronchospasm
Cholinergic agonist	Bethanechol	Synergistic effects: Increased nausea, vomiting, and diarrhea
Neuromuscular blocker	Succinylcholine, suxamethonium	Prolonged neuromuscular blockade

◊ See p. 473 for further information on drug use in pregnancy and effects on breast milk

UNAPPROVED TREATMENTS OF PSYCHIATRIC DISORDERS

Product Availability*

Several drugs traditionally used to treat medical conditions have been helpful in ameliorating or preventing symptoms of certain psychiatric disorders. This section presents a summary of some of these drugs and their uses. **As a general rule, unapproved treatments should be reserved for patients highly resistant to conventional therapies. Clinicians should be cognizant of medicolegal issues when prescribing drugs for non-approved indications.**

	Anxiety Disorders	Bipolar Disorder	Dementia	Depression	Psychosis	Substance Use Disorders
Adrenergic agents						
β-blockers (atenolol, propranolol) (p. 426)	+/C					
Doxazosin (p. 427)	PR (PTSD)					PR (alcohol)
Prazosin (p. 427)	C (PTSD)					PR/S/C (alcohol)
Thyroid hormones (p. 428)		C/S		+/S		
Anti-inflammatory agents						
Celecoxib (p. 430)	PR/S	S/C		+/S	S/C (SCZ)	
Cytokine inhibitors (e.g., adalimumab, etanercept, infliximab, tocilizumab) (p. 431)				PR		
Glucocorticoid (p. 431)	C (PTSD)					
Minocycline (p. 432)				S/C	+/S/C (SCZ)	
Pioglitazone, rosiglitazone (p. 433)				S/C	PR	
Statins (p. 434)				PR/S/C		
Cannabinoids (e.g., nabilone, dronabinol, nabiximols) (p. 434)	+ (PTSD)					+/S (cannabis withdrawal)
Dopaminergic agents						
Armodafinil (p. 435)		+/S				
Modafinil (p. 436)		PR/S		+/S		
Pramipexole (p. 436)		+/S		+/S		
GABA agents/anticonvulsants						
Baclofen (p. 437)						C (alcohol)
Pregabalin (p. 438)	+/S					+/C (alcohol)
Sodium oxybate (p. 439)						+/S (alcohol)
Hormones						
Estrogen/progesterone (p. 440)			C	+/S/C	+/S (females) (SCZ)	
Raloxifene (p. 442)					+/S/C (SCZ)	
Tamoxifen (p. 442)		PR/S (mania)				
Testosterone (p. 443)			C	S/C		