Clinical Handbook of Psychotropic Drugs

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(Editors)

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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

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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.

In this 22nd edition, we have revised the table outlining antidepressant switching recommendations and added a table summarizing unapproved treatments under investigation for treatment of substance use disorders. The chapter on pharmacogenomic information for common psychotropic medications has been restructured and expanded.

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. 415.

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 http://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 (SSRI)	Citalopram, fluoxetine, paroxetine, escitalopram, fluvoxamine, sertraline	See p. 3
Norepinephrine Dopamine Reuptake Inhibitor (NDRI)	Bupropion	See p. 16
Selective Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)	Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran	See p. 22
Serotonin-2 Antagonists/Serotonin Reuptake Inhibitors (SARI)	Trazodone, nefazodone	See p. 29
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Reversible MAO-A Inhibitor (RIMA)	Moclobemide	See p. 56
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Irreversible MAO-B Inhibitor	Selegiline	See p. 66

(*) 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. 70).

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
- One meta-analysis of "new generation" antidepressants found that escitalopram and sertraline had better efficacy and acceptability for treating MDD[1]
- Prophylaxis of depression is most effective if the therapeutic dose is maintained; continued therapy with all classes of antidepressants has been shown to significantly reduce risk of relapse
- Different antidepressant classes may be combined in patients with a partial response or in refractory cases; however, combinations should be assessed for potential interactions such as serotonin syndrome; additional monitoring should be implemented when necessary
- Tolerance (tachyphylaxis or "poop-out" syndrome) has been reported in 10–20% of patients on antidepressants, despite adherence to therapy. Possible explanations include adaptations in the CNS, increased disease severity or pathogenesis, loss of placebo effect, unrecognized rapid-cycling, incorrect diagnosis, comorbid substance use, anxiety disorders, ADHD or eating disorders [Management: check compliance; adjust dosage; switch to an alternate antidepressant (p. 78) or utilize augmentation strategies (p. 80)]

Frequency of Adverse Reactions to Antidepressants at Therapeutic Doses

Reaction	SSRI						NDRI	SNRI				SARI	
	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Bupropion	Venlafaxine	Desvenlafaxine	Duloxetine	Levomilnacipran	Trazodone	Nefazodone
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%[a]	> 10%	> 10%	> 5%	> 2%	> 2%
Excitement, hypomania*	> 2%	< 2%	> 2%	> 10%	> 2%	> 10%	> 10%[b]	> 10%[b]	> 3%	> 2%	–	–[b]	> 2%
Disorientation/confusion	< 2%	< 2%	> 10%	> 2%	< 2%	< 2%	> 2%	> 2%	?	–	–	< 2%	> 10%
Headache	> 10%	< 2%	> 10%	> 10%	> 10%	> 10%	> 10%	> 10%	> 3%	> 10%	> 10%	> 2%	> 30%
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%	> 10%	> 5%	> 10%	> 10%
Blurred vision	> 2%	< 2%	> 2%	> 2%	> 2%	> 2%	> 10%	> 2%	> 3%	> 2%	< 2%	> 2%[c]	> 10%
Constipation	> 2%	> 2%	> 2%	> 10%	> 10%	> 2%	> 10%	> 10%	> 10%	> 10%	< 10%	> 2%	> 10%
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%
Extrapyramidal Effects													
Unspecified	> 2%	< 2%	< 2%	> 2%[e]	> 2%	> 2%	< 2%	> 2%	?	< 2%	< 2%	> 2%[e]	< 2%
Tremor	> 2%	< 2%	> 10%	> 10%	> 10%	> 10%	> 10%	> 2%	?	> 2%	< 2%	> 2%	< 2%
Cardiovascular Effects													
Orthostatic hypotension/dizziness	> 2%	> 2%	> 10%	> 2%	> 10%	> 10%	> 2%[f]	> 10%[f]	> 10%[f]	> 10%[f]	> 10%	> 10%[g]	> 10%
Tachycardia, palpitations	> 2%[h]	> 2%[h]	< 2%[h]	< 2%[h]	> 2%[h]	> 2%[h]	> 2%	> 2%[i]	> 3%	> 2%	> 2%	> 2%	< 2%[h]
ECG changes***	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%[i]	< 2%	–	< 2%	> 2%	< 2%
Cardiac arrhythmia	< 2%	< 2%	< 2%[k]	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	–	< 2%	> 2%[l]	< 2%
GI distress	> 10%	> 10%	> 10%	> 30%	> 10%	> 30%	> 10%	> 30%	> 30%	> 10%	> 20%	> 10%	> 10%
Dermatitis, rash	< 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%[m]	?	> 2%	–	> 2%	> 2%
Sexual disturbances	> 30%	> 10%	> 30%[n]	> 30%	> 30%[n]	> 30%[n]	< 2%[n][o]	> 30%[n]	> 3%	> 30%	< 10%	< 2%[n]	> 2%
Seizures ##	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%	< 2%[p]	< 2%	?	< 2%	< 1%	< 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

Antidepressant Doses and Pharmacokinetics

Drug	Therapeutic Dose Range (mg)	Comparable Dose (mg)	Suggested Plasma Level (nmol/L)	Bio-availability (%)	Protein Binding (%)	Peak Plasma Level (h) (T_{max})	Elimination Half-life (h) ($T_{1/2}$)	Metabolizing Enzymes* (CYP450; other)	Enzyme Inhibition** (CYP450; other)
SSRIs									
Citalopram (Celexa)	10–40	10		80	80	4	23–45[b]	2D6[c][m], 2C19[m], 3A4[m]	2D6[w], 2C9[w], 2C19[w]
Escitalopram (Lexapro, Cipralex)	10–20	5		80	56	4–5 (metabolite = 14)	27–32[b] [d]	2D6[m], 3A4[m], 2C19[m]	2D6[w], 2C9[w], 2C19[w]
Fluoxetine (Prozac)	10–80[e]	10		72–85	94	6–8 (immediate release)	24–144 (parent)[b] 200–330 (metabolite)	1A2[w], 2B6[w], **2D6**[c] [p], 3A4[w], **2C9**[p], **2C19**[p], 2E1	1A2[m], 2B6[w], **2D6**[p], 3A4[c] [w], 2C9[w], 2C19[m]; P-gp
Fluoxetine delayed release (Prozac Weekly)	90 mg/week	10		72–85	94	6–8 (absorption delayed 1–2 h)	24–144 (parent)[b] 200–330 (metabolite)	1A2[w], 2B6[w], 2D6[c] [m], 3A4[w], **2C9**[p], **2C19**[p], 2E1	1A2[m], 2B6[w], **2D6**[p], 3A4[c] [w], 2C9[w], 2C19[m]; P-gp
Fluvoxamine (Luvox)	50–300[e]	35		60	77–80	1.5–8	9–28[b]	1A2[w], 2D6	**1A2**[p], 2B6[w], 2D6[m], 3A4[w], 2C9[m], **2C19**[p]; P-gp
Paroxetine (Paxil)	10–60[e]	10		> 90	95	5.2 (immediate release)	3–65[b] [d]	**2D6**[p]; P-gp	1A2[w], **2B6**[p], **2D6**[p], 3A4[w], 2C9[w], 2C19[m]; P-gp
Paroxetine CR (Paxil CR)	12.5–75	12.5		> 90	95	C_{max} = 6–10 (CR)	15–20	**2D6**[p]; P-gp	1A2[w], **2B6**[p], **2D6**[p], 3A4[w], 2C9[w], 2C19[m]; P-gp
Sertraline (Zoloft)	50–200[e]	25		70	98	6	22–36 (parent) [b] [d] 62–104 (metabolite)	2B6, 2D6, **3A4**[p], 2C9, 2C19[m]; UGT2B7	1A2[w], 2B6[m], 2D6[w], 3A4[w], 2C9[w], **2C19**[p]; P-gp
NDRI									
Bupropion (Wellbutrin)	225–450[f]	100[f]	75–350[a]	> 90	80–85	1.6 (immediate release)	10–14 (parent)[b]	1A2[w], **2B6**[p], 2D6[c], 3A4[w], 2C9[w], 2E1[m]	2D6[w]
Bupropion SR (Wellbutrin SR, Zyban)	150–300[f]	150[f]				3 (bupropion) 6 (metabolite) (SR)	20–27 (metabolites)		
Bupropion ER (Forfivo XL – only used after initial titration with other bupropion HCL products)	450	450				5 (fasting); delayed in fed state			
Bupropion ER (Aplenzin)	174–522	150–450				5			

Effects of Antipsychotics on Neurotransmitters/Receptors*

	Iloperidone	Paliperidone	Risperidone	Lurasidone	Ziprasidone	Clozapine	Asenapine	Quetiapine	Olanzapine	Aripiprazole	Cariprazine	Brexpiprazole
D_2 blockade	+++	++++	++++	++++	++++	++	++++	++	+++	+++++[a]	+++++[a]	+++++[a]
H_1 blockade	++	+++	+++	+	+++	++++	++++	+++	++++	+++	+++	+++
M_1 blockade	+	—	—	+	—	+++[a]	+	++	++++	—	—	+
M_3 blockade	+	—	+	?	+	+++	?	+	+++	+	—	?
α_1 blockade	++++	++++	++++	+++	+++	++++	++++	+++	+++	+++	++	+++
α_2 blockade	++	+++	++	+++	++	++	++++	+++	++	+++	?	+++
5-HT_{1A} blockade	++[a]	++	++	++++[a]	+++[a]	++[a]	++++	++[a]	+	++++[a]	++++[a]	+++++[a]
5-HT_{2A} blockade	+++++	+++++	+++++	+++++	++++	+++	+++++	+++	++++	++++	+++	+++++
5-HT_{2C} blockade	+++	+++	+++	++	+++	+++	+++++	+	++++	+++	++	?
5-HT_7 blockade	++	+++	++++	+++++	++++	+++	+++++	++	++	++++	++	++++

[a] Partial agonist

	Haloperidol	Loxapine	Pimozide	Chlorpromazine	Methotrimeprazine	Fluphenazine	Perphenazine	Thioproperazine	Trifluoperazine	Periciazine	Pipotiazine	Thioridazine	Flupenthixol	Thiothixene	Zuclopenthixol
D_2 blockade	+++++	++++	++++	++++	+++	+++++	+++++	+++++	++++	++++	+++++	++++	+++++	+++++	+++++
H_1 blockade	+	+++	+	+++	+++++	+++	++++	?	++	?	?	+++	+++	+++	+++
M_1 blockade	+	++	+	+++	?	+	+	?	+	?	?	++++	+++	+	++
M_3 blockade	+	++	?	+++	?	+	+	?	?	?	?	+++	?	?	?
α_1 blockade	+++	+++	+++	++++	?	+++	+++	?	+++	?	?	++++	+++	++	++++
α_2 blockade	+	+	++	++	?	+	++	+	+	+	?	+	++	++	++
5-HT_{1A} blockade	+	+	++	+	?	++	++	?	++	?	?	++	?	++	?
5-HT_{2A} blockade	+++	++++	+++	++++	++++	++++	++++	++	++++	?	+++	++++	++++	+++	++++
5-HT_{2C} blockade	+	+++	+	+++	?	++	++	?	++	?	?	+++	?	+	?
5-HT_7 blockade	++	+++	+++++	+++	?	++++	+++	?	++	?	?	+++	?	+++	?

Key: K_i (nM) > 10,000 = –; 1000–10,000 = +; 100–1000 = ++; 10–100 = +++; 1–10 = ++++; 0.1–1 = +++++; ? = unknown

See p. 167 for Pharmacological Effects on Neurotransmitters.

Adapted from: [7, 24, 25, 26, 27, 28, 29]. See also the National Institute of Mental Health's Psychoactive Drug Screening Program. Available at http://pdsp.med.unc.edu

* The ratio of K_i values (inhibition constant) between various neurotransmitters/receptors determines the pharmacological profile for any one drug

Comparison of Long-Acting IM Antipsychotics

	SECOND-GENERATION AGENTS (SGAs)*				THIRD-GENERATION AGENTS (TGAs)
	Olanzapine pamoate[B] (Zyprexa Relprevv)	**Paliperidone palmitate 1-monthly (Invega Sustenna)**	**Paliperidone palmitate 3-monthly (Invega Trinza)**	**Risperidone (Risperdal Consta)**	**Aripiprazole (Abilify Maintena)**
Chemical class	Thieobenzodiazepine	Benzisoxazole	Benzisoxazole	Benzisoxazole	Phenylpiperazine
Form	Yellow solid of olanzapine pamoate monohydrate crystals forming a yellow, opaque suspension on reconstitution with provided aqueous diluent	White to off-white sterile, aqueous, extended-release suspension in prefilled syringes	White to off-white sterile, aqueous, extended-release suspension in prefilled syringes	White to off-white, free-flowing powder with risperidone encapsulated in a polymer as extended-release microspheres. Must be reconstituted with provided aqueous base just prior to use	White to off-white lyophilized powder forming an opaque, milky-white suspension on reconstitution with provided sterile water for injection
Strength supplied	210 mg/vial, 300 mg/vial, 405 mg/vial	Strengths vary in different countries, e.g., US labeling indicates the amount of paliperone palmitate: 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL Canadian labeling indicates only the amount of paliperidone (not the palmitate base): 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/mL, 150 mg/1.5 mL	Strengths vary in different countries, e.g., US labeling indicates amount of paliperone palmitate: 273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, 819 mg/2.625 mL Canadian labeling indicates only the amount of paliperidone (not the palmitate base): 175 mg/0.875 mL, 263 mg/1.315 mL, 350 mg/1.75 mL, 525 mg/2.625 mL	12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial	300 mg/vial, 400 mg/vial
Administration	Gluteal muscle Deep IM injection	Deltoid muscle for days 1 and 8. Deltoid or gluteal muscle thereafter Deep IM injection	Deltoid or gluteal muscle Single, deep IM injection (not divided)	Deltoid or gluteal muscle Deep IM injection	Gluteal muscle Deep IM injection
Overlap with oral formulation	None	None	None	3 weeks	2 weeks
Starting dose[A]	For 1st 8 weeks: If previously on 10 mg/day oral = 210 mg IM/q 2 weeks or 405 mg/q 4 weeks; 15–20 mg/day oral = 300 mg/q 2 weeks. In patients who are debilitated or prone to hypotension, start with 150 mg IM/q 4 weeks	Day 1: 234 mg IM of paliperidone palmitate (150 mg of paliperidone) Day 8: 156 mg IM of paliperidone palmitate (100 mg of paliperidone) For dosing in renal or hepatic impairment see SGA Dosing section p. 111	Only to be used after treatment with paliperidone 1-monthly IM has been established as an adequate treatment for at least 4 months Initiate paliperidone 3-monthly IM when the next paliperidone 1-monthly IM dose is due (+/- 7days), using a 3.5-fold higher dose than that of the previous 1-monthly formulation injection	25 mg IM q 2 weeks Continue oral risperidone for the first 3 weeks For dosing in renal or hepatic impairment see SGA Dosing section p. 111	400 mg IM q 4 weeks Continue oral aripiprazole (10–20 mg) for the first 14 days

Class of Drug	Example	Interaction Effects
Antibiotic	Erythromycin, clarithromycin	Decreased clearance and increased plasma level of guanfacine due to inhibition of CYP3A4 metabolism
	Rifampin	Decreased guanfacine levels due to CYP3A4 induction; monitor for signs and symptoms of altered response. With the XR formulation, higher dosages (up to 8 mg/day) and dose increments (2 mg/week) may be required
Anticonvulsant	Carbamazepine	Decreased guanfacine levels due to CYP3A4 induction; monitor for signs and symptoms of altered response. With the XR formulation, higher dosages (up to 8 mg/day) and dose increments (2 mg/week) may be required
	Divalproex, valproic acid	Increased valproate levels; may be due to competition between valproate and guanfacine metabolite (3-hydroxy guanfacine) for glucuronidation enzymes
Antidepressant	Desipramine, bupropion	Clonidine withdrawal may result in excess circulating catecholamines; use caution in combination with noradrenergic or dopaminergic antidepressants
	Imipramine, desipramine, SNRI	Inhibition of antihypertensive effect of α_{2A} agonist by the antidepressant
Antifungal	Itraconazole, ketoconazole	Decreased clearance and increased plasma level of guanfacine due to inhibition of CYP3A4 metabolism
Antihypertensive	Hydrochlorothiazide, ramipril	Additive hypotension
β-blocker	Propranolol	Additive bradycardia
CNS depressant	Antihistamines, alcohol	Additive CNS depressant effects
Stimulant	Dextroamphetamine, methylphenidate	Additive effect on hyperactivity and aggression associated with ADHD Kapvay (clonidine XR) and Intuniv/Intuniv XR (guanfacine XR) are approved for adjunctive use with stimulant medications

Augmentation Strategies in ADHD

Nonresponse in ADHD

- Ascertain whether diagnosis is correct
- Ascertain if patient is adherent with therapy (speak with caregivers, check with pharmacy for late refills, count remaining pills in container and compare to prescription fill date)
- Ensure dosage prescribed is therapeutically appropriate and tailor regimen to have peak serum levels occur at those times of the day that symptoms are most prominent
- Consider trying a stimulant from an alternate class (methylphenidate class or amphetamine class) if the first trial was ineffective and the patient was adhering to therapy recommendations

Factors Complicating Response

- Concurrent medical or psychiatric condition, e.g., anxiety disorder, bipolar disorder, conduct disorder, autism spectrum disorder, learning disability
- Concurrent prescription drugs may interfere with efficacy, e.g., antipsychotics (see Drug Interactions pp. 281–282, 285, 292)
- Metabolic inducers (e.g., carbamazepine) may decrease the plasma level of methylphenidate or guanfacine
- High intake of acidifying agents (e.g., fruit juices, vitamin C) may decrease the efficacy of amphetamine preparations
- Substance use, including alcohol and marijuana, may complicate management and treatment selection; need to discontinue substance use to optimize treatment outcomes
- Poor efficacy with atomoxetine may be due to ultrarapid metabolism of CYP2D6
- Side effects to medication
- Psychosocial factors may affect response; nonpharmacological treatment approaches (e.g., behavior modification, psychotherapy, and education) can increase the probability of response

Treatment

Acute

- Treatment of substance use disorder presents challenges in patients with a diagnosed psychiatric disorder and is best done with an integrated treatment program that combines pharmacotherapy with psychosocial intervention
- See specific agents (refer to Treatment of Substance Use Disorders chapter pp. 346–369
- Diagnosis must include mental status, physical and neurological examination, as well as a drug history: Whenever possible, collateral history should be sought
- In severe cases, monitor vitals and fluid intake
- Agitation can be treated conservatively by talking with the patient and providing reassurance until the drug wears off (i.e., "talking down"). When conservative approaches are inadequate or if symptoms persist, pharmacological intervention should be considered
- Avoid low-potency antipsychotics due to anticholinergic effects, hypotension, and tachycardia

Long-Term

- The presence of comorbid psychiatric disorders in substance abusers can adversely influence outcome in treatment of the substance use disorder as well as the psychiatric disorder

Alcohol

General Comments

- Slang: Booze, hooch, juice, brew
- Up to 50% of individuals with alcohol dependence meet the criteria for lifetime diagnosis of major depression
- Related problems include withdrawal symptoms, physical violence, loss of control when drinking, surreptitious drinking, change in tolerance to alcohol, deteriorating job performance, change in social interactions, increased risk for stroke, and injury or death from motor vehicle accidents
- Alcohol acts on numerous central neurotransmission pathways and has been labeled a CNS disorganizer

Pharmacological/ Psychiatric Effects

- Effects of alcohol have a close relationship with blood alcohol levels; impaired judgment and impulsivity can occur with levels of 4–6 mmol/L (20–30 mg/100 mL); levels of 17 mmol/ (80 mg/100 mL) are associated with slurred speech, incoordination, unsteady gait, and inattention. Higher levels can intensify cognitive deficits, aggressiveness, and cause anterorgrade amnesia (blackouts)
- Effects of a single drink occur within 15 min and peak at approximately 30–60 min, depending on amount taken; elimination is about 10 g alcohol per hour (about 30 mL (1 oz) whiskey or 1 bottle of regular beer). Blood alcohol level declines by 3–7 mmol/L per hour (~ 15 mg/100 mL)

Acute

- Disinhibition, relaxation, euphoria, agitation, drowsiness, impaired cognition, judgment, and memory, perceptual and motor dysfunction

☞ **Acute alcohol intake decreases hepatic metabolism of co-administered drugs by competition for microsomal enzymes**

Chronic

- Chronic use results in an increased capacity to metabolize alcohol and a concurrent CNS tolerance; psychological as well as physical dependence may occur; hepatic metabolism decreases with liver cirrhosis

☞ **Chronic alcohol use increases hepatic metabolism of co-administered drugs**

Physical

- Hand tremor, dyspepsia, diarrhea, morning nausea and vomiting, polyuria, impotence, pancreatitis, headache, hepatomegaly, peripheral neuropathy

Mental

- Memory blackouts, nightmares, insomnia, hallucinations, paranoia, intellectual impairment, dementia, Wernicke-Korsakoff syndrome, and other organic mental disorders

Pharmacokinetics

- Absorption occurs slowly from the stomach, and rapidly from the upper small intestine
- Approximately 10% of ingested alcohol is eliminated by first-pass metabolism (less in females); percentage decreases as amount consumed increases
- Alcohol is distributed in body fluids (is not fat soluble) and the blood alcohol level depends on gender, age, and body fluid volume/fat ratio
- Metabolized in the liver primarily by alcohol dehydrogenase, CYP2E1, and CYP450 reductase (also by CYP3A4 and CYP1A2); activity of CYP2E1 is increased 10-fold in chronic heavy drinkers

Alcohol (cont.)

Toxicity

- Risk of injury or harm increases with more than 3 standard drinks for females and 4 for males on any single occasion (standard drink = approximately 5 oz or 140 mL wine, a 12 oz bottle of beer, 1.5 oz or 45 mL spirits)[1]; the legal blood alcohol concentration threshold for impaired driving in the Criminal Code of Canada is 80 mg in 100 mL blood (0.08)
- Risk increases when combined with drugs with CNS depressant activity
- Symptoms include: CNS depression, decreased or absent deep tendon reflexes, cardiac dysfunction, flushed skin progressing to cyanosis, hypoglycemia, hypothermia, peripheral vasodilation, shock, respiratory depression, and coma

D/C Discontinuation Syndrome

- Occurs after chronic use
- Most effects seen within 5–7 days after stopping

Mild Withdrawal

- Insomnia, irritability, headache
- Usually transient and self-limiting

Severe Reactions

- Phase I: Begins within hours of cessation and lasts 3–5 days. Symptoms: tremor, tachycardia, diaphoresis, labile BP, nausea, vomiting, anxiety
- Phase II: Perceptual disturbances (usually visual or auditory)
- Phase III: 10–15% untreated alcohol withdrawal patients reach this phase; seizures (usually tonic-clonic) last 0.5–4 min and can progress to status epilepticus
- Phase IV: Delirium tremens (DTs) is usually a late complication of untreated alcohol withdrawal; includes autonomic hyperactivity and severe hyperthermia; mortality associated with alcohol withdrawal reduced due to early treatment preventing delirium tremens
- Wernicke's encephalopathy can occur in patients with thiamine deficiency

Protracted Abstinence Syndrome

- Patients may experience subtle withdrawal symptoms that can last from weeks to months – include sleep dysregulation, anxiety, irritability, and mood instability
- Cognitive impairment from chronic alcohol use will persist for several weeks after abstinence is achieved
- Individuals are at high risk for relapse during this period
- Hepatic metabolism of co-administered drugs may decrease following abstinence from chronic alcohol use

Precautions

- Increased risk of drug toxicity possible in patients with alcohol-induced liver impairment or cirrhosis
- Risk and type of drug-drug interaction varies with acute and chronic alcohol consumption

Use in Pregnancy◊

- Drinking alcohol while pregnant increases the risk of problems in fetal development; fetal alcohol spectrum disorder (FASD) indicates full range of possible effects on the fetus; fetal alcohol syndrome (FAS) is characterized by severe effects of alcohol, including brain damage, facial deformities, and growth deficits. Infants should be reassessed and followed up regularly as early intervention improves long-term educational outcomes
- Withdrawal reactions reported; seen 24–48 h after birth if mother is intoxicated at birth

Breast Milk

- Milk levels attain 90–95% of blood levels; prolonged intake can be detrimental

Treatment

- In acute intoxication, minimize stimulation; effects will diminish as blood alcohol level declines (rate of 3–7 mmol/L per hour)
- Withdrawal reactions following chronic alcohol use may require
  a) vitamin supplementation (thiamine 50 mg orally or IM for at least 3 days) to prevent or treat Wernicke-Korsakoff syndrome (level of evidence 3)
  b) benzodiazepine for symptomatic relief (to control agitation) and to prevent seizures (chlordiazepoxide, lorazepam, diazepam, or oxazepam); these drugs reduce mortality, reduce the duration of symptoms, and are associated with fewer complications compared to antipsychotic drugs (level of evidence 1); risk of transferring dependence from alcohol to benzodiazepine is small; loading dose strategy used with diazepam (i.e., patient dosed until light somnolence is achieved (level of evidence 3); its long duration of action prevents breakthrough symptoms and possible withdrawal seizures)

◊ See p. 414 for further information on drug use in pregnancy and effects on breast milk

Opioids (cont.)

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

OPIOIDS (GENERAL)

Class of Drug	Example	Interaction Effects
Antibiotic	Erythromycin, clarithromycin	Increased plasma concentration of fentanyl, alfentanyl due to inhibited metabolism via CYP3A4, resulting in prolonged analgesia and adverse effects
Antidepressant	MAOI, RIMA	Increased excitation, sweating, and hypotension reported (especially with meperidine, pentazocine); may lead to development of encephalopathy, convulsions, coma, respiratory depression, and serotonin syndrome
	Doxepin, fluoxetine, imipramine, maprotiline, paroxetine, venlafaxine	Decreased efficacy of codeine due to inhibition of CYP2D6; must be metabolized to its active metabolite, morphine, (by CYP2D6) for its therapeutic effect
Antihistamine	Tripelennamine, cyclizine	"Opiate high" reported in combination with opium; euphoria
Antipsychotic	FGAs (haloperidol, perphenazine)	Decreased efficacy of codeine due to inhibition of CYP2D6; must be metabolized to its active metabolite, morphine, (by CYP2D6) for its therapeutic effect
CNS drug	Alcohol, benzodiazepines	Additive CNS effects; can lead to respiratory depression
Dextromethorphan		Decreased efficacy of codeine due to inhibition of CYP2D6; must be metabolized to its active metabolite, morphine, (by CYP2D6) for its therapeutic effect
H_2 antagonist	Cimetidine	Enhanced effect of opioid and increased adverse effects due to decreased metabolism; 22% decrease in clearance of meperidine
Opioid antagonist	Naloxone, naltrexone, nelmefene	Will precipitate withdrawal reaction
Protease inhibitor	Ritonavir	Decreased clearance of opioid due to inhibited metabolism, resulting in increased plasma level (caution with fentanyl, alfentanyl, meperidine, and propoxyphene)
Stimulant	Cocaine	May potentiate cocaine euphoria

Opioids

Drug	Comments
HEROIN Diacetylmorphine – synthetic derivative of morphine Injected (IV – "mainlining", or SC – "skin popping"), smoked, inhaled, taken orally Slang: "H", horse, junk, snow, stuff, lady, dope, shill, poppy, smack, scag, black tar, Lady Jane, white stuff, brown sugar, skunk, white horse	• Effects almost immediate following IV injection and last several hours; effects occur in 15–60 min after oral dosing • Risk of accidental overdose as street preparations contain various concentrations of heroin • Physical dependence and tolerance occur within 2 weeks; withdrawal occurs within 8–12 h after last dose, peaks in 36–72 h, and can last up to 10 days • Physical effects: Pain relief, nausea, constipation, staggering gait, and respiratory depression • CNS effects: Euphoria, drowsiness, and confusion • Toxicity: Sinus bradycardia or tachycardia, hypertension or hypotension, palpitations, syncope, respiratory depression, coma, and death • Pregnancy: High rate of spontaneous abortions, premature labor and stillbirths – babies are often small and have an increased mortality risk; withdrawal symptoms in newborn reported • Breastfeeding: Tremors, restlessness, vomiting and poor feeding reported in infants

NATURAL HEALTH PRODUCTS

General Comments

Although pharmacotherapy is generally the first line of treatment for psychiatric disorders, an increasing number of patients are turning to using natural health products (NHPs). Most NHP use is self-prescribed (60%) and undisclosed to health care providers (75%). In one study, 34% of users took NHPs to treat a mood disorder, while almost half of the users also took concurrent prescription medication. The widespread use of NHPs for highly prevalent mental illnesses makes it necessary for health care providers to understand their benefits and risks.

This chapter looks at the evidence and safety of some commonly used NHPs that are used for a variety of conditions. Although in most cases the optimum dose of the natural health product (herb or supplement) is not known, the most frequently studied dose is provided, along with the proposed mechanism of action.

Drug	Anxiety	Depression	Bipolar Disorder	Sleep Disorders	Schizophrenia	Alzheimer's Disease	ADHD
Ginkgo Biloba (p. 387)					PR/S/+	C/+	
Kava Kava (p. 389)	+/SC						
Melatonin (p. 390)				C/+			
Omega-3 Fatty Acids (p. 391)		C/S/+	C/S/+		C/S	PR	C
S-Adenosyl-L-Methionine (p. 394)		C/S/+					
St. John's Wort (p. 395)	PR/C	+†					
Valerian (p. 396)	PR			C/+			
Vitamins (p. 397)							
Vitamin B_6		PR/S			PR/S		
Vitamin B_9		PR/S					
Vitamin C					PR		
Vitamin E					PR/S	C	

† Mild to moderate depression only;

C = contradictory results, + = positive findings, PR = preliminary data, S = synergistic/adjunctive effect, SC = significant safety concerns

Further Reading

References

- McCrea CE, Pritchard ME. Concurrent herb-prescription medication use and health care provider disclosure among university students. Complement Ther Med. 2011;19(1):32–36. doi: 10.1016/j.ctim.2010.12.005

Ginkgo Biloba

Indications
(👍 approved)

Alzheimer's Disease/Dementia

- Treatment does not appear to delay the progression of Alzheimer's disease
- Cochrane Review (2009) on ginkgo biloba for cognitive impairment and dementia analyzed data from 36 controlled trials (3–52 weeks in duration). Major findings reported were:

Pharmacogenomics-Based Dose Adjustment Recommendations and Guidelines* (cont.)

Biomarkers	CYP2D6				CYP2C19			
Drug / Phenotype	**Ultrarapid Metabolizer**	**Extensive Metabolizer**	**Intermediate Metabolizer**	**Poor Metabolizer**	**Ultrarapid Metabolizer**	**Extensive Metabolizer**	**Intermediate Metabolizer**	**Poor Metabolizer**
Sertraline					Initiate therapy with recommended starting dose. If no response to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19	Initiate therapy with recommended starting dose	Initiate therapy with recommended starting dose	Consider 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19
Thioridazine			Contraindicated in patients with reduced CYP2D6 activity, also coadministration with drugs that may inhibit CYP2D6 or by some other mechanism interfere with thioridazine clearance	Contraindicated in patients with reduced CYP2D6 activity, also coadministration with drugs that may inhibit CYP2D6 or by some other mechanism interfere with thioridazine clearance				
Tramadol	Reduce dose by 30% and be alert to adverse effects (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) or select an alternative drug (e.g., acetaminophen, NSAID, morphine but not oxycodone or codeine)		Be alert to decreased efficacy. Consider dose increase. If response still inadequate, select an alternative drug but not oxycodone or codeine. Be alert to symptoms of insufficient pain relief	Select an alternative drug but not oxycodone or codeine. Be alert to symptoms of insufficient pain relief				

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