

Review of Psychotropic Drugs 2002

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Psycho pharmacology, in particular the introduction of new psychotropic agents, is perhaps the most rapidly growing area in all of clinical pharmacology. In recent years, important new drug introductions have revolutionized the treatment of various psychiatric disorders. This progress has been made possible by advances in basic neuroscience and clinical research achieved during the past few decades. Recently introduced psychotropic drugs reflect an increased understanding of the biological/biochemical mechanisms of the psychiatric disorders they target. This knowledge enables development of therapeutic agents with greater specificity for the molecular mechanisms involved, resulting in increased effectiveness and fewer untoward side effects. Psychotropic drug development continues at a rapid pace as the knowledge base of neuroscience and clinical research continues to expand. The Tables that follow summarize the current state of the art of psychotropic drugs available to clinicians. Please note

that for elderly patients, the daily doses are generally lower than the adult doses listed here.

In clinical medicine (as in the Tables), psychotropic medications are most usefully classified according to therapeutic applications, including:

- anxiolytic agents for the treatment of anxiety disorders;
- antipsychotics for the treatment of schizophrenia; these drugs are sometimes referred to as neuroleptics because of characteristic side effects on cognition and behavior that mimic neurologic diseases (some newer, atypical antipsychotics demonstrate improved side-effect profiles);
- drugs for mood (or affective) disorders, including antidepressants (mood-elevating agents) for the treatment of depression and mood-stabilizing agents for the treatment of manic (or bipolar) disorders; and
- hypnotics for the induction of sleep.

KEY

C = capsule	IM = intramuscular	OTC = over the counter	T = tablet
DR = delayed release	L = liquid	PO = by mouth	TCA = tricyclic antidepressant
EPS = extrapyramidal side effects	MAOI = monoamine oxidase inhibitor	REM = rapid eye movement	t_{1/2} = half-life
ER = extended release	N/A = not available	SR = sustained release	t_{pk} = time to peak
h = hour	NE = norepinephrine	SSRI = selective serotonin reuptake inhibitor	XR = extended release
I = injectable	OCD = obsessive-compulsive disorder	SUPP = suppository	5-HT = serotonin

DRUGS FOR MOOD DISORDERS

Antidepressants

Class	Agent	Dosage Forms	Usual Adult Daily Dosage (mg/d)	Relative Adverse-Effect Profiles						Comments
				Anticholinergic	Sedation	Orthostatic Hypotension	Sexual Dysfunction*	GI Effects	Activation/Insomnia	
TRICYCLICS	Amitriptyline Elavil, AstraZeneca; Others	T, IM	100-300	very high	very high	very high	high	very low	none	other common uses: chronic pain, hypnotic
	Clomipramine Anafranil, Mallinckrodt; Others	C	100-250	very high	very high	very high	very high	very low	none	approved for OCD; 250 mg daily maximum due to increased risk of seizures
	Desipramine Norpramin, Aventis; Others	T, C	100-300	moderate	moderate	moderate	high	very low	very low	
	Doxepin Sinequan, Pfizer; Others	C, L	100-300	very high	very high	very high	high	very low	none	
	Imipramine Tofranil, Mallinckrodt; Others	T, C, IM	100-300	very high	high	very high	high	very low	none	
	Nortriptyline Pamelor, Mallinckrodt; Aventyl, Eli Lilly; Others	C, L	50-150	moderate	moderate	moderate	high	very low	none	"therapeutic window" plasma level—must be within 50-150 ng/mL for efficacy
	Protriptyline Vivactil, Odyssey	T	20-60	very high	very low	moderate	high	very low	high	
	Trimipramine Surmontil, Odyssey	C	100-300	high	high	high	high	very low	none	
SSRIs	Citalopram Celexa, Forest	T, L	20-60	none	low	none	very high	high	low	lower end of dosage range often effective for most depressed patients; no need to titrate from smaller starting doses as done with TCAs; headache also common; much safer in overdose than TCAs; variable and significant inhibitory effect on hepatic P450 enzymes, except citalopram; caution when coprescribed with drugs that undergo extensive hepatic metabolism and have a narrow therapeutic index; effective for panic disorder, OCD, bulimia nervosa, social phobia, post-traumatic stress disorder, and premenstrual dysphoria
	Fluoxetine Prozac/Sarafem, Eli Lilly; Others	C, T, L, ER	10-80	none	none	none	very high	high	very high	
	Fluvoxamine Luvox, Solvay; Others	T	100-300	none	moderate	none	very high	high	low	
	Paroxetine Paxil, GlaxoSmithKline	T, L	20-60	low	low	none	very high	high	low	
	Sertraline Zoloft, Pfizer	T, L	50-200	none	very low	none	very high	very high	moderate	
MAOIs	Isocarboxazid Marplan, Oxford Pharm Services	T	20-60	moderate	low	very high	high	very low	moderate	other uses: panic disorders, phobic disorders; <i>Caution:</i> high tyramine diet, sympathomimetic agents; divided dosing (bid-qid)
	Phenelzine Nardil, Pfizer	T	45-90	moderate	moderate	very high	high	very low	none	
	Tranylcypromine Parnate, GlaxoSmithKline	T	20-50	moderate	none	very high	high	very low	very high	
OTHERS	Amoxapine Asendin, Lederle; Others	T	200-600	low	low	low	high	very low	none	similar lethality in overdose to TCAs; EPS possible
	Bupropion Wellbutrin, GlaxoSmithKline	T	150-450	none	none	none	none	moderate	high	safer in overdose than TCAs; SR formulation offers bid (vs tid) dosing; avoid in patients with seizure disorders; Zyban used for smoking cessation
	Maprotiline Various generics	T	150-225	moderate	moderate	moderate	moderate	very low	none	similar lethality in overdose to TCAs; maximum dosage limited due to seizure risk
	Mirtazapine Remeron, Organon	T	15-45	none	high	none	none	very low	none	safer in overdose than TCAs; less sedation at doses >15 mg/d; weight gain
	Nefazodone Serzone, Bristol-Myers Squibb	T	300-600	none	high	low	none	moderate	very low	safer in overdose than TCAs; qhs or bid dosing; potent P450 3A4 inhibitor
	Trazodone Desyrel, Apothecoon; Others	T	200-600	very low	very high	very high	none	moderate	none	safer in overdose than TCAs; priapism rare (1:1,000-1:10,000); not well tolerated at antidepressant dosage; most commonly used as a hypnotic at 50-200 mg qhs
	Venlafaxine Effexor/Effexor XR, Wyeth-Ayerst	C (XR), T	75-375	none	low	very low	high	very high	moderate	SSRI-like; side effects most common; safer in overdose than TCAs; qd for XR capsules, bid-tid dosing for tablets; also effective for generalized anxiety disorder

* Few drug-to-drug comparison trials of sexual dysfunction frequency have been done; clomipramine and SSRIs are more likely than other antidepressants to cause delayed ejaculation and anorgasmia due to their serotonergic effects.



DRUGS FOR MOOD DISORDERS

Mood Stabilizers*

Class	Agent	Dosage Forms	Usual Adult Daily Dosage	Therapeutic Plasma Level	Common Adverse Effects	Comments
ANTICONVULSANTS	Lithium Carbonate Eskalith CR, GlaxoSmithKline; Lithobid, Solvay; Others	T, C, SR	1,200-2,400 mg/d acute 900-1,200 mg/d maintenance	0.8-1.2 mEq/L 0.6-1.2 mEq/L	nausea, fine hand tremor, increased urination and thirst; toxicity: slurred speech, confusion, severe gastrointestinal effects, weight gain, acne	established standard treatment for bipolar disorder; risk of hypothyroidism with maintenance therapy; avoid in pregnancy, especially in first trimester
	Carbamazepine Carbatrol, Shire US; Eptol, Teva; Tegretol, Novartis; Others	T, DR, ER, L	10-20 mg/kg/d	6-12 mg/L [†]	nausea, dizziness, sedation, headache, dry mouth, constipation, rash	hepatic enzyme inducer; alternative to lithium or valproic acid or adjunctive treatment for bipolar disorder; avoid in pregnancy, especially in first trimester
	Valproic Acid Depakene/Depakote, Abbott; Others	T, C, L, ER, I	15-40 mg/kg/d	50-120 mg/L	nausea, diarrhea, abdominal cramps, sedation, tremor, weight gain, rash	use of Depakote greatly minimizes gastrointestinal effects; more effective than lithium for rapid cycling and mixed bipolar disorder; loading dose 20 mg/kg; avoid in pregnancy, especially in first trimester; pancreatitis may occur in rare cases

* Alternative agents include gabapentin (Neurontin, Pfizer), lamotrigine (Lamictal, GlaxoSmithKline) and topiramate (Topamax, Ortho-McNeil), although very limited clinical data are available.

† Levels are not established for therapeutic efficacy, but rather are used to monitor for toxicity.

ANXIOLYTICS

Class	Agent	Schedule	Approved Indications	Approved Oral Adult Dosage Range (mg/d)	Approximate Equivalent Doses (mg/d)	Dosage Forms	Pharmacokinetic Parameters				Comments [‡]
							Onset (PO)	t _{1/2}	Metabolic Pathway	Active Metabolite	
BENZODIAZEPINES	Alprazolam Xanax, Pharmacia; Others	IV	anxiety disorders; panic disorder	0.75-4 1.5-10	0.5	T	fast	intermediate	oxidation	alpha-hydroxy-alprazolam	anterograde amnesia; tid-qid dosing necessary
	Chlordiazepoxide Librium, ICN; Others	IV	anxiety; alcohol withdrawal; preoperative sedation	5-300	10	T, C, I	fast	long	N-dealkylation	desmethylchlordiazepoxide, demoxepam, desmethyldiazepam, oxazepam	variable bioavailability with IM dosing
	Clonazepam Klonopin, Roche; Others	IV	seizure disorders; panic disorder	1-6	0.25	T	moderate	long	reduction	none	anterograde amnesia; adjunctive for bipolar disorder and psychoses
	Clorazepate Tranxene, Abbott; Others	IV	anxiety; seizure disorders; alcohol withdrawal	7.5-60	7.5	T, C	very fast	long	oxidation	desmethyldiazepam, oxazepam	
	Diazepam Valium, Roche; Others	IV	anxiety; alcohol withdrawal; muscle spasm; preoperative sedation; status epilepticus	2-20	5	T, SR, L, I	very fast	long	oxidation	desmethyldiazepam, 3-hydroxydiazepam, oxazepam	variable bioavailability with IM dosing
	Lorazepam Ativan, Wyeth-Ayerst; Others	IV	anxiety; preoperative sedation	0.5-10	1	T, L, I	fast	short	conjugation	none	reliable bioavailability with IM dosing
	Oxazepam Various generics	IV	anxiety disorders; alcohol withdrawal	30-120	15	T, C	slow	short	conjugation	none	
OTHERS	Bupirone BuSpar, Bristol-Myers Squibb	No	anxiety	15-60	5	T	0.5-1.5 h	N/A	N/A	N/A	no sedation, no dependence; not useful on prn basis; nausea, dizziness, agitation
	Hydroxyzine Vistaril/Atarax, Pfizer; Others	No	anxiety; pruritus; preoperative and postoperative sedation	50-400	N/A	T, C, L, I	2 h	N/A	N/A	N/A	anticholinergic; sedation

‡ Avoid alcohol and other CNS depressants with these agents (except bupirone); drowsiness may impair ability to drive; use caution.



HYPNOTICS

Class	Agent	Usual Daily Adult Dosage Range (mg/d)	Pharmacokinetic Parameters				Comments [§]	
			t _{pk} (h)	t _½ (h)	Metabolic Pathway	Active Metabolites		
BENZODIAZEPINES	Estazolam ProSom, Abbott; Others	1-2	2	12-15	oxidation	none		
	Flurazepam Dalmane, ICN; Others	15-30	1	40-150	oxidation N-dealkylation	hydroxyethylflurazepam flurazepam aldehyde N-desalkylflurazepam	dosage accumulation; hangover effect; little or no REM suppression; no REM rebound	
	Quazepam Doral, Wallace	7.5-15	2	39	oxidation	2-oxoquazepam	similar to flurazepam	
	Temazepam Restoril, Mallinckrodt; Others	15-30	2-3	10-15	conjugation	none	slow onset; little or no REM suppression	
	Triazolam Halcion, Pharmacia; Others	0.125-0.25	0.5-1.5	2	oxidation	none	anterograde amnesia; rebound insomnia after discontinuation	
ANTIHISTAMINES	Diphenhydramine Benadryl, Pfizer; Others	25-100	Onset (min): N/A		Duration (h): N/A		t _½ (h): 3-10	anticholinergic; OTC
	Doxylamine Unisom, Pfizer	25-100	Onset (min): N/A		Duration (h): N/A		t _½ (h): 10	anticholinergic; OTC
OMEGA-1 RECEPTOR AGONISTS (NON-BENZODIAZEPINE)	Zaleplon Sonata, Wyeth-Ayerst	5-10	Onset (min): 30-60		Duration (h): 1		t _½ (h): 1	very short duration of effect allows dosing during night up to 4 hours before arising
	Zolpidem Ambien, Pharmacia	5-10	Onset (min): 30-60		Duration (h): 2-4		t _½ (h): 4	
OTHER	Chloral Hydrate Various generics	500-2,000	Onset (min): 30		Duration (h): N/A		t _½ (h): 8	loses hypnotic efficacy within first week; gastrointestinal irritation

§ Avoid alcohol and other CNS depressants with these agents; drowsiness may impair ability to drive; use caution.

ANTIPSYCHOTICS

Class	Agent	Dosage Forms	Dosage Equivalents (mg)	Approved Adult Oral Dosage Range (mg/d)	Relative Adverse-Effect Profiles				Comments	
					Extrapyramidal Side Effects	Anticholinergic	Sedation	Orthostatic Hypotension		
Typical Dopamine receptor antagonists	Aliphatic	Chlorpromazine Thorazine, Glaxo-SmithKline; Others	T, SR, L, I, SUPP	100 ^{ll}	50-2,000	moderate	moderate	high	high	allergic dermatitis; photosensitivity; ECG changes
	Piperidine	Mesoridazine Serentil, Novartis	T, L, I	50	100-400	low	high	high	high	patients on oral thioridazine who need injectable form may receive mesoridazine injection; ECG changes ^{ll}
		Thioridazine Mellaril, Novartis; Others	T, L	100	50-800	low	high	high	high	irreversible retinal pigmentation at doses >800 mg/d; decreased libido; retrograde ejaculation; ECG changes ^{ll}
	Piperazine	Fluphenazine Prolixin, Apothecon; Others	T, L, I	2	2-40 decanoate: 12.5-75 mg IM every 2 weeks	very high	low	low	low	
		Perphenazine Trilafon, Schering; Others	T, L, I	8	8-64	high	low	low	low	
		Trifluoperazine Stelazine, Glaxo-SmithKline; Others	T, L, I	5	5-80	high	low	low	low	
	Butyrophenone	Haloperidol Haldol, Ortho-McNeil; Others	T, L, I	2	2-40 decanoate: 50-300 mg IM every month	very high	very low	very low	very low	
	Dibenzoxazepine	Loxapine Loxitane, Watson; Others	C, L, I	10	20-250	high	low	moderate	moderate	
	Dihydroindolone	Molindone Moban, Endo	T, L	10	50-225	high	low	very low	low	less or no weight gain
	Thioxanthene	Thiothixene Navane, Pfizer, Others	C, L	4	5-60	high	low	low	low	



ANTIPSYCHOTICS (cont.)

Class	Agent	Dosage Forms	Dosage Equivalents (mg)	Approved Adult Oral Dosage Range (mg/d)	Relative Adverse-Effect Profiles				Comments	
					Extrapyramidal Side Effects	Anticholinergic	Sedation	Orthostatic Hypotension		
Atypical Dopamine and serotonin receptor antagonists; more effective for negative symptoms of schizophrenia (amotivation, affect, isolation); significantly less EPS and lower risk for tardive dyskinesia than with typical antipsychotics	Dibenzodiazepine	Clozapine Clozaril, Novartis; Others	T	50	75-900	rare	very high	very high	high	WBC monitoring required due to risk of agranulocytosis; dose-related seizure risk; hypersalivation and significant weight gain; no prolactin elevation
	Dibenzothiazepine	Quetiapine Seroquel, AstraZeneca	T	N/A	300-800 [#]	rare	very low	moderate	moderate	minimal weight gain; transient and asymptomatic increased liver function tests possible; must be given in divided doses (bid); no prolactin elevation
	Thienbenzodiazepine	Olanzapine Zyprexa/Zydis, Eli Lilly	T	N/A	10-20	very low	low	moderate	low	significant weight gain; transient and asymptomatic increased liver function tests possible; mild prolactin elevation; higher doses in smokers; Zydis orally disintegrating formulation
	Benzisothiazolylpiperazine	Ziprasidone Geodon, Pfizer	C	N/A	40-160	very low	very low	low to moderate	low to moderate	newest agent in class; capsule should not be opened or crushed; divided dosing (bid); least likely to cause weight gain; minimal prolactin elevation; caution in patients at risk for QT prolongation
	Benzisoxazole	Risperidone Risperdal, Janssen	T, L	N/A	2-6	low	very low	low	moderate	transient nausea, insomnia possible; doses above 6 mg/d associated with a higher incidence of EPS; less weight gain than with clozapine or olanzapine; greatest prolactin elevation among atypicals

|| 100 mg chlorpromazine = 2 mg haloperidol

¶ See prescribing information for blackbox warning on adverse events associated with ECG changes.

25-200 mg/d for elderly patients; 300-800 mg/d for adult patients with chronic schizophrenia.

Selected Readings

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