

## CHAPTER ONE

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# Adrenergics and Adrenergic-Blocking Agents

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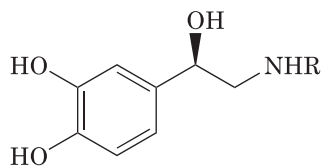
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## 1 INTRODUCTION

In both their chemical structures and biological activities, adrenergics and adrenergic-blocking agents constitute an extremely varied group of drugs whose clinical utility includes prescription drugs to treat life-threatening conditions such as asthma and hypertension as well as nonprescription medications for minor ailments such as the common cold. This extensive group of drugs includes synthetic agents as well as chemicals derived from natural products that have been used in traditional medicines for centuries. Many adrenergic drugs are among the most commonly prescribed medications in the United States, including bronchodilators, such as albuterol (**13**) for use in treating asthma, and antihypertensives, such as atenolol (**46**) and doxazosin (**42**). Nonprescription adrenergic drugs include such widely used nasal decongestants as pseudoephedrine (**5**) and naphazoline (**29**). Most of these varied drugs exert their therapeutic effects through action on adrenoceptors, G-protein-coupled cell surface receptors for the neurotransmitter norepinephrine (noradrenaline, **1**), and the adrenal hormone epinephrine (adrenaline, **2**).



- (1) norepinephrine, R = H  
 (2) epinephrine, R = CH<sub>3</sub>

Adrenoceptors are broadly classified into  $\alpha$ - and  $\beta$ -receptors, with each group being further

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subdivided. Identification of subclasses of adrenoceptors has been greatly aided by the tools of molecular biology and, to date, six distinct  $\alpha$ -adrenoceptors ( $\alpha_{1A}$ ,  $\alpha_{1B}$ ,  $\alpha_{1D}$ ,  $\alpha_{2A}$ ,  $\alpha_{2B}$ ,  $\alpha_{2C}$ ), and three distinct  $\beta$ -adrenoceptors ( $\beta_1$ ,  $\beta_2$ ,  $\beta_3$ ) have been clearly identified (1), with conflicting evidence for a fourth type of  $\beta$  ( $\beta_4$ ) (1–3). In general the most common clinical applications of  $\alpha_1$ -agonists are as vasoconstrictors employed as nasal decongestants and for raising blood pressure in shock;  $\alpha_2$ -agonists are employed as antihypertensives;  $\alpha_1$ -antagonists ( $\alpha$ -blockers) are vasodilators and smooth muscle relaxants employed as antihypertensives and for treating prostatic hyperplasia;  $\beta$ -antagonists ( $\beta$ -blockers) are employed as antihypertensives and for treating cardiac arrhythmias; and  $\beta$ -agonists are employed as bronchodilators. The most novel recent advances in adrenergic drug research have been directed toward development of selective  $\beta_3$ -agonists that have potential applications in treatment of diabetes and obesity (4–8).

## 2 CLINICAL APPLICATIONS

### 2.1 Current Drugs

U.S. Food and Drug Administration (FDA)-approved adrenergic and antiadrenergic drugs currently available in the United States are summarized in Table 1.1, which is organized in general according to pharmacological mechanisms of action and alphabetically within those mechanistic classes. Structures of the currently employed drugs are given in Tables 1.2–1.6 according to chemical class. Drugs in a given mechanistic class often have more than one therapeutic application, and may or may not all be structurally similar. Furthermore, drugs from several different mechanistic classes may be employed in a given therapeu-

**Table 1.1 Adrenergic and Antiadrenergic Pharmaceuticals**

Class and Generic Name	Trade Name <sup>e</sup>	Originator	Chemical Class	Dose <sup>b,c</sup>
<b>General agonists</b>				
Amphetamine (3)	Adderall, Dexedrine	SmithKline & French	Phenylethylamine	5-60 mg/day
Dipivefrin (4)	Propine	Klinge	Phenylethylamine	1 drop 2 × daily 0.1% soln.
Ephedrine <i>erythro</i> -(5)	various		Phenylethylamine	50-150 mg/day for asthma 10-25 mg i.v. for hypotension
Epinephrine (2)	Adrenaline	Parke-Davis	Phenylethylamine	0.3-1.5 mg s.c. 2-10 µg/min i.v. 160-250 µg inh. 30-45 mg, i.m. 0.5-30 µg/min i.v. 60-240 mg/day
Mephentermine (6)	Wyamine	Wyeth	Phenylethylamine	
Norepinephrine (1)	Levophed	Sterling	Phenylethylamine	
Pseudoephedrine <i>threo</i> -(5)	Various		Phenylethylamine	
<b>α<sub>1</sub>-Agonists</b>				
Levonordefrin (7)	na	Winthrop	Phenylethylamine	1:20,000 in local anesthetics
Metaraminol (8)	Aramine	Sharpe & Dohme	Phenylethylamine	2-10 mg, i.m.
Methoxamine (9)	Vasoxyl	Burroughs Wellcome	Phenylethylamine	10-20 mg, i.m.
Midodrine (10)	ProAmatine	Oesterreichische Sticksstoffwerke	Phenylethylamine	30 mg/day
Naphazoline (29)	Various	Ciba	Imidazoline	1-2 drops 0.05% nasal 0.03% ophthalmic
Oxymetazoline (30)	Various	Merck	Imidazoline	1-2 drops 0.05% nasal 0.025% ophthalmic
Phenylephrine (11)	Various	F. Stearns & Co.	Phenylethylamine	1-3 drops 0.25-0.5% soln. nasal 0.1-0.5 mg i.v. for shock 1-2 drops of 0.05% soln. 2-3 drops of 0.1% soln.
Tetrahydrozoline (31)	Various	Sahyun	Imidazoline	
Xylometazoline (32)	Various	Ciba	Imidazoline	
<b>α<sub>2</sub>-Agonists</b>				
Apraclonidine (33)	Iopidine	Alcon	Aminoimidazoline	3-6 drops 0.5-1% soln.
Brimonidine (34)	Alphagan	Pfizer	Aminoimidazoline	1 drop 0.2% soln., 3 × daily
Clonidine (35)	Catapress	Boehringer	Aminoimidazoline	0.2-1.2 mg/day
Guanabenz (36)	Wytensin	Sandoz	Arylguanidine	8-32 mg/day
Guanfacine (37)	Tenex	Wander	Arylguanidine	1-3 mg/day
Methyldopa (12)	Aldomet	Merck	Aromatic amino acid	500-2000 mg/day

**Table 1.1 (Continued)**

Class and Generic Name	Trade Name <sup>a</sup>	Originator	Chemical Class	Dose <sup>b,c</sup>
<b><math>\beta</math>-Agonists</b>				
Albuterol (13)	Proventil, Ventolin	Allen & Hanburys	Phenylethylamine	12-32 mg/day p.o. 2.5 mg 3-4 $\times$ daily, neb. 0.74-2.22 inh.
Bitolterol (14)	Tornalate	Sterling	Phenylethylamine	12 $\mu$ g, 2 $\times$ daily inh.
Formoterol (15)	Foradil	Yamanouchi	Phenylethylamine	2 mL 0.25% soln. inh.
Isosharine (16)	Bronkosol	I. G. Farben	Phenylethylamine	120-262 $\mu$ g, 2-6 $\times$ daily inh.
Isoproterenol (17)	Isuprel	Boehringer	Phenylethylamine	0.5-5.0 $\mu$ g/min, i.v.
Levalbuterol (13)	Xopenex	Sepracor	Phenylethylamine	0.63-1.25 mg 3 $\times$ daily neb.
Metaproterenol (18)	Alupent, Metaprel	Boehringer	Phenylethylamine	60-80 mg/day p.o. 1.3-1.95 mg, 6-8 $\times$ daily, inh. 0.2-0.4 mg 4-6 $\times$ daily, inh.
Pirbuterol (19)	Maxair	Pfizer	Pyridylethylamine	150-350 $\mu$ g/min, i.v.
Ritodrine (20)	Yutopar	Philips	Phenylethylamine	120 mg/day
Salmeterol (21)	Serevent	Glaxo	Phenylethylamine	42 $\mu$ g, 2 $\times$ daily, inh.
Terbutaline (22)	Brethine	Draco	Phenylethylamine	7.5-15 mg/day
<b>Antiadrenergics</b>				
Guanadrel (38)	Hylorol	Cutter	Guanidine	10-75 mg/day
Guanethidine (39)	Ismelin	Ciba	Guanidine	10-50 mg/day
Reserpine (60)	reserpine	Ciba	Alkaloid	0.05-0.5 mg/day
Metyrosine (23)	Demser	Merck	Aromatic amino acid	1-4 g/day
<b><math>\alpha</math>-Antagonists</b>				
Dapiprazole (61)	Rev-Eyes	Angelini-Francesco	Piperidimlytriazole	2 drops 0.5% soln.
Phenoxybenzamine (62)	Dibenzylime	SmithKline & French	Haloalkylamine	20-120 mg/day
Phentolamine (40)	Regitine	Ciba	Imidazoline	5-10 mg i.v.
Tolazoline (41)	Priscoline	Ciba	Imidazoline	40-200 mg/day
<b>Selective <math>\alpha_1</math>-antagonists</b>				
Doxazosin (42)	Cardura	Pfizer	Quinazoline	1-16 mg/day
Prazosin (43)	Minipress	Pfizer	Quinazoline	1-9 mg/day for BPH 6-20 mg/day for hypertension
Tamsulosin (24)	Flomax	Yamanouchi	Phenylethylamine	0.4-0.8 mg/day
Terazosin (44)	Hytrin	Abbott	Quinazoline	5-20 mg/day

<b><math>\beta</math>-Antagonists</b>					
Acebutolol (45)	Sectral	May & Baker		Aryloxypropanolamine	200–1200 mg/day
Atenolol (46)	Tenormin	ICI		Aryloxypropanolamine	25–150 mg/day
Betaxolol (47)	Betoptic, Kerlone	Synthelabo		Aryloxypropanolamine	Hypertension: 10–20 mg orally Glaucoma: 1–2 drops 0.5% soln. 2 $\times$ daily
Bisoprolol (48)	Zebeta	Merck		Aryloxypropanolamine	1.25–20 mg/day
Carteolol (49)	Cartrol, Ocupress	Otsuka		Aryloxypropanolamine	2.5–10 mg/day
Esmolol (50)	Brevibloc	American Hospital Supply		Aryloxypropanolamine	50–100 $\mu$ g/kg/min
Levobetaxolol S-(–)-(47)	Betaxon	Alcon		Aryloxypropanolamine	1 drop 0.5% soln., 2 $\times$ daily
Levobunolol (51)	Betagan	Warner-Lambert		Aryloxypropanolamine	1–2 drops 0.5% soln., 1–2 $\times$ daily
Metipranolol (52)	OptiPranolol	Boehringer		Aryloxypropanolamine	1 drop 0.3% soln., 2 $\times$ daily
Metoprolol (53)	Lopressor, Toprol-XL Toprol-XL	AB Hässle		Aryloxypropanolamine	100–450 mg/day XL 50–100 mg/day
Nadolol (54)	Corgard	Squibb		Aryloxypropanolamine	40–320 mg/day
Penbutolol (55)	Levadol	Hoechst		Aryloxypropanolamine	20–80 mg/day
Pindolol (56)	Visken	Sandoz		Aryloxypropanolamine	10–60 mg/day
Propranolol (57)	Inderal, Inderal LA	ICI		Aryloxypropanolamine	160–640 mg/day
Sotalol (25)	Betapace	Mead Johnson		Phenylethylamine	160–320 mg/day
Timolol (58)	Timoptic	Frosst		Aryloxypropanolamine	Hypertension: 10–60 mg/day Glaucoma: 1 drop 0.25% soln., 2 $\times$ daily
<b><math>\alpha/\beta</math>-Antagonists</b>					
Carvedilol (59)	Coreg	Boehringer		Aryloxypropanolamine	13–50 mg/day
Labetalol (26)	Normodyne	Allen & Hanburys		Phenylethylamine	200–2400 mg/day
<b>Agonist/Antagonists</b>					
Dobutamine (27)	Dobutrex	Lilly		Phenylethylamine	2–20 $\mu$ g/kg/min, i.v.
Isoxsuprine (28)	Vasodilan	Philips		Aryloxypropanolamine	30–80 mg/day

<sup>a</sup>Not all trade names are listed, particularly for drugs no longer under patent.

<sup>b</sup>All dose information from *Drug Facts and Comparisons 2002* (14).

<sup>c</sup>Not all doses and dosage forms are listed. For further information consult reference (14).

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