Pharmaceutical Press

Martindale

Thirty-sixth edition

THE COMPLETE DRUG REFERENCE

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The Complete Drug Reference

Thirty-sixth edition

Edited by

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London • Chicago Pharmaceutical Press

Published by the Pharmaceutical Press
An imprint of RPS Publishing

1 Lambeth High Street, London SE1 7JN, UK
100 South Atkinson Road, Suite 200, Grayslake, IL 60030-7820, USA

RPS Publishing is the publishing organisation of the Royal Pharmaceutical Society of Great Britain

First edition of *Martindale: The Extra Pharmacopoeia* was published in 1883. *Squire's Companion* was incorporated in the twenty-third edition in 1952.

Thirty-sixth edition published 2009

Printed in China by Everbest Printing Co. Ltd

ISBN 978 0 85369 840 1

ISSN 0263-5364

A catalogue record for this book is available from the British Library

CHF 3500.—

Martindale: The Complete Drug Reference

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Preface

The aim of Martindale is to provide healthcare professionals with unbiased evaluated information on drugs and medicines used throughout the world. It therefore has to develop as the body of knowledge on existing drugs grows, new drugs emerge, new preparations are launched, and old preparations are abandoned, reformulated, or redefined. It also has to reflect the changing needs of those practising pharmacy and medicine. We try to ensure that each new edition continues to meet all these needs.

In order to provide more up-to-date information the interval between the publication of the printed versions of Martindale has been reduced over successive editions and the book is now produced about every 2 years. For those who require even more up-to-date information from Martindale there are various electronic versions, sections of which are updated more frequently.

The year 2008 saw the publication of the third Spanish edition of Martindale, the translation having again been undertaken by our colleagues at Grupo Ars XXI, and also saw the appearance of the first edition of a Chinese language version of Martindale.

Martindale has been continuously expanded since it was first published in 1883, and to present all the extra information this edition of Martindale maintains the recent return to a two-volume publication. The first volume contains this preface and the drug monographs, and the second holds the proprietary preparations and the index, as well as manufacturers' contact information.

As always the contents have been extensively revised, with all the text scanned and revalidated where necessary by a team of experienced pharmacists. Over 260 monographs have been added, and 89 removed from the book (abbreviated information on the latter remains available in the electronic versions). In our continuing attempts to improve the clinical relevance of the book, the chapters on Prostaglandins and Hypothalamic and Pituitary Hormones have been split up and most of their contents added to new chapters on Obstetric Drugs and Growth Hormone and its Modulators. The chapter on Sex Hormones has been reorganised and renamed Sex Hormones and their Modulators.

The disease treatment reviews, 668 in all and generally located in the chapter introductions, have also been revised in order to reflect current trends and provide key references. Cross-references to these reviews appear in the monographs of the drugs cited; the reviews can also be accessed via the general index. It is hoped that these reviews will be of use to readers who want an overview of a particular disease and its drug treatment and will provide a useful starting point for those who want to pursue particular aspects further.

Martindale contains much nomenclature information intended to assist the reader in identifying a particular drug or compound, and for this edition we have again greatly expanded our coverage of synonyms, with the addition of names from Poland and Turkey, and increased coverage of Russian synonyms and 'street names' for substances of abuse. Coverage of ATC codes has been expanded to include codes assigned to veterinary medicines

This edition of Martindale also sees the number of graphical representations of the chemical structures increased.

The information on proprietary preparations, an important feature of Martindale, has been updated and more countries have been covered for this edition.

Martindale is based on published information and more than 47 700 selected references are included. The amount of drug information now published electronically has increased significantly since the last printed edition of Martindale and this edition now includes nearly 2700 citations to material available on the Internet as web pages. Because of the nature of the Internet, there is no way to guarantee that the material referred to by a URL will remain at that location, as many sites are subject to periodic reorganisation; additionally, the content of Internet documents may change without warning. All URLs in Martindale are rechecked shortly before publication to ensure that a document is present. The accession date given in the citation represents the last date on which the content of the document referred to was revalidated.

Our objective is to evaluate the literature, covering important studies, guidelines, and useful reviews and placing them in context. Multicentre studies, meta-analyses, and systematic reviews play an important role in the study of drug treatment, and their findings and conclusions are considered in many of our chapters. However, there is also a place for the anecdotal report and the small study, and information from such sources is included where appropriate. In compiling the text of a Martindale monograph extensive use is made of the drug's licensed product information as published in various countries and approved by the relevant regulatory health bodies. Acknowledgement is also given to information referenced from a number of authoritative sources including the *British National Formulary*, the *British National Formulary for Children*, the *British Pharmacopoeia*, the *European Pharmacopoeia*, the *United States National Formulary*, and the *United States Pharmacopeia*.

Martindale is not a book of standards. Inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Philosophy and methodology

Martindale's uses are as varied as its users. However, our primary aims are:

- to summarise clinically useful information on all drugs and medicines around the world
- to provide accurate, unbiased, reasonably comprehensive, and regularly re-evaluated information in a concise format
- to provide a lead-in to the published evidence base from which we derive our information

In order to achieve the aims specified above, our working practices have to optimise internal knowledge management.

MARTINDALE STAFF. Martindale is currently produced by a team of 21 people, 18 of whom are pharmacists or pharmacy technicians with relevant expertise. The team is divided into 5 revising groups each of 2 staff editors, as well as 5 assistant editors, 1 editor-in-chief, a co-ordinator for the processing of information on proprietary medicines, and 4 clerical and support staff. A number of pharmacists work as external evaluators to maintain coverage of non-UK preparations.

Staff editors receive formal training in literature evaluation and searching techniques, as well as specific, 'on-the-job' training in internal procedures. Each revision team has responsibility for the re-evaluation and update of a particular group of chapters. Senior editorial staff edit and approve the output of the teams. Staff are responsible for ongoing data collection as well as the revision process.

DATA COLLECTION. In order to reduce the amount of formal data collection required at revision, a prospective data-collection roster is in operation. This involves all staff members in hand-searching selected major medical journals, as well as regular searches of the internet sites of regulatory authorities (EMEA, FDA, and MHRA), and sources of high-quality systematic reviews and guidelines (such as Bandolier, Clinical Evidence, Cochrane, and NICE), for drug information. In addition, pharmacopoeial, governmental and WHO publications are hand-searched for information relating to drugs and drug therapy.

The list of sources used has been iteratively developed over many years by analysis of previous citations, and is reviewed and updated regularly.

PROPRIETARY PREPARATIONS. The Martindale proprietary preparations team evaluate licensed product information for 40 countries and regions, in order to maintain the widest possible coverage of drugs in use internationally. Preparation names, manufacturers, ingredients, and licensed uses are included in the internal Martindale database for review during the revision process, and any significant additional information is forwarded to the relevant revision team.

REVISION. In order to maintain the quality and currency of our content, it is constantly revised and updated. Our revision processes cover both scheduled, in-depth revision of the content of every chapter in the book on a chapter-by-chapter basis, and updates in reaction to new information as it arrives. The revision procedure involves the formalised re-evaluation of all standing information, the assessment of new collected references for quality and relevance, and the selective use of search techniques on bibliographic databases and the Internet to identify further candidate information.

CHECKING. Once the material for a given chapter has been re-evaluated and updated it undergoes a rigorous check, designed to ensure not only that all changes are valid and appropriate, but also that important points have not been missed.

EDITING. The chapter is then passed to a member of the senior editorial staff, who performs a second check and preliminary editing of the data. This process is designed to ensure consistency of approach and style, as well as offering an opportunity to pick up any errors missed at the first check. Changes and questions are fed back to the revision team in an iterative process that may involve more than one cycle. Once past its preliminary edit the chapter is sent to the Editor for a final check and approval, which again may require changes to be made and checked, before passing it to the next stage.

KEYING, PROOF-READING, AND DOSE-CHECKING. Once approved by the Editor, amendments can be incorporated into the database, which remains untouched until this stage as a security measure. These changes are then proofread for errors, corrected if necessary, and any corrections checked. Extensive electronic testing for spelling, style, and format is also carried out at all stages. The amended chapter then undergoes an independent check of the dose information against its recorded sources. This check is performed by a member of staff outside the original revising and editing team, and is an additional safeguard against the inadvertent introduction of potentially dangerous dose errors. Once past these stages the data are cleared for release, and can be published in the next update of the Martindale electronic products, and, at appropriate points in the publishing cycle, in the book.

ADDITIONAL CHECKS FOR PUBLICATION. Some additional checks are made before publishing a print edition of Martindale. An second independent dose check of all chapters is made by an external expert, all cross-references are revalidated, and tests of the typesetting and page structure are made. In addition our extensive index is generated and carefully checked for accuracy, order, and consistency.

FEEDBACK. We are always grateful to get feedback from our users and, whenever possible, we try to incorporate information or suggestions that help us to improve Martindale. Anyone wishing to comment on the editorial content of Martindale can contact us at the following e-mail address: martindale@rpsgb.org

Arrangement

VOLUME 1: • MONOGRAPHS ON DUGS AND ANCILLARY SUBSTANCES (pages 1–2418). This section contains 5827 monographs arranged in 54 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. The introductions of those chapters that describe drugs used in the management of disease may contain disease treatment reviews—descriptions of those diseases together with reviews of the choice of treatments.The last chapter in this section consists of a series of monographs arranged in the alphabetical order of their main titles. It includes monographs on drugs not easily classified, on herbals, and on drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

VOLUME 2: • PREPARATIONS (pages 2191–2880). This section contains over 146 000 proprietary preparations from a range of countries and regions. For this edition we have covered Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, the United Arab Emirates, UK, USA, and Venezuela. We have also included some proprietary preparations from Japan. The information provided includes the proprietary name, the manufacturer or distributor, the active ingredients with cross-references to the drug monographs, and a summary of the indications as given by the manufacturer.

• DIRECTORY OF MANUFACTURERS (pages 3205–3274). In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address and website if it is available. This directory contains nearly 13 000 entries.

• GENERAL INDEX (pages 3275–3694). To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index, prepared from 153 000 entries, includes entries for drugs (approved names, synonyms, and chemical names), preparations, pharmacological and therapeutic groups, and clinical uses (disease treatment reviews). As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page. To improve clarity and the ease of location of index entries long chemical names have been omitted from the index.

This edition includes both nonproprietary and proprietary names in Russian, and these names may be found in Russian alphabetical order in the Cyrillic section of the index immediately following the entries in the Latin alphabet.

Nomenclature

TITLES AND SYNONYMS. The title of each monograph is in English, with preference usually being given to International Nonproprietary Names (INN), British Approved Names (BAN), and United States Adopted Names (USAN). These 3 authorities are shown where appropriate. A European Directive (92/27/EEC) requires the use of Recommended International Nonproprietary Names (rINNs) in the labelling of medicinal products throughout member states of the European Community and where the BAN and INN differed in the past the BAN has been changed to accord with the rINN. The major exception to this convention is the retention of the names adrenaline and noradrenaline, these being the terms used as the titles of the monographs in the European Pharmacopoeia and therefore the official names in the member states. In some approved names it is now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. Inevitably there may be some inconsistencies of style with older approved names but wherever possible the names used for drugs or radicals in Martindale have been altered in accordance with the guidelines on the use of INNs for pharmaceutical substances. A table of contracted names for ions and groups used in approved names and titles is given on page xi. INNs in the four other main official languages (French, Latin, Russian, and Spanish) have also been included in the list of synonyms where these differ from the English INN. BAN names for substance combinations and United States Pharmacy Equivalent Names (PEN) for dosage forms containing two or more active ingredients are given in the text of the relevant monographs; these names start with the prefix 'Co-'.

This section also includes names given as synonyms such as commonly used abbreviated names; Latin versions of the titles in the European Pharmacopoeia; English, American, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. Official titles and synonyms used in the British, European, and US Pharmacopoeias are given in the section on pharmacopoeias where the relevant pharmacopoeial substance is described.

STREET NAMES. This edition of Martindale once again includes greatly expanded coverage of 'street names' for substances of abuse. Street terms and other slang names for drugs of abuse are included for guidance only and should be used with caution. Because of the very nature of their origin they cannot be relied upon for definitive identification of a substance. The use of such terms changes rapidly, and can vary between different geographical locations, and any given name may potentially be applied to more than one substance or even to a mixture of substances. Furthermore, established or well recognised generic drug names or herbal names have sometimes been misused as street terms for completely unrelated substances. In order to enable the reader to distinguish them from better validated synonyms, in the index, such names are included in italics and in quotation marks.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parentheses.

ATC CODES. Codes from the Anatomical Therapeutic Chemical (ATC) classification system (see http://www.whocc.no) have been provided, where available, for each monograph substance to help readers refer to other information systems. The codes assigned in the equivalent classification system for veterinary medicines (ATC Vet—see http://www.whocc.no/atcvet) have been included where possible.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 2007 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry (IUPAC) and based on the ^{12}C scale (see page xiii). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. A description of the substance and a summary of the pharmaceutical information (see below) that appears in the British, European, or US Pharmacopoeias is also included. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: *British, British Veterinary, Chinese, European, French, German, International, Italian, Japanese, Polish, Spanish, Swiss, United States* (including the *National Formulary*), and *Vietnamese*. The abbreviations for these pharmacopoeias are included in the list of abbreviations

used in Martindale, see page viii, which also includes details of the edition and/or supplement(s) consulted.

Several countries are parties to the Convention on the Elaboration of a European Pharmacopoeia. This means that they must adopt the standards of the European Pharmacopoeia. These countries are currently Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the Former Yugoslav Republic of Macedonia. Hence the European Pharmacopoeia is cited in the drug monograph lists of pharmacopoeias rather than these individual national pharmacopoeias.

Official preparations, mainly from the current British, European, and US Pharmacopoeias, are listed at the end of drug monographs.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at temperatures between 15° and 25°. The information usually relates to w/v solubilities but in some cases is v/v if the monograph substance itself is a liquid. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility	
very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. The term 'a cool place' is generally used to describe a place in which the temperature is between 8° and 15°. In general, the storage conditions apply to the monograph substance and not its solutions or preparations.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Drugs in Sport

Wherever possible we have attempted to indicate those drugs and substances that may be subject to restriction in some or all sports, either in their own right, or because they are a derivative of a restricted substance or a member of a prohibited group. Proprietary preparations containing such compounds are also marked in the preparation section in Volume 2. The definitive guide used for identifying restricted drugs for this edition is the 2008 Prohibited List issued by the World Anti-Doping Agency (WADA—see www.wada-ama.org). However, these regulations, which are issued annually, are subject to interpretation and therapeutic exemption, and may vary from sport to sport; particular sporting authorities may also issue additional restrictions, and competitors should always check with the appropriate body. The rules are constantly evolving and the absence of any indication of restriction in Martindale should not be taken as absolute confirmation that the substance may legitimately be taken by a competitor.

Pharmacological and Therapeutic Information

Information on adverse effects, treatment of adverse effects, precautions (including contra-indications), interactions, pharmacokinetics, and uses and administration of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications. This edition contains about 15 000 such abstracts or reviews based on information in an ever widening range of publications.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Licensed product information and manufacturers' literature has been considered in the light of other available information.

The risks of giving drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the fetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Some drugs given to the mother are distributed into breast milk and therefore may pose a risk to a breast-fed infant. Whenever possible, information has been included to help determine the safety of continuing to breast feed while the mother is receiving a particular drug. Safety during breast feeding should not be inferred from the absence of a statement for any drug.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when given by mouth. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v and sodium chloride injection is 0.9% w/v.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

Acknowledgements

The Editor gratefully acknowledges the advice and assistance of the many experts who have suggested amendments to the text of Martindale. Thanks are also due to K Baxter, M Jane, CR Lee, DK Mehta, F Post, and AB Prasad, for advice and comments on specific issues during revision. The Editor is grateful to the many organisations that have helped in providing information, including the World Health Organization, the British Pharmacopoeia Commission, and our Spanish colleagues at Grupo Ars XXI.

Martindale staff have been able to call on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to J Martin and the staff of the British National Formulary, and the staff of the library and information department. Thanks are due to I Baxter, M Davis, S Driver, EJ Laughton, R McLarney, and SJ Shankie for their editorial tasks. Thanks are also due to PJ Weller, C Fry and the staff of the Pharmaceutical Press for their support.

The contents of this 36th edition were planned, written, checked, indexed, keyed, proofed, and processed by the Martindale staff. The Editor is pleased to acknowledge the skills and commitment of all the Martindale staff and to record his gratitude: to Christine Iskandar for clerical assistance; to Michael Evans for Knowledge Systems support; to Chloë Hatwal, Elizabeth King, James O'Reilly, and Elen Shute for editorial assistance; to the Staff Editors Catherine Cadart, Kathleen Eager, Sue Handy, Fauziah Hashmi, Sue Ho, Joanna Humm, Jean Macpherson, Melissa Siew, Sandra Sutton, and Gerda Viedge; to the Assistant Editors Alison Brayfield, Julie McGlashan, Gail Neathercoat, and Anne Parsons; and to the Senior Assistant Editor Paul Blake.

London October 2008

Abbreviations

For abbreviations of the names of manufacturers or their distributors, see Directory of Manufacturers, page 3205.

ACE—angiotensin-converting enzyme.
ADHD—attention deficit hyperactivity disorder.
agg.—aggregate (in botanical names), including 2 or more species which resemble each other closely.
AIDS—acquired immunodeficiency syndrome.
a.m.—*ante meridiem*, 'before noon'.
ARC—AIDS-related complex.
Arg.—Argentina.
ATC—Anatomical Therapeutic Chemical classification.
AUC—area under the concentration-time curve.
Austral.—Australia.
AV—atrioventricular.
BAN—British Approved Name.
BANM—British Approved Name Modified.
Belg.—Belgium.
BMA—British Medical Association.
BMI—body mass index.
BNF—British National Formulary.
BNFC—British National Formulary for Children.
b.p.—boiling point.
BP—British Pharmacopoeia. Unless otherwise specified, BP references are to the 2008 edition.
BP(Vet)—British Pharmacopoeia (Veterinary) 2008.
BPC—British Pharmaceutical Codex.
Br.—British.
Braz.—Brazil.
Bulg.—Bulgaria.
BUN—Blood-urea-nitrogen.
°C—degrees Celsius (centigrade). Unless otherwise indicated in the text, temperatures are expressed in this thermometric scale.
Canad.—Canada.
CAPD—continuous ambulatory peritoneal dialysis.
CAS—Chemical Abstracts Service.
CCPD—continuous cycle peritoneal dialysis.
CDC—Centers for Disease Control and Prevention (USA) (formerly Centers for Disease Control).
Chin. P.—Chinese Pharmacopoeia 2005.
CHM—Commission on Human Medicines (UK).
CI—Colour Index.
CMV—cytomegalovirus.
CNS—central nervous system.
cP—centipoise(s).
CPMP—Committee on Proprietary Medicinal Products of the European Union.
CSF—cerebrospinal fluid.
CSM—Committee on Safety of Medicines (UK) (now subsumed within the Commission on Human Medicines).
cSt—centistokes.
Cz.—Czech Republic.
D & C—designation applied in USA to dyes permitted for use in drugs and cosmetics.
d.c.—direct current.
DEFRA—Department for Environment, Food, and Rural Affairs (UK).
Denm.—Denmark.
DHSS—the former Department of Health and Social Security (UK).
dL—decilitre(s).
DNA—deoxyribonucleic acid.
DoH—Department of Health (UK).
DTF—Drug Tariff Formulary.
ECG—electrocardiogram.
ECT—electroconvulsive therapy.
Ecuad.—Ecuador.
ed.—editor(s) *or* edited by *or* edition.
EEC—European Economic Community, now the European Union.
EEG—electro-encephalogram.
e.g.—*exempli gratia* 'for example'.
EMEA—European Medicines Agency.
ENL—erythema nodosum leprosum.
ESRD—end-stage renal disease.
et al.—*et alii*, 'and others': for three or more co-authors or co-workers.
et seq.—and what follows.
EU—European Union.
Eur. P.—see Ph. Eur.
Ext. D & C—designation applied in USA to dyes permitted for use in external drug and cosmetic preparations.
°F—degrees Fahrenheit.
FAC—Food Additives and Contaminants Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FAO—Food and Agriculture Organization of the United Nations.
FAO/WHO—Food and Agriculture Organization of the United Nations *and the* World Health Organization.
FDA—Food and Drug Administration of USA.
FdAC—Food Advisory Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FD & C—designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics.
FEV_1—forced expiratory volume in 1 second.
Fin.—Finland.
FIP—Fédération Internationale Pharmaceutique.
f.p.—freezing point.
FPA—Family Planning Association (UK).
Fr.—France.
Fr. P.—French Pharmacopoeia 1982 (Pharmacopée Francaise, X^e Edition) and updates up to 2003.
g—gram(s).
Ger.—Germany.
Ger. P.— German Pharmacopoeia (Deutsches Arzneibuch, 2007).
GFR—glomerular filtration rate.
G6PD—glucose-6-phosphate dehydrogenase.
Gr.—Greece.
HAART—highly active antiretroviral therapy.
Hb— haemoglobin.
Hib—*Haemophilus influenzae* type b.
HIV—human immunodeficiency virus.
HLA—human lymphocyte antigens.
HLB—hydrophilic-lipophilic balance.

HRT—hormone replacement therapy.
HSE—Health and Safety Executive (UK).
Hung.—Hungary.
IARC—International Agency for Research on Cancer.
ibid.—*ibidem*, 'in the same place (journal or book)'.
idem—'the same': used for the same authors and titles.
i.e.—*id est*, 'that is'.
Ig—immunoglobulin.
Indon.—Indonesia.
INN—International Nonproprietary Name.
INNM—International Nonproprietary Name Modified.
Int. P.—International Pharmacopoeia 4th ed., 2006.
IPCS—International Programme on Chemical Safety.
IQ—intelligence quotient.
Irl.—Ireland.
ISH—International Society of Hypertension.
It. P.—Italian Pharmacopoeia 11th ed., 2002 (Farmacopea Ufficiale della Repubblica Italiana, XI Edizione, 2002).
Ital.—Italy.
IUD—intra-uterine device.
IUPAC—International Union of Pure and Applied Chemistry.
IVF—*in-vitro* fertilisation.
J—joule(s).
Jpn—Japan.
Jpn P.—The Pharmacopoeia of Japan, 15th ed., 2006.
K—kelvin.
kcal—kilocalorie(s).
kg—kilogram(s).
kJ—kilojoule(s).
lb—pound(s) avoirdupois.
LD50—a dose lethal to 50% of the specified animals or micro-organisms.
m—metre(s).
m^2—square metre(s).
m^3—cubic metre(s).
M—molar.
MAFF—the former Ministry of Agriculture, Fisheries and Food (UK), now Department of Environment, Food, and Rural Affairs (DEFRA).
MAOI—monoamine oxidase inhibitor.
max.—maximum.
MBC—minimum bactericidal concentration.
MCA—Medicines Control Agency, now MHRA (UK).
mEq—milliequivalent(s).
Mex.—Mexico.
mg—milligram(s).
MHRA—Medicines and Healthcare products Regulatory Agency (UK).
MIC—minimum inhibitory concentration.
min—minute.
min.—minimum.
MJ—megajoule(s).
mL—millilitre(s).
mm—millimetre(s).
mm^2—square millimetre(s).
mm^3—cubic millimetre(s).
mmHg—millimetre(s) of mercury.
mmol—millimole.
mol—mole.
mol. wt—molecular weight.
Mon.—Monaco.
mosmol—milliosmole.
m.p.—melting point.
MRC—Medical Research Council (UK).
MRSA—meticillin-resistant *Staphylococcus aureus*.
µg—microgram(s).
µm—micrometre(s).
Neth.—The Netherlands.
NICE—National Institute for Health and Clinical Excellence (formerly the National Institute for Clinical Excellence) (UK).
NIH—National Institutes of Health (USA).
nm—nanometre(s).
NMDA—*N*-methyl-D-aspartate.
NNRTI—non-nucleoside reverse transcriptase inhibitor.
Norw.—Norway.
NRTI—nucleoside reverse transcriptase inhibitor.
NSAID—nonsteroidal anti-inflammatory drug.
NYHA—New York Heart Association.
NZ—New Zealand.
OP—over proof.
o/w—oil-in-water.
P—probability.
Pa—pascal(s).
pCO_2—plasma partial pressure (concentration) of carbon dioxide.
p_aCO_2—arterial plasma partial pressure (concentration) of carbon dioxide.
PEN—Pharmacy Equivalent Name, see page vi.
pg—picogram(s).
pH—the negative logarithm of the hydrogen ion concentration.
Ph. Eur.—European Pharmacopoeia, 6th ed., 2008 and Supplements 6.1 and 6.2.
Pharm. Soc. Lab. Rep.—Royal Pharmaceutical Society's Laboratory Report.
Philipp.—Philippines.
PHLS—Public Health Laboratory Service (UK).
pINN—Proposed International Nonproprietary Name.
pINNM—Proposed International Nonproprietary Name Modified.
pK_a—the negative logarithm of the dissociation constant.
p.m.—*post meridiem*, 'afternoon'.
pO_2—plasma partial pressure (concentration) of oxygen.
p_aO_2—arterial plasma partial pressure (concentration) of oxygen.
Pol.—Poland.
Pol. P.—Polish Pharmacopoeia 6th ed., 2002 (Farmakopea Polska VI, 2002) and Supplement 2005.
Port.—Portugal.
ppm—parts per million.
PSGB—The Pharmaceutical Society of Great Britain. Now the Royal Pharmaceutical Society of Great Britain.
PUVA—psoralen with UVA light irradiation.
PVC—polyvinyl chloride.
RCGP—Royal College of General Practitioners (UK).
RIMA—reversible inhibitor of monoamine oxidase type A.
rINN—Recommended International Nonproprietary Name.
rINNM—Recommended International Nonproprietary Name Modified.
RNA—ribonucleic acid.
RPSGB—The Royal Pharmaceutical Society of Great Britain.
RSV—respiratory syncytial virus.
S. Afr.—South Africa.
SGOT—serum glutamic oxaloacetic transaminase (serum aspartate aminotransferase *now preferred*).

SGPT—serum glutamic pyruvic transaminase (serum alanine aminotransferase *now preferred*).

SI—Statutory Instrument *or* Système International d'Unités (International System of Units).

sic—written exactly as it appears in the original.

SLE—systemic lupus erythematosus.

sp.—species (plural spp.).

sp. gr.—specific gravity.

Span.—Spanish.

Span. P.—Spanish Pharmacopoeia 2nd ed., 2002 (Real Farmacopoea Española, Segunda Edición, 2002) and Supplement 2.1.

SSRI—selective serotonin reuptake inhibitor.

St—stokes.

subsp.—subspecies.

suppl—supplement(s).

Swed.—Sweden.

Swiss P.—Swiss Pharmacopoeia 2006 (Pharmacopoea Helvetica, 10 Ausgabe, Deutsche Ausgabe).

Switz.—Switzerland.

Thai.—Thailand.

TNF—tumour necrosis factor.

TPN—total parenteral nutrition.

Turk.—Turkey.

UAE—United Arab Emirates.

UK—United Kingdom.

UNICEF—United Nations Children's Fund.

UP—under proof.

Urug.—Uruguay.

US and ***USA***—United States of America.

USAN—United States Adopted Name.

USNF—The United States 'National Formulary 26', 2008, and Supplements 1 and 2.

USP—The United States Pharmacopeia 31, 2008, and Supplements 1 and 2.

UV—ultraviolet.

var.—variety.

Venez.—Venezuela.

Viet.—Vietnamese.

Viet. P.—Vietnamese Pharmacopoeia 2002 (Pharmacopoeia Vietnamica, Editio III).

vol.—volume(s).

v/v—volume in volume.

v/w—volume in weight.

WHO—World Health Organization.

w/o—water-in-oil.

wt—weight.

wt per mL—weight per millilitre.

w/v—weight in volume.

w/w—weight in weight.

Contracted Names for Ions and Groups

Contracted Name	Chemical Name
acefurate	acetate (ester) and furan-2-carboxylate (ester)
aceglumate	*rac*-hydrogen *N*-acetylglutmate
aceponate	acetate (ester) and propionate (ester)
acetonide	isopropylidenedioxy or propane-2,2-diylbis(oxy)
aceturate	*N*-acetylglycinate
acibutate	acetate (ester) and 2-methylpropanoate (ester)
acistrate	acetate (ester) and stearate (salt)
acoxil	acetoxymethyl or (acetyloxy)methyl
alfoscerate	(2*R*)-2,3-dihydroxypropyl hydrogen phosphate
alideximer	poly([oxy(2-hydroxyethane-1,1-diyl)]{oxy[1-(hydroxymethyl)ethane-1,2-diyl]}) partly *O*-etherified with carboxymethyl groups with some carboxy groups amide linked to the tetrapeptide residue (glyglyglycyl-L-phenylalanylglycyl)
amsonate	4,4′-diaminostilbene-2,2′-disulfonate or 2,2′-ethene-1,2-diylbis(5-aminobenzene-1-sulfonate)
anisatil	2-(4-methoxyphenyl)-2-oxoethyl or *p*-methoxyphenacyl
arbamel	2-(dimethylamino)-2-oxoethyl or ester with *N,N*-dimethylglycolamide
argine	30^{B}α-L-argine-30^{B}β-L-argine
aritox	ricin A chain-MAB immunotoxine
aspart	28^{B}-L-aspartic acid-
axetil	(*RS*)-1-acetoxyethyl or *rac*-1-(acetyloxy)ethyl
beloxil	benzyloxy
benetonide	*N*-benzoyl-2-methyl-β-alanine (ester) and acetonide
besilate (besylate)	benzenesulfonate
betadex	β-cyclodextrin
bezomil	(benzoyloxy)methyl
buciclate	*trans*-4-butylcyclohexanecarboxylate
bunapsilate	3,7-di-*tert*-butylnaphthalene-1,5-disulfonate
buteprate	butyrate (ester) and propionate (ester)
camsilate (camsylate)	camphor-10-sulfonate or (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate
caproate	hexanoate
carbesilate	4-sulfobenzoate
ciclotate (cyclotate)	4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylate
cilexetil	(*RS*)-1-{[(cyclohexyloxy)carbonyl]oxy}ethyl or *rac*-1-{[(cyclohexyloxy)carbonyl]oxy}ethyl
cipionate (cypionate)	cyclopentanepropionate or 3-cyclopentylpropanoate
cituxetan	*rac*-*N*-(4-{2-[bis(carboxymethyl)amino]-3-({2-[bis(carboxymethyl)amino]ethyl}(carboxymethyl)amino)propyl}phenyl)thiocarbamoyl
clofibrol	2-(4-chlorophenoxy)-2-methylpropyl
closilate (closylate)	4-chlorobenzene-1-sulfonate
crobefate	*rac*-{3-[(3*E*)-4-methoxybenzylidene]-2-(4-methoxyphenyl)chroman-6-yl phosphate(2-)}
cromacate	2-[(6-hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetate
cromesilate	6,7-dihydroxycoumarin-4-methanesulfonate or (6,7-dihydroxy-2-oxo-2*H*-chromen-4-yl)methanesulfonate

Contracted Name	Chemical Name
crosfumaril	(2*E*)-but-2-enedioyl
cyclamate	cyclohexylsulfamate
daloxate	L-alaninate (ester) and (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl
daropate (dapropate)	*N,N*-dimethyl-β-alaninate or 3-(dimethylamino)propanoate
deanil	2-(dimethylamino)ethyl
decil	decyl
defalan	des-1^{B}-L-phenylalanine-insulin
detemir	tetradecanoyl
dibudinate	2,6-di-*tert*-butylnaphthalene-1,5-disulfonate
dibunate	2,6-di-*tert*-butylnaphthalene-1-sulfonate
dicibate	dicyclohexylmethyl carbonate
diftitox	*N*-L-methionyl-387-L-histidine-388-L-alanine-1-388-toxin (*Corynebacterium diphtheriae* strain C7) (388→2′)-protein
digolil	2-(2-hydroxyethoxy)ethyl
diolamine	2,2′-azanediyldiethanol or diethanolamine
docosil	docosyl
dofosfate	octadecyl hydrogen phosphate
ecamate	*N*-ethylcarbamate
edamine	ethane-1,2-diamine or ethylenediamine
edetate	ethylenediamine-*NNN′N′*-tetra-acetate
edisilate (edisylate)	ethane-1,2-disulfonate
embonate	4,4′-methylenebis(3-hydroxynaphthalene-2-carboxylate) or 4,4′-methylenebis(3-hydroxy-2-naphthoate) (=pamoate)
enantate (enanthate)	heptanoate
enbutate	acetate (ester) and butanoate (ester)
epolamine	1-pyrrolidineethanol or 2-(pyrrolidin-1-yl)ethanol
erbumine	*tert*-butylamine or 2-methylpropan-2-amine
esilate (esylate)	ethanesulfonate
estolate	propanoate (ester) and dodecyl sulfate (salt) or propionate dodecyl sulfate
etabonate	(ethoxycarbonyl)oxy (=ethyl carbonate)
etilsulfate	ethyl sulfate
farnesil	(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl
fendizoate	2-(6-hydroxybiphenyl-3-carbonyl)benzoate
fostedate	tetradecyl hydrogen phosphate
furetonide	1-benzofurane-2-carboxylate (ester) and propane-2,2-diylbis(oxy)
gamolenate	(6*Z*,9*Z*,12*Z*)-octadeca-6,9,12-trienoate
glargine	21^{A}-glycine-30^{B}α-L-arginine-30^{B}β-L-arginine
gluceptate	D-*glycero*-D-*gulo*-heptanoate or D-*glycero*-D-*gulo*-heptonate
glulisine	[3^{B}-L-lysine,29^{B}-L-glutamic acid]
glutamer	glutaraldehyde polymer
guacil	2-methoxyphenyl
hemisuccinate	hydrogen butanedioate

Contracted Name	Chemical Name
hexacetonide	3,3-dimethylbutanoate (ester) and propan-2,2-diylbis(oxy) or 3,3-dimethylbutyrate (ester) and acetonide
hibenzate (hybenzate)	2-(4-hydroxybenzoyl)benzoate
hyclate	monohydrochloride hemi-ethanolate hemihydrate
hydroxynaphtoate	3-hydroxynapthalene-2-carboxylate
isetionate (isethionate)	2-hydroxyethane-1-sulfonate
laurate	dodecanoate
lauril	dodecyl
laurilsulfate (lauryl sulphate)	dodecyl sulfate
lisetil	L-lysinate (ester) and diethyl (ester)
lisicol	{*N*-[(5*S*)-5-carboxy-5-(3α,7α,12α-trihydroxy-5β-cholan-24-amido)pentyl]carbamothioyl}amino
lispro	28^{B}-L-lysine-29^{B}-L-proline
mafenatox	enterotoxin A (227-alanine) (*Staphylococcus aureus*)
medoxomil	(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl
megallate	3,4,5-trimethoxybenzoate
meglumine	*N*-methylglucamine
merpentan	4,5-bis(2-mercaptoacetamido) valeric acid or {*N*,*N*′-[1-(3-oxopropyl)ethane-1,2-diyl]bis(2-sulfanylacetamidato)}(4-)
mertansine	tetrakis{(4*RS*)-4[(3-{[(1*S*)-2-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.$1^{10,14}$.$0^{3,5}$]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}-1-methyl-oxoethyl]methylamino}-3-oxopropyl)disulfanyl]pentanoyl}
mesilate (mesylate)	methanesulfonate
metembonate	4,4′-methylenebis(3-methoxynaphthalene-2-carboxylate)
methonitrate	*N*-methyl, nitrate (salt)
metilsulfate	methyl sulfate
metiodide	*N*-methyl, iodide (salt)
methylbromide	*N*-methyl, bromide (salt)
mofetil	2-(morpholino)ethyl or 2-(morpholin-4-yl)ethyl
napadisilate	naphthalene-1,5-disulfonate
napsilate (napsylate)	naphthalene-2-sulfonate
nicotinate	pyridine-3-carboxylate
octil	octyl
olamine	2-aminoethanol or ethanolamine
oleate	(9*Z*)-octadec-9-enoate
oxoglurate	hydrogen 2-oxopentanedioate
palmitate	hexadecanoate
pamoate	4,4′-methylenebis(3-hydroxy-2-naphthoate) (=embonate)
pegol	α-(2-carboxyethyl)-ω-methoxypoly(oxyethane-1,2-diyl)
pendetide	N^{6}-{*N*-[2-({2-[bis(carboxymethyl)amino]-ethyl}(carboxymethyl)amino)ethyl]-*N*-(carboxymethyl)glycyl}-N^{2}-(*N*-glycyl-L-tyrosyl)-L-lysine
pentexil	(*RS*)-1-[(2,2-dimethylpropanoyl)oxy]ethyl
phenpropionate	3-phenylpropionate
pivalate	2,2-dimethylpropanoate (ester) or trimethylacetate
pivoxetil	*rac*-1-[(2-methoxy-2-methylpropanoyl)oxy]ethyl or 1-(2-methoxy-2-methylpropionyloxy)ethyl
pivoxil	(2,2-dimethyl-1-oxopropoxy)methyl or [(2,2-dimethylpropanoyl)oxy]methyl or (pivaloyloxy)methyl
poliglumex	[poly(L-glutamic acid)$_z$—(L-glutamate-γ-ester)—poly(L-glutamic acid)$_y$]$_n$
probutate	17-(1-oxobutoxy) (ester) and 21-(1-oxopropoxy) (ester) or propionate (ester) and butyrate (ester)
proxetil	1-[(isopropoxycarbonyl)oxy]ethyl or *rac*-1-{[(propan-2-yloxy)carbonyl]oxy}ethyl
raffimer	(2*S*,4*R*,6*R*,8*S*,11*S*,13*S*)-2,4,8,13-tetrakis(hydroxymethyl)-4,6,11-tris(ylomethyl)-3,5,7,10,12-pentaoxatetradecane-1,14-diyl
salicylate	2-hydroxybenzoate
sesquioleate	(9*Z*)-octadec-9-enoate(1.5)
soproxil	{[(propan-2-yloxy)carbonyl]oxy}methyl
steaglate	2-(octadecanoyloxy)acetate (ester)
stearate	octadecanoate
stinoprate	*N*-acetylcysteinate (salt) and propanoate (ester)
succinil	3-carboxypropanoyl
sudotox	248-L-histidine-249-L-methionine-250-L-alanine-251-L-glutamic acid-248-613-endotoxin A (*Pseudomonas aeruginosa* reduced)
suleptanate	monosodium 8-[methyl(2-sulfoethyl)amino]-8-oxooctanoate or monosodium 7-[methyl(2-sulfonatomethyl)carbamoyl]heptanoyl
sulfoxylate	sulfinomethyl, monosodium salt
tafenatox	enterotoxin A (*Staphylococcus aureus*)
tartrate	(2*R*,3*R*)-2,3-dihydroxybutanedioate
tebutate	*tert*-butylacetate or 3,3-dimethylbutyrate
tenoate	thiophene-2-carboxylate
teoclate	8-chloro-1,3-dimethyl-2,6-dioxo-3,6-dihydro-1*H*-purin-7-(2*H*)-ide or 8-chlorotheophyllinate
teprosilate	3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propane-1-sulfonate
tidoxil	*rac*-2-(decyloxy)-3-(dodecylsulfanyl)propyl
tiuxetan	*N*-(4-{(2*S*)-2-[bis(carboxymethyl)amino]-3-[(2*RS*)-{2-[bis(carboxymethyl)amino]propyl}(carboxymethyl)amino]propyl}phenyl)thiocarbamoyl
tocoferil	*rac*-(2*R*)-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]chroman-6-yl
tofesilate	3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)ethane-1-sulfonate
tosilate (tosylate)	4-methylbenzene-1-sulfonate or toluene-4-sulfonate
triclofenate	2,4,5-trichlorophenolate
triflutate	trifluoroacetate
trioleate	(9*Z*)-octadec-9-enoate(3) or tris[(9*Z*)-octadec-9-enoate]
tristearate	octadecanoate(3) or tris(octadecanoate)
trolamine	2,2′,2″-nitrilotriethanol or triethanolamine
troxundate	[2-(2-ethoxyethoxy)ethoxy]acetate or 3,6,9-trioxaundecanoate
undecylate	undecanoate
undecylenate	undec-10-enoate
valerate	pentanoate
xinafoate	1-hydroxynaphthalene-2-carboxylate or 1-hydroxy-2-naphthoate

Atomic Weights of the Elements— $^{12}C=12$

Atomic Number	Name	Symbol	Atomic Weight
89	Actinium	Ac	*
13	Aluminium	Al	26.9815386
95	Americium	Am	*
51	Antimony	Sb	121.760
18	Argon	Ar	39.948
33	Arsenic	As	74.92160
85	Astatine	At	*
56	Barium	Ba	137.327
97	Berkelium	Bk	*
4	Beryllium	Be	9.012182
83	Bismuth	Bi	208.98040
107	Bohrium	Bh	*
5	Boron	B	10.811
35	Bromine	Br	79.904
48	Cadmium	Cd	112.411
55	Caesium	Cs	132.9054519
20	Calcium	Ca	40.078
98	Californium	Cf	*
6	Carbon	C	12.0107
58	Cerium	Ce	140.116
17	Chlorine	Cl	35.453
24	Chromium	Cr	51.9961
27	Cobalt	Co	58.933195
29	Copper	Cu	63.546
96	Curium	Cm	*
110	Darmstadtium	Ds	*
105	Dubnium	Db	*
66	Dysprosium	Dy	162.500
99	Einsteinium	Es	*
68	Erbium	Er	167.259
63	Europium	Eu	151.964
100	Fermium	Fm	*
9	Fluorine	F	18.9984032
87	Francium	Fr	*
64	Gadolinium	Gd	157.25
31	Gallium	Ga	69.723
32	Germanium	Ge	72.64
79	Gold	Au	196.966569
72	Hafnium	Hf	178.49
108	Hassium	Hs	*
2	Helium	He	4.002602
67	Holmium	Ho	164.93032
1	Hydrogen	H	1.00794
49	Indium	In	114.818
53	Iodine	I	126.90447
77	Iridium	Ir	192.217
26	Iron	Fe	55.845
36	Krypton	Kr	83.798
57	Lanthanum	La	138.90547
103	Lawrencium	Lr	*
82	Lead	Pb	207.2
3	‡Lithium	Li	6.941
71	Lutetium	Lu	174.9668
12	Magnesium	Mg	24.3050
25	Manganese	Mn	54.938045
109	Meitnerium	Mt	*
101	Mendelevium	Md	*
80	Mercury	Hg	200.59
42	Molybdenum	Mo	95.96
60	Neodymium	Nd	144.242
10	Neon	Ne	20.1797
93	Neptunium	Np	*
28	Nickel	Ni	58.6934
41	Niobium	Nb	92.90638
7	Nitrogen	N	14.0067
102	Nobelium	No	*
76	Osmium	Os	190.23
8	Oxygen	O	15.9994
46	Palladium	Pd	106.42
15	Phosphorus	P	30.973762
78	Platinum	Pt	195.084
94	Plutonium	Pu	*
84	Polonium	Po	*
19	Potassium	K	39.0983
59	Praseodymium	Pr	140.90765
61	Promethium	Pm	*
91	†Protactinium	Pa	231.03588
88	Radium	Ra	*
86	Radon	Rn	*
75	Rhenium	Re	186.207
45	Rhodium	Rh	102.90550
111	Roentgenium	Rg	*
37	Rubidium	Rb	85.4678
44	Ruthenium	Ru	101.07
104	Rutherfordium	Rf	*
62	Samarium	Sm	150.36
21	Scandium	Sc	44.955912
106	Seaborgium	Sg	*
34	Selenium	Se	78.96
14	Silicon	Si	28.0855
47	Silver	Ag	107.8682
11	Sodium	Na	22.98976928
38	Strontium	Sr	87.62
16	Sulfur	S	32.065
73	Tantalum	Ta	180.94788
43	Technetium	Tc	*
52	Tellurium	Te	127.60
65	Terbium	Tb	158.92535
81	Thallium	Tl	204.3833
90	†Thorium	Th	232.03806
69	Thulium	Tm	168.93421
50	Tin	Sn	118.710
22	Titanium	Ti	47.867
74	Tungsten	W	183.84
112	Ununbium	Uub	*
116	Ununhexium	Uuh	*
118	Ununoctium	Uuo	*
115	Ununpentium	Uup	*
114	Ununquadium	Uuq	*
113	Ununtrium	Uut	*
92	†Uranium	U	238.02891
23	Vanadium	V	50.9415
54	Xenon	Xe	131.293
70	Ytterbium	Yb	173.054
39	Yttrium	Y	88.90585
30	Zinc	Zn	65.38
40	Zirconium	Zr	91.224

Elements marked (*) have no stable nuclides and IUPAC states "there is no general agreement on which of the isotopes of the radioactive elements is, or is likely to be judged 'important' and various criteria such as 'longest half-life', 'production in quantity', 'used commercially', etc., have been applied in the Commission's choice." However, atomic weights are given for radioactive elements marked (†) as they do have a characteristic terrestrial isotopic composition. Commercially available lithium (‡) materials have atomic weights ranging from 6.939 to 6.996; if a more accurate value is required, it must be determined for the specific material.

IUPAC Commission on Atomic Weights and Isotopic Abundances. Atomic Weights of the Elements 2007. Available at http://www.chem.qmul.ac.uk/iupac/AtWt/

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Volume 2

Volume 1

Monographs on Drugs and Ancillary Substances

Analgesics Anti-inflammatory Drugs and Antipyretics

The drugs described in this chapter are used mainly in the relief of pain, inflammation and, in some cases, fever. They can be grouped broadly into one of the categories briefly described below.

Aspirin and other salicylates

Aspirin and other salicylates have analgesic, anti-inflammatory, and antipyretic properties. Like other NSAIDs (see below) they are inhibitors of the enzyme cyclo-oxygenase; however, aspirin (though not the non-acetylated salicylates) irreversibly acetylates the enzyme whereas other NSAIDs compete with arachidonic acid for the active site. Salicylates are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Some salicylates are applied topically in rubefacient preparations for the relief of muscular and rheumatic pain. Aspirin also inhibits platelet aggregation and is used in cardiovascular disorders. Non-acetylated salicylates do not have antiplatelet activity.

For further discussion of the actions and uses of salicylates, see Aspirin, p.20.

Described in this chapter are
- Aloxiprin, p.18
- Aluminium Aspirin, p.19
- Ammonium Salicylate, p.19
- Amyl Salicylate, p.19
- Aspirin, p.20
- Bornyl Salicylate, p.28
- Carbasalate Calcium, p.33
- Choline Magnesium Trisalicylate, p.36
- Choline Salicylate, p.36
- Diethylamine Salicylate, p.47
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- Salamidacetic Acid, p.121
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- Salol, p.122
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- Sodium Salicylate, p.124
- Sodium Thiosalicylate, p.124
- Thurfyl Salicylate, p.129
- Trolamine Salicylate, p.132

Disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs) have anti-inflammatory properties thought to be mediated, in some cases, by the inhibition of the release or activity of cytokines. They are used in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis; some are also of benefit in ankylosing spondylitis and psoriatic arthritis. Many DMARDs also possess other therapeutic properties and are used in non-rheumatic conditions. The DMARD gold is referred to below; other DMARDs include sulfasalazine (p.1773), penicillamine (p.1456), the antimalarials chloroquine (p.599) and hydroxychloroquine (p.604), rituximab (p.767), and the immunosuppressants azathioprine (p.1818), ciclosporin (p.1822), cyclophosphamide (p.702), and methotrexate (p.745).

Described in this chapter are
- Abatacept, p.14
- Actarit, p.15
- Adalimumab, p.15
- Anakinra, p.19
- Etanercept, p.50
- Golimumab, p.62
- Infliximab, p.69
- Leflunomide, p.75

Gold compounds

Gold compounds are used mainly for their anti-inflammatory effect in active progressive rheumatoid arthritis and progressive juvenile idiopathic arthritis; they may also be beneficial in psoriatic arthritis. The mechanism of action of gold compounds in rheumatic disorders is as yet unknown.

For further discussion of the actions and uses of gold compounds, see Sodium Aurothiomalate, p.122.

Described in this chapter are
- Auranofin, p.25
- Aurothioglucose, p.26
- Aurotioprol, p.26
- Gold Keratinate, p.62
- Sodium Aurothiomalate, p.122
- Sodium Aurotiosulfate, p.124

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of structurally unrelated organic acids that have analgesic, anti-inflammatory, and antipyretic properties (see p.96). NSAIDs are inhibitors of the enzyme cyclo-oxygenase, and so directly inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p.2374). There are 2 forms of cyclo-oxygenase (COX), COX-1, which is the constitutive form of the enzyme, and COX-2, which is the form induced in the presence of inflammation. Inhibition of COX-2 is therefore thought to be responsible for at least some of the analgesic, anti-inflammatory, and antipyretic properties of NSAIDs whereas inhibition of COX-1 is thought to produce some of their toxic effects, particularly those on the gastrointestinal tract. Most of the NSAIDs currently available for clinical use inhibit both COX-1 and COX-2, although selective COX-2 inhibitors such as celecoxib are now available.

NSAIDs are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Indometacin and some other NSAIDs are used to close patent ductus arteriosus in premature neonates. Some NSAIDs are applied topically for the relief of muscular and rheumatic pain, and some are used in ophthalmic preparations for ocular inflammatory disorders. Aspirin (see above) is considered to be an NSAID, although it also has other properties.

Described in this chapter are
- Aceclofenac, p.14
- Acemetacin, p.15
- Alminoprofen, p.18
- Aminophenazone, p.19
- Aminopropylone, p.19
- Ampiroxicam, p.19
- Amtolmetin Guacil, p.19
- Azapropazone, p.26
- Bendazac, p.27
- Benoxaprofen, p.27
- Benzydamine, p.27
- Beta-aminopropionitrile, p.28
- Bromfenac, p.28
- Bufexamac, p.28
- Bumadizone, p.28
- Butibufen Sodium, p.31
- Carprofen, p.34
- Celecoxib, p.34
- Clofexamide, p.37
- Clofezone, p.37
- Clonixin, p.37
- Dexibuprofen, p.39
- Diclofenac, p.44
- Dipyrone, p.49
- Eltenac, p.50
- Epirizole, p.50
- Etodolac, p.52
- Etofenamate, p.53
- Etoricoxib, p.53
- Felbinac, p.54
- Fenbufen, p.54
- Fenoprofen, p.55
- Fentiazac, p.60
- Fepradinol, p.60
- Feprazone, p.60
- Firocoxib, p.60
- Floctafenine, p.60
- Flufenamic Acid, p.60
- Flunixin, p.61
- Flurbiprofen, p.61
- Furprofen, p.62
- Glafenine, p.62
- Glucametacin, p.62
- Ibuprofen, p.64
- Ibuproxam, p.66
- Indometacin, p.66
- Isonixin, p.72
- Kebuzone, p.72
- Ketoprofen, p.73
- Ketorolac, p.74
- Lonazolac, p.77
- Lornoxicam, p.77
- Loxoprofen, p.78
- Lumiracoxib, p.78
- Meclofenamic acid, p.79
- Mefenamic Acid, p.80
- Meloxicam, p.80
- Mofebutazone, p.86
- Mofezolac, p.86
- Morniflumate, p.86
- Nabumetone, p.91
- Naproxen, p.92
- Nepafenac, p.95
- Niflumic Acid, p.95
- Nimesulide, p.95
- Oxaprozin, p.105
- Oxyphenbutazone, p.107
- Parecoxib, p.111
- Phenazone, p.116
- Phenylbutazone, p.117
- Piketoprofen, p.117
- Piroxicam, p.117
- Pranoprofen, p.119
- Proglumetacin, p.119
- Propyphenazone, p.119
- Proquazone, p.119
- Ramifenazone, p.120
- Rofecoxib, p.121
- Sulindac, p.126
- Suprofen, p.128
- Suxibuzone, p.128
- Tenoxicam, p.128
- Tepoxalin, p.129
- Tetridamine, p.129
- Tiaprofenic Acid, p.129
- Tiaramide, p.129
- Tolfenamic Acid, p.130
- Tolmetin, p.130
- Valdecoxib, p.132
- Vedaprofen, p.133
- Zaltoprofen, p.133

Opioid analgesics

Opioid analgesics include the opium alkaloids morphine and codeine and their derivatives as well as synthetic substances with agonist, partial agonist, or mixed agonist and antagonist activity at opioid receptors (see p.101). The term opiate analgesics refers only to those opioids derived from opium, or their semisynthetic congeners. The term narcotic analgesics has legal connotations and is no longer used pharmacologically or clinically.

Most opioids are used as analgesics, and morphine is the standard against which all other opioid analgesics are compared. Opioids such as codeine or dextropropoxyphene are used in the treatment of less severe pain, and are often combined with non-opioid analgesics such as aspirin, other NSAIDs, or paracetamol. More potent opioids such as morphine are used in severe acute and chronic pain, in-

cluding cancer pain. Some opioids such as codeine, morphine, and diamorphine are also used as antitussives, although the latter two are usually reserved for use in terminal lung disease. Some opioid analgesics such as fentanyl and its congeners are used mainly as adjuncts to anaesthesia; some of these may also be used in higher doses as the sole anaesthetic drug.

Some opioids are rarely if ever used as analgesics and are described elsewhere; they include the antitussives dextromethorphan (p.1555) and pholcodine (p.1570), and the antidiarrhoeals diphenoxylate (p.1724) and loperamide (p.1741).

Opioids can produce physical dependence and withdrawal symptoms if suddenly stopped. They are also subject to abuse.

Described in this chapter are

- Alfentanil, p.16
- Anileridine, p.20
- Buprenorphine, p.29
- Butorphanol, p.32
- Carfentanil, p.34
- Codeine, p.37
- Dextromoramide, p.39
- Dextropropoxyphene, p.40
- Diamorphine, p.42
- Dihydrocodeine, p.48
- Dipipanone, p.49
- Embutramide, p.50
- Ethoheptazine, p.52
- Ethylmorphine, p.52
- Etorphine, p.54
- Fentanyl, p.55
- Hydrochlorides of Mixed Opium Alkaloids, p.105
- Hydrocodone, p.63
- Hydromorphone, p.63
- Ketobemidone, p.73
- Levacetylmethadol, p.77
- Levomethadone, p.77
- Levorphanol, p.77
- Meptazinol, p.81
- Methadone, p.82
- Morphine, p.86
- Nalbuphine, p.91
- Nicomorphine, p.95
- Opium, p.105
- Oxycodone, p.106
- Oxymorphone, p.107
- Papaveretum, p.105
- Pentazocine, p.112
- Pethidine, p.113
- Piritramide, p.117
- Remifentanil, p.120
- Sufentanil, p.124
- Tilidine, p.129
- Tramadol, p.130
- Trimeperidine, p.132

Paracetamol and other para-aminophenols

Paracetamol is the principal para-aminophenol derivative in use. Acetanilide and phenacetin have generally been replaced by safer analgesics. Propacetamol is hydrolysed to paracetamol in the plasma.

Paracetamol has analgesic and antipyretic properties and weak anti-inflammatory activity. The mechanism of analgesic action remains to be fully elucidated, but may be due to inhibition of prostaglandin synthesis both centrally and peripherally. Paracetamol is used for the relief of mild to moderate pain and minor febrile conditions.

Described in this chapter are

- Acetanilide, p.15
- Paracetamol, p.108
- Phenacetin, p.115
- Propacetamol, p.119

Analgesia and Pain

Pain is defined by the International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'

Under normal circumstances pain is the result of stimulation of peripheral receptors that transmit impulses through pain pathways to the brain. Pain receptors or nociceptors are of two basic types:

- *mechanoheat receptors* have a high stimulation threshold and respond to intense or potentially damaging noxious stimuli. These receptors are associated with rapidly conducting, thinly myelinated Aδ fibres, and their stimulation produces rapid sharp localised pain that serves to activate withdrawal reflexes
- *polymodal nociceptors* respond to mechanical, thermal, or chemical insults. These receptors are also activated by cellular components that are released after tissue damage. Their impulses are transmitted slowly along unmyelinated C type fibres and produce dull, aching, and poorly localised pain with a slower onset

Nerve fibres from nociceptors terminate in the dorsal root of the spinal cord before transmission by ascending pathways to the brain. There have been many theories on the processing of pain signals at the spinal level but the 'gate theory' proposed by Melzack and Wall is one of the best known. This theory postulates that the transmission of impulses to the brain is modulated by a gate mechanism in the substantia gelatinosa. Stimulation of small fibres opens the gate and facilitates transmission whereas stimulation of large fibres, which normally carry non-painful sensory input, can close the gate and inhibit transmission. Transmission also appears to be modulated by several other mechanisms which can influence the sensitivity of the gate.

Inflammatory mediators such as bradykinin, histamine, serotonin, and prostaglandins produced in response to tissue damage can produce peripheral sensitisation so that receptors respond to low intensity or innocuous stimuli; central sensitisation also occurs. Pain associated with tissue damage hence results in increased sensitivity of the sensory system so that the pain can occur in the absence of a clear stimulus. There may be a reduction in the pain threshold (*allodynia*) resulting in an exaggerated response (*hyperalgesia*) or a prolonged effect (*hyperpathia*).

Pain is often classified as being acute or chronic in nature.

- **Acute pain** is associated with trauma or disease and usually has a well-defined location, character, and timing. It is accompanied by symptoms of autonomic hyperactivity such as tachycardia, hypertension, sweating, and mydriasis.

- **Chronic pain** is usually regarded as pain lasting more than a few months. It may not be clearly associated with trauma or disease or may persist after the initial injury has healed; its localisation, character, and timing are more vague than with acute pain. Furthermore, as the autonomic nervous system adapts, the signs of autonomic hyperactivity associated with acute pain disappear. Some forms of pain regarded as being chronic may consist of intermittent attacks of pain followed by relatively long pain-free periods. Patients with chronic pain experience physical, psychological, social, and functional deterioration which contributes towards exacerbation of the pain.

Physiologically, pain may be divided into nociceptive pain and neuropathic pain.

- **Nociceptive pain** follows activation of nociceptors by noxious stimuli as described above but is not associated with injury to peripheral nerves or the CNS. It may be somatic or visceral, depending on which receptors or nerves are involved. *Somatic pain* is usually well localised and may be described as deeply located, sharp or dull, nagging, stabbing, throbbing, or pressure-like. *Visceral pain* is generally less localised and more diffuse than somatic pain and may be referred to remote areas of the body. Depending on the structure involved it is variously described as deeply located, aching, nagging, cramping, or pressing and may be accompanied by nausea and vomiting. Nociceptive pain usually responds to treatment with conventional analgesics.

- Pain resulting from damage or dysfunction of peripheral nerves/receptors or of the CNS is known as **neuropathic pain** (or neurogenic pain). The term covers *sympathetically maintained pain* including causalgia and reflex sympathetic dystrophy, and painful conditions such as postherpetic and trigeminal neuralgia, and diabetic neuropathy. Neuropathic pain associated with central nervous tissue, such as in central post-stroke pain (the thalamic syndrome) is referred to as *central pain*. The clinical signs of neuropathic pain can vary greatly. Some of the more common features include heightened pain sensitivity and sensations of superficial burning or stabbing (lancinating) pain. The pain may be associated with areas of sensory deficit or some form of autonomic instability. Neuropathic pain responds poorly to conventional analgesics and can be difficult to treat.

Early **treatment** of pain is important as unrelieved pain can have profound psychological effects on the patient, and acute pain that is poorly managed initially can degenerate into chronic pain, which may prove to be much more difficult to treat. It is important to assess and treat the mental and emotional aspects of the pain as well as its physical aspects. Although drug therapy is a mainstay of pain treatment (see below), physical methods such as physiotherapy (including massage and the application of heat and cold), surgery, and nervous system stimulation techniques such as acupuncture and transcutaneous electrical nerve stimulation (TENS) are also used.

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Choice of analgesic

Paracetamol and **NSAIDs** are the first choice analgesics for treating mild to moderate pain and are also used in moderate to severe pain to potentiate the effects of opioids. They are suitable for use in acute or chronic pain. Effective relief of acute pain can be achieved with oral NSAIDs and with paracetamol (particularly in combination with an opioid—see below). Dependence and tolerance are not a problem with non-opioid analgesics but they have a rather flat dose-response curve: as the dose is increased, the increase in pain relief may be quite small. Aspirin and other non-selective NSAIDs inhibit blood platelet function, adversely affect the gastrointestinal tract, and can precipitate hypersensitivity reactions including asthma. The risk of severe upper gastrointestinal adverse effects may be less with selective inhibitors of cyclo-oxygenase-2 (COX-2) such as the coxibs, but their use has been greatly restricted by concerns about serious cardiovascular effects. Paracetamol does not have the haematological or gastrointestinal adverse effects of aspirin but large doses can produce severe or sometimes fatal hepatotoxicity. Giving paracetamol with an NSAID improves analgesia.

For the treatment of moderate or moderate to severe opioid-sensitive pain **codeine** is the traditional choice; alternatives include **dihydrocodeine** and **tramadol**. They are often given with non-opioid analgesics. Combinations of codeine with paracetamol at full doses produce a small but significant increase in analgesia compared with paracetamol alone and are one of the most effective options for acute pain, but the incidence of adverse effects increases with repeated use. Combinations of **dextropropoxyphene** with paracetamol or aspirin are no more effective in acute pain than the non-opioid alone; efficacy in chronic pain is unclear and adverse effects may become troublesome. The combination preparation co-proxamol (dextropropoxyphene with paracetamol) has been gradually withdrawn from the UK market because of poorly established efficacy and the risk of toxicity in overdose.

More potent opioids such as **morphine** are mainly used in the treatment of severe acute non-malignant pain and cancer pain (see below). Their use in chronic non-malignant pain is somewhat controversial because of fears of psychological dependence and respiratory depression. However, in practice such problems rarely occur and those fears should not prevent patients being given effective analgesic therapy. Opioids may also be of value in neuropathic pain in some patients.

Morphine is the opioid of choice in severe pain. It is absorbed when given orally and has a short half-life so that the use of immediate-release oral preparations offers a flexible means of dosage titration in, for example, palliative care. Once initial pain relief has been achieved, administration of a modified-release preparation every 12 or 24 hours is more convenient for maintenance of analgesia in severe chronic pain. It may also be given parenterally (e.g. for control of acute severe pain in emergency departments or in patient-controlled analgesia—see also below), or rectally or transdermally, where there would be problems with the oral route.

Occasionally **other opioids** may be useful. Switching to an alternative opioid may be effective in patients who have inadequate pain control or intolerable adverse effects with morphine. Methadone (which also acts as an NMDA antagonist) or oxycodone have a longer duration of action than morphine, but it should be noted that methadone, which has a long half-life, should not be given more than twice daily when used long term because of the risk of progressive CNS depression and overdosage. A rapid onset of action is provided by alfentanil and fentanyl but use of pethidine is no longer recommended. Diamorphine or hydromorphone may be preferred to morphine when the parenteral route has to be used because they are more soluble and can be given in a smaller volume. Tramadol, which may impair respiratory and gastrointestinal function less than other opioids at equianalgesic doses, is also of benefit in neuropathic pain.

Adverse effects of opioids include sedation, nausea, vomiting, constipation, and, most seriously, respiratory depression. Tolerance generally develops to all of these effects except constipation, which may be prevented by regular use of laxatives.

A number of other groups of drugs have significant roles in pain management either alone or as **analgesic adjuvants**.

Subantidepressant doses of tricyclic **antidepressants** (usually amitriptyline) are considered to be useful in refractory chronic pain, including neuropathic pain of the burning, dysaesthetic type such as postherpetic neuralgia and diabetic neuropathy; shooting pain has also been reported to respond. They may be used in addition to conventional analgesics, notably in the treatment of cancer pain of mixed aetiology. There is little evidence for benefit in acute pain although musculoskeletal pain has sometimes responded. Amitriptyline has also been found to be useful for tension-type headache and for the prophylaxis of migraine. The role of other antidepressants in the treatment of neuropathic pain is less clear although venlafaxine may be useful.

Antiepileptics (often carbamazepine and, more recently, gabapentin and pregabalin) have been found useful in the relief of neuropathic pain, especially when there is a stabbing (lancinating) element, as in trigeminal neuralgia; there have also been reports of efficacy in the treatment of diabetic neuropathy and for migraine prophylaxis.

Benzodiazepines and **other muscle relaxants** such as baclofen or dantrolene are useful for relieving painful muscle spasm in acute or chronic conditions.

Bone modulating drugs such as calcitonin and bisphosphonates may be useful in cancer pain arising from bone metastases (see below) but have a slow onset of action and are second choice to NSAIDs. Bisphosphonates may cause an initial transient increase in bone pain.

Caffeine has been used with the aim of enhancing the effects of non-opioid and opioid analgesics but is of debatable benefit. There are similar doubts about whether caffeine enhances the effect of ergotamine in the treatment of migraine (see Pharmacokinetics, p.621); it may also add to gastrointestinal adverse effects and in large doses can itself cause headache.

Corticosteroids have produced improvement, often substantial, in neuropathic pain. They can also relieve headache caused by raised intracranial pressure and refractory pain caused by bone metastases, and have the added benefits of increasing well-being and appetite.

Some **inhalational anaesthetics** are used in subanaesthetic doses as inhalation analgesics for acute pain. In particular, nitrous oxide is given with oxygen for pain relief in obstetrics and during dental and other procedures, and in emergency management. Isoflurane, enflurane, and in some countries methoxyflurane or trichloroethylene have been used similarly.

Miscellaneous drugs. Following the discovery that epidural or intrathecal injection of opioids can produce effective analgesia many other drugs have been tried by these routes, either alone or with opioids or local anaesthetics, but their role, if any, in the management of pain remains to be determined. Some of these drugs, such as clonidine and ketamine, also appear to have analgesic properties when given by other routes, and ketamine may be useful in reducing opioid requirements. Some antiarrhythmics (including systemic lidocaine) may be effective in chronic neuropathic pain, but must be used with extreme caution. The use of antipsychotics, such as the phenothiazines, as adjuvant analgesics is controversial; levomepromazine is sometimes used as an adjunct in palliative care.

See below for discussions of the use of patient-controlled analgesia, and rubefacients and topical analgesics. Nerve blocks are discussed under Pain, on p.1852.

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Choice of analgesics in children

Pain has often been undertreated in infants and children because of fears of respiratory depression, cardiovascular collapse, depressed levels of consciousness, and addiction with potent opioid analgesics. Assessment of pain is also a problem in children of all ages[1-3] and it is not that long since it was widely believed that neonates were incapable of feeling pain.

Non-opioid analgesics are used in ***infants and children***, either alone for minor pain or as an adjunct to opioid analgesics in severe pain,[4,5] (they can reduce opioid requirements,[1,6] perhaps by up to 40%[5]). Paracetamol is frequently used but it lacks any anti-inflammatory effect. NSAIDs such as ibuprofen are useful for minor pain,[4,5,7] especially when associated with inflammation or trauma. The use of aspirin is greatly restricted by its association with Reye's syndrome.

The **opioids** are still the mainstay of analgesia for moderate to severe pain in paediatric patients, and morphine is the standard against which the others are compared. It is given intravenously for rapid relief of severe pain (for example after burns, fractures or other injuries), and is titrated to achieve a suitable analgesic dose.[4,5,7,8] Where intravenous access is not readily achievable, oral morphine may be given but its onset is slower and less predictable; some favour intranasal diamorphine as an alternative to intravenous morphine.[4] Continuous intravenous morphine infusion with or without initial loading doses has become popular for postoperative pain relief,[6,8] but titration of the infusion rate is necessary to achieve a balance between analgesia and respiratory depression (particular care is needed in neonates, see below). Subcutaneous infusions of morphine have also been used,[5] mostly for the relief of terminal cancer pain in children. Intramuscular injections are painful[7-10] and therefore probably only suitable for short-term use. Fentanyl has also been widely used for short-term analgesia in surgical procedures,[6-8,10,11] and other opioids such as buprenorphine, hydromorphone, oxycodone, and tramadol have been given.[5] Patient-controlled analgesia using morphine has been tried in children (see below).

Morphine has also been given to children by the epidural route;[8] experience with the intrathecal route is more limited. Other methods of opioid drug delivery of possible value in paediatric analgesia include transmucosal,[6,11] nasal,[4,7] and transdermal[6,9] dosage.

Cancer pain in children may be treated using the analgesic ladder scheme described under Cancer Pain (see below).

Inhaled **nitrous oxide** and oxygen mixtures may be useful for preliminary pain relief and short, painful procedures.[4,7,8,10]

Local anaesthetics are especially suitable for the management of acute pain in day-care situations. Single injections given by the epidural route are often used to provide analgesia during and after surgery. Continuous epidural infusions of local anaesthetics have also been used. However, simpler techniques such as wound infiltration or peripheral nerve blocks can also provide effective analgesia for some procedures and are free of the problems of lower limb weakness or urinary retention associated with caudal blocks.[5,7,8,10] Application of eutectic creams (see Surface Anaesthesia, p.1866) containing lidocaine with prilocaine to intact skin, to produce surface anaesthesia, may be sufficient for some minor painful procedures in children.[6-9,11]

Ketamine is used in outpatients for brief, painful procedures such as fracture reduction and to provide immobility for repair of facial lacerations in young children.[11,12] The emergence reactions that limit its use in adults are less common in children,[11] and can be ameliorated by benzodiazepines.[7,10]

Most ***neonates*** requiring analgesia and receiving respiratory support can be managed with an infusion of morphine but in neonates who are breathing spontaneously there is a substantial risk of respiratory depression. Morphine has been used in such neonates[8] but should be limited to those under intensive care, as for example after major surgery (see also Intensive Care, p.957). Fentanyl citrate[1] and codeine phosphate have also been used in neonates. **Sucrose** and other sweet tasting solutions have been shown to reduce physiologic and behavioural indicators of stress and pain in neonates undergoing painful procedures[9] although there had been some doubt expressed over whether this indicates effective analgesia.[13] The American Academy of Pediatrics has suggested that oral sucrose together with other non-pharmacological methods such as swaddling should be used for minor routine procedures; topical local anaesthetics may be used for more painful procedures such as venepuncture if time permits. Opioids should be the basis of postoperative analgesia after major surgery in the absence of regional anaesthesia; a rapidly acting opioid such as fentanyl is advocated, together with infiltration of the site with a local anaesthetic where time permits, for insertion of a chest drain.[14] Similar recommendations for painful procedures in neonates have been made by an international consensus group.[15]

The use of **analgesic adjuncts** (see Choice of Analgesic, above) has also been advocated in some children.[16]

1. American Academy of Pediatrics and Canadian Paediatric Society. Prevention and management of pain and stress in the neonate. *Pediatrics* 2000; **105:** 454–61. Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;105/2/454.pdf (accessed 23/06/08)