Contents

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

List of contributors

BOTHAINA B JERAGH ALHADDAD, BSc, MSc, PhD | Assistant Professor and Lecturer in Clinical Pharmacy, Department of Pharmaceutical Sciences, Public Authority for Applied Education and Training, Shwaikh, Kuwait

FATEMAH MOHAMMAD ALSALEH, BPharm, MSc, PhD | Assistant Professor, Department of Pharmacy Practice, Faculty of Pharmacy, Kuwait University, Kuwait

SOTIRIS ANTONIOU, MRPharmS, MSc, DipMgt | Independent prescriber; Consultant Pharmacist, Cardiovascular Medicine, Bart's Health NHS Trust, London, UK

ANA ARMSTRONG, BPharm, PgDipClinPharm | Lead Pharmacist, Medical Division, Surrey and Sussex Healthcare NHS Trust, UK

NELA RONČEVIĆ ASHTON, BSc, PgDip | Clinical Tutor, School of Pharmacy and Biomedical Sciences, University of Central Lancashire; Advanced Primary Care Pharmacist, Cumbria and Lancashire Clinical Support Unit, UK

ZOE ASLANPOUR, BPharm, PhD | Member of UKPHR, FRSPH, Head of Pharmacy and Public Health Practice, University of Hertfordshire; Consultant in Public Health, NHS Bedfordshire, UK

PAUL BAINS, DipClinPharm, MRPharmS | Independent prescriber; Senior Lead Pharmacist for Medicine, Imperial College Healthcare NHS Trust, Pharmacy Department, Hammersmith Hospital, London, UK

JOANNE BARTLETT, BPharm, ClinDipPharm | Specialist Clinical Pharmacist, End of Life Care, John Taylor Hospice, Birmingham, UK

GORDON BECKET, BPharm, PhD, MRPharmS, MRSC, FNZCP | Professor of Pharmacy Practice, School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, Lancashire, UK

SIÂN BENTLEY, BPharm, MRPharmS, DipClinPharm | Specialist Pharmacist, Paediatrics, Royal Brompton and Harefield NHS Foundation Trust, London, UK

RANIA BETMOUNI, BPharm, DipClinPharm | Independent prescriber; MSc Quality and Safety in Healthcare, Clinical Pharmacist – BUPA Cromwell Hospital, London, UK

ANNETT BLOCHBERGER, DipClinPharm | Independent prescriber; Lead Pharmacist, Neurosciences, St George's NHS Healthcare Trust, London, UK

LISA BOATENG, BSc, MSc, MRPharmS, Certificate in Clinical Pharmacy | Independent prescriber; Highly Specialised Pharmacist, Antimicrobials and Infection Control, London, UK

MARK BORTHWICK, MPharmS, MSc | Consultant Pharmacist, Critical Care, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford, UK

SIMONE BRACKENBOROUGH, BSc, DipClinPharm | Independent prescriber; Senior Lead Pharmacist for Medicine at Imperial College Hospitals NHS Trust (St Mary's Hospital Site), London, UK

NADIA BUKHARI, BPharm, MRPharmS, PgDipFHEA | Clinical Lecturer, MPharm Student Support Manager & Pre Registration Coordinator, UCL School of Pharmacy, London, UK

MEE-ONN CHAI, MSc, DipClinPharm, BPharm | Clinical Pharmacist, Team Leader – Renal Services, King's College Hospital NHS Foundation, London, UK

BARBARA CLARK, MPharm(Hons), GPhC, ClinDip | Lead Clinical Pharmacist, London Bridge Hospital; Chair UKCPA Haemostasis, Anticoagulation and Thrombosis (HAT) Group, London, UK

JESSICA CLEMENTS, MPharm, CertPharm Pract, DipPharmPract, Cert Independent prescribing practice | Highly Specialised Pharmacist HIV at Medway Maritime Hospital, Gillingham, Kent, UK

LOUISE COGAN, BSc, MRPharmS, PgDipFHEA | Teacher Practitioner, University of Central Lancashire, Preston, Lancashire, UK

ANDREW CONSTANTI, BSc, PhD, FBPharmacolS | Reader in Pharmacology, UCL School of Pharmacy, London, UK

SHANI CORB, MRPharmS, MSc | Independent prescriber; Lead Pharmacist, Paediatric Oncology, Royal Alexandra Children's Hospital, BSUH NHS Trust, Brighton, Sussex, UK

JOYETA DAS, MPharm, DipClinPharm | Independent prescriber; Lead Pharmacist, Hepatology, Imperial College London NHS Trust, London, UK

HALA M FADDA, MPharm, PhD | Assistant Professor, College of Pharmacy and Health Sciences, Butler University, Indianapolis, IN, USA

JOSEPHINE FOLASADE FALADE, BPharm, MSc, FHEA | Highly Specialist Pharmacist, Bart's Health NHS Trust; Clinical Lecturer, UCL School of Pharmacy, London, UK

SALLY-ANNE FRANCIS, BPharm, PhD, MRPharmS, FHEA | Honorary Senior Lecturer, UCL School of Pharmacy, London, UK

CLAIRE GOLIGHTLY, MPharm ClinDipHosp, PGCertEd | Lecturer in Professional Practice, Bradford School of Pharmacy, University of Bradford, Bradford, UK

LARRY GOODYER, PhD, MRPharmS, FFTMRCPS(Glas), FRGS | Professor, Head of the Leicester School of Pharmacy, Faculty of Health and Life Sciences, De Montfort University, Leicester, UK

NICOLA J GRAY, BSc, PhD, MRPharmS, FHEA, FSAHM(US) | Independent pharmacist researcher; Director, Green Line Consulting Limited, Manchester, UK

KATIE GREENWOOD, MRPharmS, PGCertTLHE, FHEA | Lecturer in Pharmacy Practice, Placement Co-ordinator and Pre-Registration Facilitator, School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, Lancashire, UK

ELIZABETH HACKETT, BSc, MSc | Independent prescriber; Principal Pharmacist for Diabetes, University Hospitals Leicester, Leicester, UK

DELYTH HIGMAN JAMES, PhD, MSc, BPharm, MRPharmS, AMBPsS, FHEA | Senior Lecturer, Programme Director, MSc in Pharmacy Clinical Practice (Community and Primary Care), Cardiff, South Wales, UK

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

TIM HILLS, MRPharmS, DipClin | Independent prescriber; Lead Pharmacist Antimicrobials and Infection Control, Nottingham University Hospitals NHS Trust, Nottingham, UK

STEPHEN HUGHES, MPharm | Specialist Renal Pharmacist, Central Manchester Foundation Trust, Manchester, UK

LYNN HUMPHREY, BPharm, DipPharmPrac, IPP | Senior Lead Pharmacist – Cardiovascular, Imperial College Healthcare NHS Trust, London, UK

ANDY HUSBAND, DProf, MSc, BPharm, MRPharmS | Dean of Pharmacy, Durham University, Durham, UK

MATTHEW D JONES, MPharm, PhD, MRPharmS | Senior Pharmacist – Medicines Information, Royal United Hospital Bath NHS Trust, Bath, UK

SARAH C JONES, MPharm, MSc, MRPharmS | Locality Lead Pharmacist, Avon and Wiltshire Mental Health Partnership NHS Trust, Bath, UK

NAVEED IQBAL, MPharm, PGClinDip, MSc | Teaching Fellow, Aston University; Prescribing Support Pharmacist for NHS, Birmingham Cross City CCG; community pharmacist

KUMUD KANTILAL, BSc(Pharm), DipPharmPract, Postgraduate award in clinical oncology | Macmillan Principal Pharmacist, Lead for Cancer Education and Training, Guy's and St Thomas' NHS Foundation Trust, London, UK

NAZANIN KHORSHIDI, MPharm, PGDip | Highly Specialist Pharmacist; Orthopaedics and Plastics at Guy's and St Thomas' NHS Foundation Trust, London, UK

STEPHANIE KIRSCHKE, PhD | Senior Lead Pharmacist Haematology, Imperial College Healthcare NHS Trust, London, UK

ROGER DAVID KNAGGS, BSc, BMedSci, PhD, MRPharmS | Associate Professor in Clinical Pharmacy Practice, University of Nottingham; Advanced Pharmacy Practitioner – Pain Management, Nottingham University Hospitals NHS Trust, Nottingham, UK

SARAH KNIGHTON, MPharm, MPharmS | Independent prescriber; Clinical Pharmacy Team Leader, Liver and Private Patient Services, King's College Hospital NHS Foundation Trust, London, UK

ROMAN LANDOWSKI, BSc(Pharm), DipClinPharm | Ward Pharmacist, Maternity Care Unit, University College Hospital, London, UK

JEREMY LEVY, MBBChir, PhD, FHEA, FRCP | Consultant Nephrologist, Imperial College Healthcare NHS Trust, London, UK

NATALIE LEWIS, MPharm, ClinDipPharm, PGCertEd | Senior Pharmacist – Teacher Practitioner, Aston University and University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

TRACY LYONS, BSc(Pharm), MSc | Lead Pharmacist, Infection, Imperial College Healthcare NHS Trust, London, UK

FIONA MACLEAN, MSc, MRPharmS | Independent prescriber; Lead Clinical Pharmacist, Cancer and Neurosciences, NHS Greater Glasgow and Clyde, Glasgow, UK

JANET E MCDONAGH, MB BS, MD, FRCP | Clinical Senior Lecturer in Paediatric and Adolescent Rheumatology, University of Birmingham and Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK

DUNCAN MCROBBIE, MSc, FRPharmS | Associate Chief Pharmacist, Guy's and St Thomas' NHS Hospital Trust; Clinical Reader, Kings College London, London, UK; Visiting Professor, UCL, UK

CARL MARTIN, PhD, GPhC registrant, MRPharmS, PGCHE | Senior Clinical Teacher, Department of Practice and Policy, UCL School of Pharmacy, London, UK

JAYMI MISTRY, MPharm, DipGPP | Highly Specialist Pharmacist – Acute Medicine (general medicine) and Medicines Safety, London, UK

SANDEEP SINGH NIJJER, MPharm, MBA, GPhC | Pharmacist, UK

LELLY OBOH, BPharm, DipClinPharm | Independent prescriber; Consultant Pharmacist, Care of Older People, Guy's and St Thomas' Community Health Services, London, UK

JIGNESH PATEL, PhD, MRPharmS | Clinical Senior Lecturer/ Honorary Consultant Pharmacist, Anticoagulation, King's College London/King's College Hospital, London, UK

NEIL POWELL, MPharm, ClinDip, MRPharmS | Antibiotic and HIV Pharmacist, Royal Cornwall Hospital Trust, Truro, UK

ANNA PRYOR, MPharm, MRPharmS | Lead Pharmacist, A&E and Admissions, Imperial College Healthcare NHS Trust (St Mary's site), London, UK

GEMMA QUINN, PGDip, MRPharmS | Course Director MSc Clinical Pharmacy (Hospital) and MPharm Stage Tutor (Stage 4), University of Bradford, Bradford, UK

TIMOTHY RENNIE, MPharm, PhD | Head of School of Pharmacy (Associate Dean), University of Namibia, Namibia, Africa

IAN ROWLANDS, MRPharmS, DipClinPharm | Independent prescriber; Lead Pharmacist Stroke Services, Imperial College Healthcare NHS Trust, London, UK

IMOGEN SAVAGE, BPharm, PhD, MRPharmS | Senior Lecturer (retired), UCL School of Pharmacy, London, UK

JENNY SCOTT, BSc, PhD, MRPharmS | Independent prescriber; Senior Lecturer in Pharmacy Practice, University of Bath, Bath, UK

LOUISE SEAGER, BPharm, ClinDipPharm, MRPharmS | Senior Specialist Clinical Pharmacist End of Life Care, John Taylor Hospice, Birmingham, UK

RITA SHAH, BPharm, MRPharmS, MSc | Senior Clinical Pharmacist, Critical Care, King's College Hospital NHS Foundation Trust, London, UK

KATE SHARDLOW, MBBS, BPharm, MRCGP | GP and speciality doctor in genitourinary medicine, Chelmsford, Essex, UK

NEELAM SHARMA, BA, PGCert Psychiatric Therapeutics | Registered Pharmacy Technician, Chief Pharmacy Technician, Medicines Management and E&T, South London and Maudsley NHS Foundation Trust, London, UK

ROB SHULMAN, BScPharm, MRPharmS, DipClinPharm, DHC (Pharm) | Lead Pharmacist – Critical Care, Pharmacy Department, University College Hospital; Honorary Associate Professor in Clinical Pharmacy Practice, UCL School of Pharmacy; Honorary Lecturer, Department of Medicine, University College London, London, UK

MERVYN SINGER, MBBS MD MRCP | Professor of Intensive Care Medicine; Head, Research Department of Clinical Physiology, Division of Medicine, University College London, UK

TIMOTHY J SNAPE, PhD MSci MRSC, CChemCSci | Lecturer in Medicinal Chemistry, University of Central Lancashire, Preston, Lancashire, UK

NUTTAN KANTILAL TANNA, MRPharmS, DComP, PhD | Pharmacist Consultant, Women's Health and Older People, Women's Services and affiliated with the Arthritis Centre, NW London Hospitals NHS Trust, London, UK

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

NEIL TICKNER, MPharm, MRPharmS, PGDipClinPharm | Lead Pharmacist Paediatrics, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK

ADAM TODD, MPharm, PhD, MPharmS, MRSC | Lecturer in Pharmacy Practice, Division of Pharmacy, Durham University, Durham, UK

MARK TOMLIN, PhD, FRPharmS | Independent prescriber; Consultant Pharmacist Critical Care, Southampton General Hospital, Southampton, UK

STEPHEN TOMLIN, BPharm, FRPharmS | Consultant Pharmacist – Children's Services, London, UK

CHARLES TUGWELL, BPharm, MSc, MRPharmS, MCLIP | Specialist Clinical Pharmacist, Neurology/Neurosurgery, Royal London Hospital, Bart's Health NHS Trust, London, UK

SINEAD TYNAN, MPharm, IP, ClinDip, MSc, MRPharmS | Senior Clinical Pharmacist – Liver Services, King's College Hospital, London, UK

SAMIR VOHRA, BPharm | Lecturer in Clinical Pharmacy Practice, School of Pharmacy and Biomedical Science, University of Central Lancashire, Preston, Lancashire, UK

PETER S WHITTON, BSc, MSc, PhD | Senior Lecturer in Pharmacology, UCL School of Pharmacy, London, UK

HELEN WILLIAMS, BPharm, PGDip(Cardiol), MRPharmS | Independent prescriber; Consultant Pharmacist for Cardiovascular Disease, South London, hosted by Southwark CCG, London, UK

ELIZABETH M WILLIAMSON, BSc, PhD, MRPharmS, PhD, FLS | Professor of Pharmacy and Director of Practice, University of Reading School of Pharmacy, Reading, UK

KEITH A WILSON, BSc, PhD | Professor, Aston University, Birmingham, UK

STEWART WILSON, BPharm, ClinDipPharm | Lead Pharmacist Cardiology, Imperial College NHS Healthcare Trust, London, UK

KAY WOOD, BSc, DipClinPharm, PhD, MRPharmS, PGPCTL | Senior Lecturer in Clinical Pharmacy, Birmingham, UK

KIRSTY WORRALL, BSc, MRPharmS | Teacher Practitioner working with Boots and UCL School of Pharmacy, London, UK

PAUL WRIGHT, MRPharmS, MSc | Specialist Cardiac Pharmacist, Bart's Health NHS Trust, London, UK

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

Introduction

An integrated approach to learning

Within the healthcare team, pharmacists are the recognised medicines experts. They have a breadth and depth of understanding about all aspects of medicines that set them apart from other health professionals. As a result of their extensive, specialist education and training, pharmacists can conceptualise a drug molecule, together with its formulation and delivery, as a medicine, and can ensure its safe and effective use by patients. Pharmacists also have a deep understanding of pharmacology and therapeutics, the physicochemical properties of drugs and excipients, biopharmacy and pharmacokinetics, side effects, contraindications and drug interactions. This is combined with knowledge of the legal and ethical framework in which medicines are supplied, as well as biological causes of disease, and the social and behavioural factors that determine whether a patient will obtain optimal benefit from their medication. This hugely varied, complex, integrated, expert knowledge allows pharmacists to make professional judgements relating to medicines, giving them an unchallengeable sphere of expertise, which, when utilised for patient benefit, legitimises pharmacists' professional status.

To be effective, pharmacists' education must prepare them to be scholars, scientists, practitioners and professionals – no mean feat. A modern undergraduate Masters pharmacy curriculum recognises the importance of both pharmaceutical science and pharmacy practice, which, when seamlessly integrated, prepares graduates for the many professional roles and activities that they will be called upon to undertake now and in the future. Nowadays, pharmacy programmes aim to achieve this integration during a student's studies, increasingly incorporating opportunities for workplace learning to provide a context in which they learn and apply their scientific knowledge.

In the UK, the General Pharmaceutical Council (GPhC) regulates the education and training of pharmacists. The GPhC is responsible for accrediting pharmacy degrees and ensuring that they are fit for purpose. It has published a document containing a comprehensive set of standards and outcomes against which programmes are accredited and reaccredited (GPhC, 2011). This document highlights: 'Curricula must be integrated … the component parts of education and training must be linked in a coherent way' and 'Learning opportunities must be structured to provide an integrated experience of relevant science and pharmacy practice'.

The conception and design of this book

Integration of science with practice, together with its practical application, is at the core of modern pharmacy programmes. The need for pharmacy students to integrate their learning has been a guiding principle in the design and production of this book. True integration of all the elements that contribute to pharmacists' knowledge is difficult. This text aims to present the fundamental aspects of pharmaceutical chemistry, pharmacology, pharmaceutics and therapeutics within a patient-care context. Traditional attempts at integration commonly begin with sections of 'underpinning' science, and then build clinical and professional elements onto it. This approach can be superficial and undermines the credibility of any resultant learning exercise. By contrast, in this text, with the help of many experienced practitioner colleagues, each case study is grounded in a real-life clinical setting, which has then been used as a starting point to illustrate how pharmacists' practice and decision-making are informed by pharmaceutical science.

Thus, the case studies in this book were initially written by pharmacist practitioners, based on their own practice and experience, with additional science content being incorporated later through collaboration with the editorial team. In this way, the science concepts included have a direct relevance to contemporary practice. In particular the science is included in the case because it helps inform understanding and decision-making in real-life practice settings: it has earned the right to be there!

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

The cases have been organised into sections, broadly based on the *British National Formulary*, the most widely used reference source in pharmacy, where the chapters relate to particular systems of the body (e.g. the cardiovascular system) or to aspects of medical care (e.g. infections). Although this has allowed us to impose some structure, our cases are very diverse and reflect the fact that real patients experience multiple pathologies. They include material relevant to the wider clinical picture.

We have striven to include cases covering the broadest range of clinical conditions, from both community and hospital practice. All the case studies have a similar structure. Within each case we have integrated a significant science component from one or more of pharmaceutical chemistry, pharmacology or pharmaceutics, and in many cases all three. We have included what we believe are the key science concepts. However, it would be impossible to cover in a single set of case studies all the pharmaceutical, clinical and behavioural science that appears in an undergraduate pharmacy programme. The goal here is to demonstrate the potential diversity of clinical scenarios and the relevance of science across all.

Most cases describe the use of many drugs in a particular clinical setting. Again it has not been possible to detail the chemistry, pharmacology, indications, posology, contraindications, side effects and formulations for every drug. However, these case studies can be used as a starting point to expand learning and application of knowledge across the science and practice disciplines. Each case ends with references/further reading and extended learning points, designed to take the reader's learning beyond the specific case; highlighting other relevant, tangential areas of science and practice.

How to use this book

This book has been designed primarily for use by undergraduate pharmacy students and pre-registration trainees. However, it may also be useful for qualified pharmacists, pharmacy technicians and other health professionals. It will also provide a resource for tutors and lecturers to plan and use in learning activities.

We intend this book to be free standing: a learning and teaching aid to promote integration and contextualisation of material learned during undergraduate studies. It is not a textbook. There are plenty of excellent textbooks that will provide a detailed understanding of the subjects that are introduced here. The case studies provided are of varying complexity, independent of each other and not intended to be read sequentially.

Each case begins with a set of **Learning outcomes** which provides an overview of what is contained in the case study and highlights what the reader should be able to do having studied the case.

Each, detailed **Case study** begins with contextual information about a patient, including the medical and drug histories. This equates to the level of information likely to be available to a pharmacist on consulting medical notes, or talking with other members of the healthcare team or to the patient and/or their carer. The cases are interspersed with, and followed by, a series of questions. These are the sort of questions that pharmacists will ask themselves when encountering such a case in practice, or questions that might be asked of pharmacists by patients or other health professionals. We recommend that readers consider each question based initially on their current knowledge, before accessing additional sources such as the current *British National Formulary*, lecture notes, NICE guidance, websites and textbooks. At times, supplementary information may be revealed as the case progresses, which may take readers in a different direction or cause them to reflect and re-evaluate their previous responses and recommendations.

The cases and questions are followed by a section entitled **Case discussion**. We have chosen not to supply discrete answers for each question. Such an approach gives the impression that a definite answer is possible; that all questions have right and wrong answers. Professional practice demonstrates that real-life issues cannot be considered in such a black-and-white manner, and what demarcates the professional is their appreciation and acceptance of uncertainty and their ability to make judgements based on the available evidence. 'Answers' to the questions can be found in this section, but there is much more besides, because the case is considered in its clinical, practice and science context. Having read this section, refer back to the questions posed in the case, consider how you might answer them in light of this information, and think of what additional questions you might now ask and what

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

further information you would like. This is the spur to **References and further reading**. We have also provided some **Extended learning** questions, representing our own thoughts for how this case might encourage useful further study. Hopefully, you will also have formulated your own questions. Finally, although all the cases are 'practice' focused, in some instances we have included **Additional practice points**, highlighting supplementary practice issues that may be tangentially linked to the substance of the case study, or alluding to pertinent debates and concerns within pharmacy.

The cases have been written by practitioners with academic input, representing current clinical and scientific knowledge, and are informed by the experience, expertise and opinions of the authors. They should not be taken as a template for professional practice. Readers are reminded that knowledge, pharmacotherapy and treatment guidelines are continually changing and that pharmacists are called on to make judgements based on their own knowledge and experience. Be prepared, at times, to disagree with what you read!

Conventions used in the text

With the widely different backgrounds of the contributing authors, there were inevitably differences in terminologies, units of measurement, etc., between cases. Also clinical and science conventions often diverge. Thus, in this text we express drug doses as mg, micrograms (written in full), etc., as is accepted in clinical practice (to minimise the risk of prescribing errors), but follow scientific conventions for clinical data and other measurements, e.g. we have used μg throughout (rather than microgram or mcg) to express 10^{-6} grams.

Most cases include medicines that are currently being used or are to be used by a patient. Note that all doses are for the oral route (p.o.), unless otherwise stated; dosing instructions are indicated as standard Latin abbreviations, e.g. t.d.s. We have ensured that the names of the medicines referred to in the case studies are as found in the most current version of the *British National Formulary* (*BNF* 68, September 2014) at the time of writing. Occasionally, the proprietary name of a product has also been included, where this is appropriate to the context of the case.

The editorial team and the case study authors

The authors of the cases were chosen because of their experience as practising pharmacists, their unique knowledge of a particular area of practice or therapeutics, and their ability to communicate to early years pharmacists. The large majority of the authors currently practise as pharmacists in the community and hospitals, and the cases reflect that contemporary practice. Their enormous, learned contributions to this text are testament to the vast expertise that UK clinical pharmacists now possess and use daily for patient benefit.

The editorial team, all with pharmacy degrees, has extensive experience in teaching undergraduate and postgraduate pharmacists, as well as pharmacy technicians. Between them, they conduct research and teach in the core disciplines of pharmacy, namely pharmacy practice, pharmaceutics, chemistry and pharmacology. They have worked together building up the case studies supplied by the authors to ensure that each case integrates current science and practice, is coherent, and provides a tool for effective learning.

The authors and editors have worked together with the shared belief that this is a valuable and worthwhile project. The collaboration has led to an innovative learning resource, which has drawn on the collective knowledge and experience of a very diverse group.

This collection of case studies has been a great pleasure to produce. In the process, we have realised the enormous range of subjects of which pharmacists require a deep knowledge and understanding, in order to make their unique contribution to healthcare. We hope that readers will derive the same enjoyment, and that this book clearly illustrates how the various disciplines that comprise pharmacy can complement, support and inform each other, such that pharmacists truly are medicines experts.

Reference

General Pharmaceutical Council. *Future Pharmacists: Standards for the initial education and training of pharmacists.* London: GPhC, 2011.

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

3
Respiratory cases

INTRODUCTION

This section contains five cases centred on patients with respiratory diseases, namely: asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis and cough.

Case 1
Asthma ► 89

This case is based on a patient with asthma who is receiving regular treatment with a salbutamol pressurised metered-dose inhaler (pMDI). The pathophysiology, signs and symptoms of asthma are outlined, then the treatment options in asthma are described, particularly in relation to stepping up and stepping down therapy. The mainstays of asthma therapy are inhaled β_2-adrenoreceptor agonists and glucocorticoids, and the chemistry of these agents is briefly outlined. The most frequently prescribed inhalation devices, pMDIs, are described and their formulation considered. To enhance the efficiency of drug delivery in the airways, and ease of use by patients who experience difficulties with pMDIs, they may be used with spacer devices. Alternatively dry powder inhalers may be prescribed as a means of delivering drugs to the lungs. The formulation and use of these devices are outlined. Ultimately, as the case illustrates, the benefit that patients receive from prescribed medicines will depend on their adherence to the prescribed regimen and the ability to use their inhalation device correctly.

Case 2
Treating an acute severe asthma exacerbation ► 93

This case continues the theme of asthma, with an acute exacerbation as the focus. It considers the pathophysiology and classifications of acute asthma, and the signs and symptoms of acute asthma exacerbations. Common triggers of an exacerbation, such as medicines, allergens, exercise, non-compliance and infection, are identified. The chemistry and delivery of beclometasone dipropionate are considered, before the various treatment options in asthma exacerbations, such as high-flow oxygen, nebulised β_2-adrenergic receptor agonists, oral steroids and nebulised ipratropium bromide, are outlined. The pharmaceutical monitoring, follow-up and treatment are described. The case also allows for a comparison of the key features of various types of inhalation device (pMDIs, dry powder inhalers, nebulisers) and emphasises the need for patient counselling in the use of these devices.

Case 3
Nebulised therapy for chronic obstructive pulmonary disease ► 97

This case describes an elderly ex-smoker, previously diagnosed with, and treated for, COPD, requiring hospitalisation for an exacerbation. The pathophysiology, symptoms, signs and diagnosis of COPD are outlined, followed by the treatment options, particularly in relation to exacerbations. The chemistry and pharmacology of long- and short-acting β_2-adrenergic receptor agonists, particularly salbutamol and salmeterol, are described, and related to their clinical use and adverse effects. The place of nebuliser therapy in COPD is described, together with the operating principles and designs of commercially available nebulisers (air-jet, ultrasonic and mesh). Practical considerations relating to patients' use and maintenance of nebulisers are considered.

Case 4
Paediatric cystic fibrosis ► 101

This case describes the treatment of allergic bronchopulmonary aspergillosis (ABPA) in a child with cystic fibrosis (CF). The aetiology of CF and the role of different medications routinely

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

prescribed for a patient with CF are outlined. The chemistry and mode of action of the proton pump inhibitor (PPI), omeprazole, used to treat gastro-oesophageal reflux, frequently presenting in CF patients, are described. Itraconazole is used to treat patients with ABPA. The formulation strategies to enhance this water-insoluble drug's bioavailability are outlined. The clinical use and delivery of nebulised antibiotics and dornase alfa (DNase), an enzyme that cleaves extracellular DNA in the sputum, aiding its removal, are described. The case ends with a discussion of the use of shared-care protocols to ensure consistency of care across the primary care–secondary care interface, and consideration of medicines management in the home, which can be a complex task for this patient group.

Case 5
Cough ▸ 108

This case describes the treatment of cough in a young person, which is, possibly, smoking related. The case starts by considering the pathophysiology, signs, symptoms and diagnosis of different types of cough and the appropriate treatment. The use of mnemonics such as WWHAM is outlined, to ensure effective questioning of a patient when determining a diagnosis. The chemistry and mechanism of action of expectorants and opiate antitussives, widely used to treat coughs, are considered. Symptoms indicating that a patient with a cough should be referred to another healthcare professional are described. The opportunity for a pharmacist to offer lifestyle advice, particularly in relation to smoking cessation, is highlighted.

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

Case 1
Asthma

GEMMA QUINN

LEARNING OUTCOMES

At the end of this case, you will be able to:

- Outline the pathophysiology, and signs and symptoms of asthma
- Describe the treatment options in asthma, particularly in relation to stepping up and stepping down therapy
- Outline the chemistry of glucocorticoids and β_2-adrenoreceptor agonists used in the treatment of asthma
- Outline the formulation of pressurised metered-dose inhalers
- Describe the use of spacers with pressurised metered-dose inhalers
- Outline the formulation of dry powder inhalers
- Consider the issues that may affect adherence in asthma, and make appropriate treatment recommendations to improve this

Case study

Miss GN is a 19-year-old young woman who is currently studying for a degree in English at the local university. She was diagnosed with asthma when she was 7 years old and her regular prescription is for salbutamol pMDI 200 micrograms when required.

- What is asthma?
- What are the most common signs and symptoms of asthma?
- How is a diagnosis made?
- What non-pharmacological treatment options are available?
- What is the first-line pharmacological treatment in asthma?

Miss GN came to the pharmacy to collect her third prescription for a salbutamol pMDI in 4 weeks. The pharmacist asked to speak to her and discovered that she was currently using her inhaler five to six times a day. Miss GN was referred to her GP and returned a few days later with a prescription for beclometasone (Clenil) 200 micrograms twice daily, via a spacer.

- When is it appropriate to start treatment with inhaled corticosteroids?
- What is a pMDI and what are the benefits of using a spacer?

Miss GN continued to collect her prescriptions for salbutamol and beclometasone, but after a few months she complained that she was still using her salbutamol up to four times a week and was waking at night. She also found it difficult to carry the spacer and two inhalers around with her, meaning that she sometimes missed doses. The pharmacist suggested seeing her GP again for a review. Miss GN subsequently presented with a prescription for budesonide/formoterol (Symbicort 100/6 Turbohaler), two puffs twice daily and one puff when required (SMART regimen: single inhaler maintenance and reliever therapy).

- What sort of inhalation device is a Turbohaler, and how does it differ from a pMDI?
- Draw the structures of budesonide and formoterol. How are they related to other steroids and β_2-adrenergic receptor agonists used in asthma?
- What issues may affect adherence with asthma treatments, particularly in Miss GN's case?
- What is the SMART regimen and when is it recommended?

Miss GN asks you whether she might be able to reduce her inhalers in the future.

- When should inhaler therapy be stepped down?

Case discussion

— Asthma and its pathophysiology

Asthma is one of the most common respiratory diseases in the UK, with about a fifth of children (21%) and 15% of adults affected. It is characterised by 'reversible' obstruction of the airways, caused by a combination of bronchial hyper-responsiveness, inflammatory changes in the airways, and increased numbers of eosinophils and activated T cells. It is usually an allergic condition, with common triggers including pollen, dust,

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

animal dander, respiratory infections, medicines (e.g. β-blockers and non-steroidal anti-inflammatory drugs [NSAIDs]), cold air, strong emotions and exercise.

— Signs and symptoms of asthma

Symptoms characteristic of asthma include wheeze, breathlessness, chest tightness and cough. Symptoms usually occur in response to a trigger and are often worse at night and early in the morning. There is also frequently a family history of asthma or atopic (hyperallergic) disorders.

There is no agreed definition of asthma, so a diagnosis is made based on the pattern of signs and symptoms, where there is no probable alternative diagnosis. Spirometry is the preferred method of demonstrating fluctuating airflow obstruction in asthma, although a normal spirogram does not exclude a diagnosis of asthma.

— Pharmacological and non-pharmacological treatment options for asthma

Many patients can identify triggers for their asthma and, where possible, these should be avoided, particularly where they include dust mites and passive smoking. Where dust mites are felt to be a trigger, patients can try methods such as mattress barrier systems and high temperature washing of bed linen. However, this can be expensive and is not of proven benefit.

Management of asthma is mainly pharmacological, with the aim of achieving 'complete control'. This can be defined as:

- No daytime symptoms
- No night-time awakening due to asthma
- No need for rescue medication (β_2-agonist)
- No exacerbations
- No limitations on activity, including exercise
- Normal lung function (FEV_1 and/or PEF >80% of predicted or best)
- Minimal side effects of medication.

Mild asthma may be managed with a β_2-adrenoreceptor agonist taken only when required. The British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines do not recommend one drug over any other, but in practice salbutamol is the usual choice.

— Stepping up treatment: initiating inhaled corticosteroids

Patients should be considered for inhaled corticosteroids if they are symptomatic and/or need to use their β_2 agonist three times a week or more, if their symptoms wake them at least once a week or if they have had an exacerbation in the last 2 years. The use of two or more canisters of β_2 agonist a month, or 10–12 puffs per day, indicates that patients are poorly controlled and at risk of fatal or near-fatal asthma.

Adults are usually started on the equivalent of 200 micrograms beclometasone twice daily, whereas 100 micrograms twice daily is usually prescribed for children. It is important to note that different formulations of beclometasone are not bioequivalent; some pMDI products are solution formulations in hydrofluoroalkane (HFA) propellants and others are suspension formulations producing different drug deposition profiles within the lung. Consequently, preparations should always be prescribed by brand proprietary name.

— Chemical properties of glucocorticoids and β_2-adrenoreceptor agonists

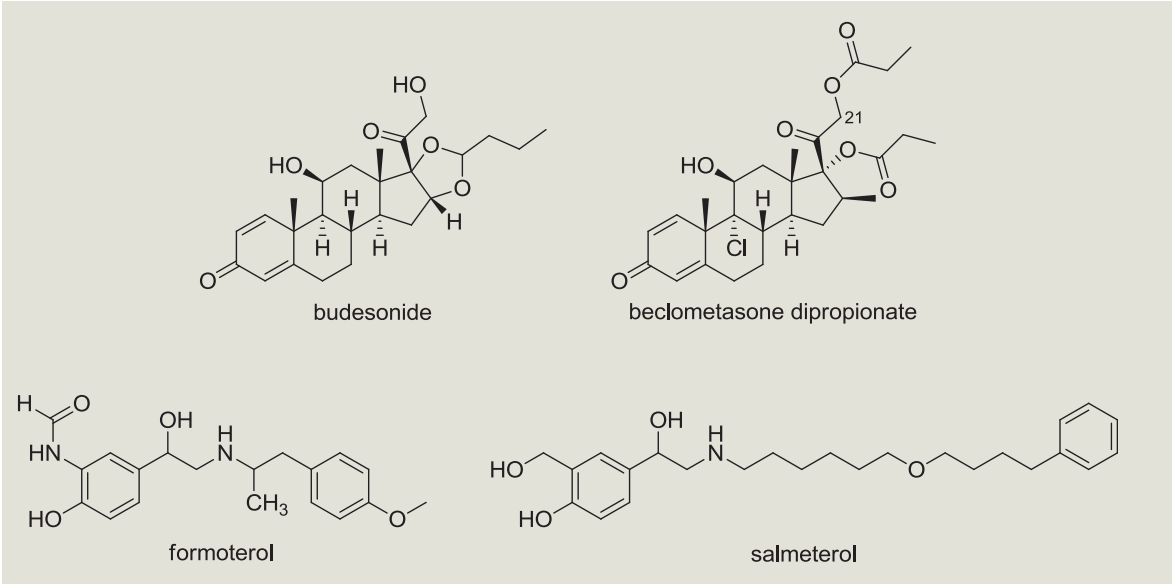
Budesonide is a glucocorticoid that is closely related to beclometasone dipropionate, and both drugs have essentially the same steroid skeleton. The principal difference is that beclometasone is prepared as the dipropionate ester, whereas budesonide contains an acetal group. Beclometasone dipropionate is a prodrug: the less-hindered ester (at carbon-21) is hydrolysed to give the more active monopropionate metabolite. Budesonide already has a free primary hydroxyl at carbon-21 so is not a prodrug.

Formoterol is structurally similar to other long-acting β_2-adrenoreceptor agonists such as salmeterol. Formoterol has an extended lipophilic substituent on the secondary amine nitrogen. This results in a greater affinity for, and longer residence time, on the β_2-receptor, thereby prolonging its duration of action. Only the (*R*,*R*) stereoisomer of formoterol is biologically active.

— Pressurised metered-dose inhalers

The pMDIs comprise an aluminium container/canister containing a liquefied aerosol propellant (HFA 134a or 227). The drug is either dissolved or dispersed as micronised particles (usually 2–5 μm) in the propellant liquid within the canister. Evaporation of propellant within the headspace of the canister provides a pressure (the saturation vapour pressure of the propellant gas), which expels liquid from the canister, via a metering valve; this sits in a plastic actuator. Excipients in

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015



the formulation may include a surfactant, such as sorbitan ester, lecithin or oleic acid, which acts as a suspending agent in suspension formulations, and ethanol as a co-solvent to aid in the dissolution of drug or surfactant.

— Use of spacers

Many patients find using a pMDI very difficult and use it incorrectly. One study found that only 23–43% of patients can use a pMDI correctly; this figure was 55–57% for patients using a pMDI with a spacer.

Spacers are plastic devices used by some patients together with a pMDI. They reduce the velocity of the aerosol emitted from the pMDI, remove large droplets by impaction with the spacer walls, provide time and space for propellant to evaporate from droplets, allowing a fine aerosol to be produced, and remove the need for patients to inhale at the same time as actuating the pMDI.

The use of a β_2-adrenoreceptor agonist with a spacer in mild and moderate exacerbations has been shown to be as effective as treatment with a nebuliser, making a spacer a vital part of an asthma personal management plan. It is important to note that spacers should be cleaned monthly and changed at least every 6–12 months.

The use of a spacer with inhaled corticosteroids may also reduce the risk of oral candidiasis. Rinsing the mouth with water or brushing the teeth after inhaling the dose are also sometimes tried, but there is little evidence to confirm the effectiveness of any of these interventions.

— Dry powder inhalers

The Symbicort Turbohaler is a dry powder inhaler (DPI) from which drug is inhaled as a cloud of fine particles. DPIs have several advantages over pMDIs. They are propellant free and usually do not contain any excipients, other than a carrier (see below). They are breath actuated, so the problems for patients of coordinating actuation and inhalation are removed.

The drug (with a particle size usually <5 μm) and excipients (if present) is either preloaded in an inhalation device (e.g. Turbohaler, Accuhaler), or put into hard gelatin capsules (e.g. Handihaler), which are loaded into a device before use.

The small drug particles produced by micronisation (milling) have poor flow properties, due to their high surface energy. To improve their flow, and aid device manufacture and delivery of drug from the device, particles are generally mixed with larger 'carrier' particles (30–150 μm) of an excipient, usually lactose. Some formulations also contain fine lactose particles or magnesium stearate to optimise the formulation properties. During inhalation, the turbulent airflow generated within the inhalation device should be sufficient for the deaggregation of the drug/carrier aggregates, with drug particles carried in the inhaled air deep into the airways. Most DPI formulations contain a carrier; some Turbohaler

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

formulations do not. Instead, drug particles are loosely aggregated, and these aggregates are broken up by turbulent airflow created in the device during inhalation by patients.

— Factors affecting adherence with asthma treatments

Patients may find it difficult to adhere to treatments for asthma. This may be intentional or unintentional. As already discussed, achieving correct inhaler technique is very difficult. DPIs may be preferable (53–59% of patients use correct inhaler technique), although alternative devices to a pMDI should be prescribed according to patient preference and local cost. The type of device may be limited by the drug, so it may be appropriate to change the drug, e.g. beclometasone is not available as a Turbohaler, whereas budesonide is. There are also devices available to measure patients' inspiratory flow and match this to the most appropriate device.

The side effects of inhaled corticosteroids may discourage patients from adhering to their prescribed regimen, as may lifestyle issues. As a student Miss GN may have a busy social life and live away from home; this may impact on her ability to have inhalers with her when needed and she may benefit from having more than one of each inhaler available, e.g. one to keep at both her student and her home addresses.

Pharmacists can make a huge impact by teaching patients how to use their inhalers correctly, recommending changes to alternative devices when appropriate and making other practical suggestions that may help with adherence.

— The SMART regimen

Studies have shown that the SMART (single inhaler maintenance and reliever therapy) combination of budesonide/formoterol can safely and effectively be used as an asthma reliever as well as a preventer in primary care asthma management, with formoterol acting as quickly as salbutamol. This can be prescribed if control is not achieved with standard dose inhaled corticosteroids. When this regimen is prescribed, the total daily dose of inhaled steroid should not be decreased, and patients should be advised that the regimen will require review if they need to use the reliever once a day or more on a regular basis.

This may aid adherence because the patient requires only one dry powder inhaler (and therefore no spacer).

— Stepping down treatment

Once a patient's asthma has been controlled, 'stepping down' should be considered. The most appropriate drug to be reduced should be considered in view of current dose, side effects and beneficial effects of the current dose, as well as the severity of asthma and patient preference.

If stepping down inhaled steroids, reductions should be considered every 3 months, with a dose reduction of 25–50% at a time.

EXTENDED LEARNING

- How are inhalation products formulated and manufactured?
- What are the mechanisms whereby inhaled particles are deposited in and cleared from the airways?
- Why is particle size such an important property of inhalation aerosols?
- What methods are used to reduce the size of particles and to measure the size distribution of particles?

ADDITIONAL PRACTICE POINT

- How will you counsel a patient to use a pMDI, pMDI with spacer or DPI?

Further reading

British Thoracic Society/Scottish Intercollegiate Guidelines Network (2012). *British Guidelines on the Management of Asthma*. London: BTS/SIGN, May 2008, updated January 2012.

Murphy A (2010). Asthma: The condition and its diagnosis. *Clin Pharmacist* **2**:203–07.

Murphy A (2010). Asthma: Treatment and monitoring. *Clin Pharmacist* **2**:209–14.

Taylor KMG (2013). Pulmonary drug delivery. In: Aulton ME, Taylor KMG (eds), *Aulton's Pharmaceutics: The design and manufacture of medicines*, 4th edn, Elsevier: London, 638–56.

Thomas M, Pavord I (2012). Single inhaler maintenance and reliever therapy (SMART) in general practice asthma management: where are we? *Primary Care Respir J* **21**:8–10.

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

Case 2

Treating an acute severe asthma exacerbation

ANNA PRYOR

LEARNING OUTCOMES

At the end of this case, you will be able to:

- Outline the pathophysiology of asthma
- Explain the signs, symptoms and common triggers of acute asthma exacerbations
- Outline the different classifications of acute asthma
- Discuss the treatment options in asthma exacerbations
- Outline the key features of the various inhalation devices (pressurised metered dose inhalers, dry powder inhalers, nebulisers)
- Outline the pharmaceutical monitoring required when looking after asthma patients and be able to make recommendations on therapy

Case study

Miss SA is a 19-year-old white young woman who has had asthma since the age of 5. She has been brought to the A&E by ambulance suffering with an asthma attack after collapsing during a local charity summer fun run.

Her mother tells you that her regular medications are as follows:

Beclometasone pMDI 100 micrograms two puffs b.d.
Salbutamol pMDI 100 micrograms two puffs p.r.n.

Past medical history: hay fever

Miss SA has recently been taking ibuprofen 400 mg which she purchased over the counter (OTC) for a knee sprain she sustained while training for the fun run.

She has been admitted to hospital with her asthma before, as a child, but hasn't had any problems for a long time and 'hasn't been using her brown inhaler much lately'.

On admission, she is severely short of breath and unable to speak in full sentences; she is holding on to the sides of the trolley, leaning forward and gasping for breath. Her observations are as shown in the box.

On examination

- Blood pressure (BP) 95/75 mmHg
- Heart rate (HR) 120 beats/min
- Respiratory rate (RR) 30 breaths/min
- Widespread expiratory polyphonic wheeze
- Oxygen saturations PaO_2 = 59 mmHg (7.8 kPa) (normal 80–100 mmHg [10–13 kPa]); SpO_2 = 92% on air (normal >92%)
- arterial blood pH 7.3
- Peak expiratory flow (PEF) = 200 L/min (best = 450 L/min)

- What is the underlying pathophysiology of asthma?
- What factors could have contributed to Miss SA's asthma exacerbation?
- Beclometasone is administered as the dipropionate ester. How is beclometasone metabolised in lung tissue to give its active metabolite?
- What is the fate of the beclometasone dipropionate that is NOT deposited in the respiratory tract?
- What other investigations should be performed on Miss SA and why?
- How would you classify the severity of her asthma attack? What features of her history and presentation give cause for concern?
- What treatment should she be given immediately?

She does not respond to initial treatment.

- What further therapy could you recommend?
- What are the key differences between the various types of inhaler devices available?

Once she has been stabilised, she is taken to the admissions ward.

- What recommendations would you make for her further treatment and which specific parameters should you monitor as a pharmacist?

Case discussion

— Pathophysiology of asthma

Asthma is a chronic inflammatory disorder of the airways, characterised by bronchoconstriction,

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

increased vascular permeability, excess mucus production and impaired mucociliary clearance (the process whereby the cilia of the cells lining the airways propel mucus, and deposited materials, upwards towards the throat). Due to airway hyper-responsiveness, both specific and non-specific stimuli can trigger the complex inflammatory response in people with asthma, which is mediated by eosinophils, mast cells lymphocytes and neutrophils.

— Possible trigger factors for an exacerbation in this case

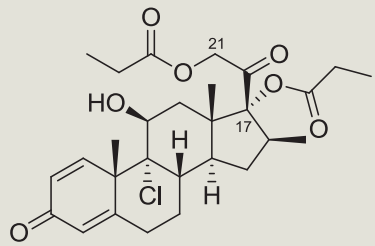
- *Medicines*: NSAIDs, such as ibuprofen, can induce bronchospasm in people with asthma. This is due to the drug's effect on arachidonic acid metabolism: production of prostaglandins is blocked, causing increased production of leukotrienes which cause bronchoconstriction.
- *Allergens*: grass pollen is prevalent in June and July and mould spores (*Cladosporium* and *Alternaria* spp.) are common in late summer. Given that Miss SA is known to have hay fever and was outside participating in the 'fun run', this could have been a contributory factor. No antihistamine medication is mentioned. Of note, in the UK there is a peak of asthma deaths in people aged up to 44 years in July and August.
- *Running*: vigorous exercise causes narrowing of the airways in most people with asthma.
- *Non-compliance with medication*: Miss SA mentioned that she has not been using her steroid inhaler as prescribed.
- *Infection*: respiratory tract infections can provoke a transient increase in airway responsiveness in normal individuals, as well as people with asthma. Upper respiratory tract infections, principally of viral aetiology, are the most common trigger factor for acute asthma.

— Less likely triggers in this case

- Changes in weather, particularly high humidity
- Possible premenstrual component
- Psychological stimuli, such as stress or anxiety.

— Beclometasone dipropionate

Beclometasone is a potent glucocorticoid steroid. In the management of asthma, beclometasone is administered as a diester – the hydroxyl groups at carbon-17 and carbon-21 are both esterified as the propionate (propanoate) esters. After inhalation, the more accessible ester at carbon-21 is rapidly cleaved by lung esterases to give the highly active beclometasone 17-monopropionate (17-BMP) metabolite. After absorption from the lungs, the 17-BMP is rapidly cleared to inactive metabolites in the liver.



beclometasone dipropionate

Only around 10–30% of an inhaled dose is deposited in the respiratory tract, the remainder being deposited in the oral mucosa and subsequently swallowed. Very little beclometasone dipropionate is absorbed from the gastrointestinal (GI) tract due to its very low polarity and very poor water solubility; most is simply eliminated unchanged in the faeces. Any small fraction that is absorbed undergoes significant first-pass metabolism in the liver, minimising systemic availability.

— Recommended further investigations

- *Chest radiograph*: although not recommended as routine, radiography is useful to rule out other causes for breathlessness, such as pneumothorax or pneumonia.
- *Arterial blood gas (ABG)*: this will help determine the severity of Miss SA's asthma. A low PaO_2 (partial pressure of oxygen dissolved in arterial blood) could be indicative of life-threatening asthma and an SpO_2 (blood oxygen saturation: percentage of Hb molecules bound to oxygen) <92% is associated with a risk of hypercapnia (elevated arterial CO_2; normal $PaCO_2$ = 40 mmHg [5.3 kPa]).
- *Blood tests*: including CRP (C-reactive protein, produced by the liver as a measure of general level of inflammation in the body) and full blood count (FBC) to look for evidence of infection.
- *Temperature*: to diagnose or exclude infection.
- *Echocardiogram (ECoG)*: to exclude a cardiac cause or complication for her symptoms.

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

— Signs of acute severe asthma: considerations in this case

In this case, Miss SA's PEF is <50% of her best, and both her heart rate (HR) and respiratory rate (RR) are elevated. She is unable to complete sentences and is having to use her accessory muscles to breathe (note: 'holding on to the sides of the trolley, leaning forward and gasping for breath').

FEATURES OF ACUTE ASTHMA

- Peak expiratory flow (PEF) 33–50% of best (use percentage predicted if recent best unknown)
- Cannot complete sentences in one breath
- Respirations ≥25 breaths/min
- Pulse ≥110 beats/min

Miss SA is also exhibiting worrying signs that could indicate that she is close to progression to life-threatening asthma, including hypotension and dangerously low oxygen saturation. A blood gas reading would be essential at this stage to determine her risk and plan her treatment.

LIFE-THREATENING FEATURES OF ASTHMA

- PEF <33% of best or predicted
- PaO_2 <8 kPa and/or low pH[a] on ABG
- SpO_2 <92%
- Silent chest, cyanosis or feeble respiratory effort
- Hypotension
- Exhaustion
- Altered conscious level, confusion or coma
- Arrhythmias

[a]Normal arterial pH = 7.35–7.45

— Immediate treatment of an asthma exacerbation

High-flow oxygen is the most important immediate treatment and should be the first intervention, because hypoxia can put the patient at risk of cell injury and death. Give 15 L O_2 via a re-breathe mask, aiming for an arterial SpO_2 94–98%.

High-dose nebulised β_2-agonist, either salbutamol 5 mg or terbutaline 10 mg: there is no evidence to suggest superior efficacy of either agent. This must be delivered via an oxygen-driven nebuliser with a minimum flow rate of at least 6 L/min because of the risk of desaturation with air-driven devices. Back-to-back nebulisation is recommended, e.g. salbutamol 5–10 mg/h.

Steroids: early administration of steroids is imperative. Their use has been shown to reduce mortality and lower requirements of β_2-agonist therapy. Oral steroids are as effective as parenteral therapy, provided that the patient is able to swallow and retain the tablets. Recommended doses are prednisolone 40–50 mg daily, hydrocortisone 100 mg 6-hourly or methylprednisolone 160 mg intramuscularly.

Nebulised ipratropium bromide (anticholinergic) 500 micrograms 4- to 6-hourly via an oxygen-driven nebuliser: combining an anticholinergic with the nebulised β_2-agonist will produce significantly greater bronchodilatation than the β_2-agonist alone.

— Possible add-on therapy

Magnesium sulfate: there is some evidence that, in adults, magnesium sulfate has bronchodilator effects. A single dose has been shown to be safe and effective in acute severe asthma unresponsive to initial therapy. The recommended dosage is 1.2–2 g intravenous infusion administered over 20 minutes.

Intravenous fluid rehydration: patients with acute asthma tend to be dehydrated because they are too breathless to drink adequate amounts of fluid, in addition to experiencing increased fluid loss from the respiratory tract. Dehydration causes the production of more viscous mucus, making clearance more difficult and risking mucus plugging. Consider potassium supplementation to compensate for the hypokalaemic effect of salbutamol and corticosteroids.

Antibiotics: routine prescribing of antibiotics is not indicated in asthma exacerbations. Most infective precipitants are viral in origin. Only if there is objective evidence of bacterial infection, e.g. elevated white cell and neutrophil counts, high temperature and radiological changes, should broad-spectrum antibiotics, such as amoxicillin, be initiated.

Intravenous aminophylline: some patients may derive benefit from the addition of an infusion of intravenous (i.v.) aminophylline; however, it is no longer considered routine therapy. The loading dose is 5 mg/kg over 20 min followed by

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

▼ TABLE 3.1
Comparison of inhaler devices

Device	A pMDI	DPI	Nebuliser
Principle of operation	Pressurised gas, e.g. HFA	Powder particles dispersed by patient's inhalation	Compressed air/oxygen, or: Ultrasonic Mesh
Drug presentation	Drug dissolved or suspended in liquid propellant	Micrometre-sized drug particles as powder	Drug dissolved or suspended in water
Possible excipients	Propellant, surfactant, co-solvent	Carrier particles, e.g. lactose	Tonicity and pH modifiers
Storage of medication	In inhaler	In inhaler or capsules	As unit-dose 'nebules', independent of device (rarely multidose in vials)
Treatment time	<1 s	One breath	Up to 20 min
Advantages	Small, portable, no preparation	Small, portable, minimal preparation	Ease of use, potential for delivering large doses
Disadvantages	Poor patient compliance	Inspiratory effort required	Relatively large, cost, duration of treatment, non-availability of devices on NHS

DPI, dry powder inhaler; HFA, hydrofluoroalkane; pMDI, pressurised metered-dose inhaler.

continuous infusion of 500 micrograms/kg per hour (maximum concentration 25 mg/mL). Be sure to check the drug history and for interactions. Therapeutic drug monitoring will be required if the infusion is continued for more than 24 hours.
Parenteral β_2-agonist: intravenous salbutamol may be beneficial in addition to the nebulised route in severe cases, or for patients who are ventilated, although there is limited evidence to support this. Recommend prescribing: 5 mg salbutamol 1 mg/mL diluted in 500 mL 5% glucose or 0.9% sodium chloride and infusing at 0.3–2 mL/min (3–20 micrograms/min) and titrating to response.

— Recommended pharmaceutical monitoring, follow-up and treatment

- PEF: PEF readings should improve, but be careful to watch out for any diurnal variation – asthmatics typically dip first thing in the morning and failure to consider this could lead to inappropriately hasty step-down of treatment and discharge.
- Electrolytes: watch for hypokalaemia in view of the high dose steroid and salbutamol therapy.
- Side effects: monitor for side effects from all drugs, e.g.:
  - Salbutamol: tremor, tachycardia, headaches, palpitations
  - Ipratropium: dry mouth, urinary retention, nausea, headache
  - Steroids: hyperglycaemia, hypertension.
- Switch steroids to oral prednisolone 40 mg daily and continue for at least 5 days. At this dose, they can be stopped abruptly on discharge with no need for weaning. Tapering is necessary only if the patient has had repeated courses, doses >40 mg prednisolone or received over 3 weeks of treatment.
- Step-up inhaler therapy: suggest switching to a combination inhaler containing a long-acting β-agonist + corticosteroid, e.g. Symbicort 200/6 or Seretide 125/25 (step 3 of BTS guidelines); this can be stepped down at a later date as control is maintained.

— The key difference between types of inhaler device

See Table 3.1.

— Counselling

It is important to reinforce the need for compliance with treatment, and to ensure that inhalers are used correctly with the optimal devices prescribed. Using these devices to achieve optimum effect is not easy. In particular, pMDIs require coordination of inhaling and actuation, as part of a routine with a number of steps to promote effective drug delivery to the lungs. Patients should be assisted to ensure that they

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

sustain a good technique in the operation of devices.

A personalised self-management plan should be devised and a written plan issued to the patient on discharge. These, together with self-management education, have been shown to reduce hospitalisation and A&E attendance, particularly in people with asthma who have had recent exacerbations.

The plan should include:

- Structured education, with specific advice about recognising loss of asthma control assessed by symptoms and/or PEF monitoring
- What to do if asthma deteriorates, such as seeking medical attention, increasing inhaled steroids or starting oral steroids, depending on severity.

Consider the need for supplementary treatments such as non-sedating antihistamines, e.g. cetirizine 10 mg daily.

EXTENDED LEARNING

- Outline the British Thoracic Society guidelines for treatment of asthma.
- Describe the pharmacology of long- and short-acting β_2-agonists.
- Describe the anatomy of the lung – how does this impact on the way in which therapeutic aerosols are deposited and cleared from the airways?
- Describe how particles delivered from inhaler devices deposit in the airways, and outline the importance of particle size and density in these mechanisms.

Further reading

Taylor KMG (2013). Pulmonary drug delivery. In: Aulton ME, Taylor, KMG (eds), *Aulton's Pharmaceutics: The design and manufacture of medicines*, 4th edn. London: Elsevier, 638–56.

Case 3

Nebulised therapy for chronic obstructive pulmonary disease

BOTHAINA ALHADDAD

LEARNING OUTCOMES

At the end of this case, you will be able to:

- Outline the pathophysiology, symptoms, signs and diagnosis of COPD
- Describe the treatment options in COPD, particularly in relation to exacerbations
- Outline the place of nebuliser therapy in COPD, and describe the variations in operating principles and designs of available nebulisers
- Describe the practical aspects relating to patients' use and maintenance of nebulisers
- Outline the pharmacological mechanism of action of β_2-adrenergic receptor agonists on bronchial smooth muscle
- Outline the common side effects of β_2-adrenergic receptor agonists
- Appreciate the structural characteristics of long- and short-acting β_2-adrenergic receptor agonists that are important in their pharmacological activity and clinical use

Case study

Mrs MM is a 75-year-old white woman, who has smoked for the previous 40 years. She was diagnosed with COPD 5 years ago, and has since been prescribed bronchodilators, including salmeterol, delivered from a pMDI to relieve her breathlessness. Salmeterol is a long-acting β_2-adrenergic receptor agonist.

- What is COPD?
- What are the classic symptoms of COPD?
- How is a diagnosis of COPD confirmed?
- How is stable COPD managed?

Mrs MM began to feel unwell on Christmas Eve. She was increasingly breathless despite using her inhalers and had just managed to call for an ambulance. The paramedics noted that Mrs MM was out of breath and her PaO_2 was markedly low. She was given oxygen as well as nebulised bronchodilators. During her stay in hospital, Mrs MM was started on an antibiotic and a course of oral steroids. On discharge, she was lent a nebuliser by the hospital for use with prescribed

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

salbutamol nebules. Salbutamol is a short-acting β_2-adrenergic receptor agonist.

- What is an exacerbation of COPD?
- How is it managed?
- What is the mechanism of action of salbutamol and salmeterol in the treatment of respiratory disease?
- What structural characteristics of the salmeterol molecule result in a longer duration of action compared with shorter-acting β_2-agonists, such as salbutamol?
- What other structural features are important in the clinical use of these agents?
- What is the rationale for using a nebuliser in the management of COPD?
- What are the advantages of using a nebuliser rather than a dry powder or pressurised metered-dose inhaler in this case?

Mrs MM's condition improved and she was stabilised after 14 days. She visited her GP who recommended that she continue to use a nebuliser because her COPD had not been adequately controlled with her previous medication; she had increased breathlessness, which limited her daily activities, a productive cough with purulent sputum, and a history of recurrent respiratory infections in the last few years.

Mrs MM is very keen on controlling her symptoms and wanted the GP to help her choose the 'best' nebuliser available.

- What are the different types of nebuliser systems available?
- Given the variation between different available nebuliser systems, what factors should influence the choice of the doctor/patient?
- What factors will determine the proportion of drug in the prescribed salbutamol nebules that will reach the deep lung of a patient using a nebuliser?

Mrs MM comes to the pharmacy and asks you for guidance on the use of her nebuliser.

- Can you explain when and how the nebuliser should be used, giving clear instructions on cleaning and maintenance?

Case discussion

— COPD and its pathophysiology

Chronic obstructive pulmonary disease, characterised by airflow obstruction that is not fully reversible and does not change over several months, is usually progressive and frequently caused by smoking. COPD is an umbrella term used to describe a range of different overlapping conditions affecting the airways, such as chronic bronchitis, emphysema, long-standing asthma and small airway disease. In COPD, the airways become inflamed as a result of an exogenous factor, often smoking, and produce *elastases* which, over time, result in disruption of the elastin/elastase balance in the lung. This, coupled with inactivation of the protective anti-elastases in the lung (as a result of the oxidants in cigarette smoke), leads to loss of lung elastin, destruction of lung tissue and emphysema. Loss of elastin also causes the lungs to become hyperinflated due to air being trapped in the small airways. In addition, smoking causes inflammation and mucus production, which accelerate the decline in lung function and predispose patients to infections. The consequences of this are breathlessness on exertion, hypoxia, pulmonary hypertension and peripheral oedema.

— Symptoms, signs and diagnosis of COPD

Patients with COPD often experience symptoms of breathlessness on exertion, coughing, sputum production and wheezing. However, clinical signs such as barrel chest, prominent accessory muscle of respiration, recession of lower costal margins, abdominal breathing, weight loss, central cyanosis, peripheral oedema and raised jugular venous pressure (JVP) are seen only when the disease is in the severe stage. Diagnosis of COPD often includes full clinical assessments for symptoms and the presence of any clinical signs, as well as complete history taking. Measurement of lung function by spirometry is essential in making a diagnosis of COPD. However, in uncertain cases, bronchodilator or steroid reversibility testing may be useful.

Spirometry is a standardised measure of a forced expiration (and sometimes inspiration) into a spirometer (a calibrated measuring device). Spirometers usually measure flow and then calculate volume with respect to time. The most common measurements are:

- FEV_1: the forced expiratory volume in 1 s, which is the amount of air blown out in 1 s.
- FVC: the forced vital capacity, which is the total amount of air blown out in one breath.
- A FEV_1 : FVC ratio is then calculated.

There are several manufacturers of equipment, and all spirometers need, as a minimum, to meet

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

the standards of measuring and recording as specified in international guidelines. To perform quality-assured spirometry testing and provide valid results for patients, a systematic approach would need to be employed by trained staff according to local standards.

— Treatment options for stable COPD, and during an exacerbation

COPD is mainly managed in primary care with pharmacological and non-pharmacological options. Drug options include inhaled bronchodilators, theophylline, oral or inhaled corticosteroids, and combination therapy of more than one of these. Non-pharmacological options include smoking cessation, pulmonary rehabilitation programmes and oxygen therapy. Exacerbations are common health problems in the natural development of COPD. The National Institute for Health and Care Excellence (NICE) defines an exacerbation as 'a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour. The change in these symptoms often necessitates a change in medication.' Treatment of an exacerbation includes large doses of inhaled bronchodilators, systemic corticosteroids, antibiotics, intravenous theophylline and oxygen.

— Pharmacology of β_2-adrenergic receptor agonists

The clinical usefulness of drugs such as salbutamol and salmeterol as bronchodilators relies on their ability to 'select' for the β_2-subtype of adrenergic receptor that is present on bronchial smooth muscle cells. Salbutamol was originally introduced into practice for bronchodilatation in 1968 and immediately became successful in asthma and COPD treatment, because it produced fewer serious (particularly cardiac) side effects. (The most common side effects reported for inhaled β_2-adrenergic receptor agonists in the *BNF* are: fine tremor in the hands, nervous anxiety, dizziness, headache, muscle cramps, dry mouth and palpitations/cardiac arrhythmias.)

Up to that time, the less-selective β-adrenergic agonist drugs isoprenaline and orciprenaline were commonly used for such conditions, but their cardiovascular, central nervous system (CNS) and gastrointestinal (GI) side effects were considered too significant and potentially life threatening, and so were withdrawn. The main pharmacologic effects of β_2-adrenergic receptor agonists on bronchial smooth muscle are mediated through a coupling of the β_2-adrenergic receptor with a so-called stimulatory G-protein (G_s), which then activates intracellular adenylyl cyclase, the enzyme responsible for catalysing the conversion of intracellular adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). The increased intracellular cAMP levels, via activation of protein kinase A, lead to a decrease in intracellular Ca^{2+} concentration and myosin light chain kinase activity, which ultimately causes smooth muscle relaxation (bronchodilatation). In addition, β_2-agonists directly open large (size) conductance Ca^{2+}-activated potassium [BK(Ca)] channels in the cell membrane, leading to hyperpolarisation and relaxation of airway smooth muscle cells. The combination of all these effects is responsible for the beneficial bronchodilator action.

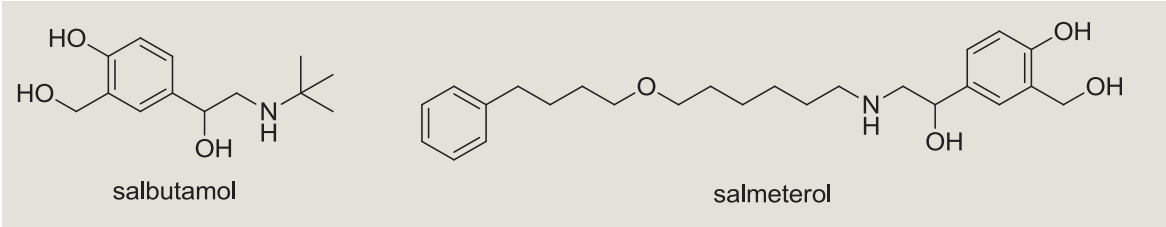
— Chemistry of salbutamol and salmeterol

Salmeterol is considerably more lipophilic than salbutamol due to the extended lipophilic substituent on the nitrogen atom. This extended lipophilic group makes a specific non-covalent hydrophobic interaction with part of the β_2-adrenergic receptor resulting in a higher (10-fold) potency, and localises the drug in the active site for longer.

The secondary amino group nitrogen atom present in both β_2-agonists is basic, with a pK_a value of around 9.0 for the conjugate acid. At physiological pH 7.4, the amino group is protonated and therefore positively charged. This positive charge is essential in making an electrostatic force of attraction with a negatively charged part of the receptor. The basic amino group also means that both agonists can be formulated as salts, which have improved water solubility and dissolution. Hence, salbutamol nebules contain an aqueous solution of salbutamol as the salbutamol sulphate salt.

The carbon atom bonded to the hydroxyl group (-OH) is a chiral centre. Although both salmeterol and salbutamol are manufactured as racemic mixtures (50 : 50 mixtures of *R*- and *S*-enantiomers), only the *R*-enantiomer has the correct shape to bind to the β_2-receptor, because the *R*-enantiomer

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015



has the same relative configuration as the neurotransmitter noradrenaline and the circulating hormone adrenaline.

A bulky substituent on the nitrogen atom and a hydroxymethyl (-CH_2OH) substituent on the aromatic ring are important for β_2 selectivity. The hydroxymethyl group also hydrogen bonds with the receptor-binding site and prevents the drug's metabolism by COMT (catechol-*O*-methyl transferase – the enzyme responsible for metabolising noradrenaline).

— Nebulisers and their modes of operation

A nebuliser is a device that converts a drug solution or, less frequently, a suspension into a fine aerosol for inhalation. The nebuliser system consists of a nebuliser chamber and a driving/energy source. Broadly speaking, there are three types of nebuliser:

1 Air-jet nebulisers, which are most commonly used in practice and comprise a nebuliser chamber and a compressor that generates air at high pressure to atomise the nebuliser liquid
2 Ultrasonic nebulisers, which use high-frequency sound waves to agitate the fluid and cause the drug-containing droplets to be generated from the surface
3 Mesh nebulisers, in which fluid is forced through a mesh with micrometre-sized holes to form droplets.

Each of these devices has advantages and disadvantages. The proportion of available drug that reaches the deep airways depends on the design and mode of operation of the nebuliser, duration of nebulisation, fluid volume (which can be increased by diluting the contents of the nebule) and fluid physicochemical properties, such as viscosity and surface tension. In addition to the device/fluid characteristics, patient technique and breathing pattern are important factors that determine the proportion of drug that reaches the site of action and hence the effectiveness of therapy and clinical outcomes.

— Rationale for using a nebuliser to inhale bronchodilators during an exacerbation

The mode of bronchodilator delivery is changed from regular hand-held inhalers to a nebuliser during an exacerbation. A nebuliser is preferred in this situation as higher doses can be administered to the patient more easily. It is also convenient for healthcare staff to administer, as less patient education and cooperation are required, since the drug is administered during normal tidal breathing, via a mouthpiece or facemask. This is particularly helpful if the patient is distressed. Additionally, the nebulised medication may reduce the viscosity of the mucus and assist in its expectoration from the airways.

— Prescribing nebuliser therapy

Nebulisers are indicated when a patient has severe, distressing breathlessness, despite optimal therapy with pMDIs or DPIs, or is too ill or incapable of using a hand-held inhaler. Domiciliary nebuliser therapy is prescribed after assessment of COPD patients in hospital or general practice. Components of the assessment should include a review of the diagnosis, peak flow rate monitoring at home, and sequential testing of different treatment regimens using peak flow and subjective responses. Only patients who have a clear subjective and peak flow response to domiciliary nebuliser treatment should be advised to continue. If there is a subjective response with $<15\%$ improvement over baseline peak flow, a physician should make a clinical judgement, whereas all other outcomes should not result in continued treatment.

— Use and maintenance of nebulisers

When a nebuliser is prescribed, patients (and/or carers) should be provided with the equipment, servicing, advice and support, and should have regular reviews. They are given clear instructions on how and when to use the nebuliser, how to clean it, when to replace parts and when to service the equipment. The nebuliser chamber and the mouthpiece or facemask should be washed in warm soapy water and dried after each use.

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

Tubing should not be washed because it is difficult to dry. It is advised that air be blown through tubing by running the compressor for a few seconds to dry it out, after the nebulisation session is complete and the chamber is detached from tubing. The chambers should be replaced after 3 months of regular use and the compressor should be serviced regularly according to the manufacturer's recommendations.

EXTENDED LEARNING

- How are COPD and asthma distinguished?
- What are the latest developments in nebuliser design and therapy?
- What conditions other than COPD and asthma may be treated by nebulised therapy?
- What is the place and operation of smoking cessation programmes in the prevention of chronic disease?

ADDITIONAL PRACTICE POINTS

- Familiarise yourself with a nebuliser and its component parts
- Topical use of β-adrenergic receptor *blockers* such as timolol, betaxolol, levobunolol or carteolol in the treatment of glaucoma may lead to sufficient drug being absorbed systemically to pose a threat to patients with asthma or COPD, due to bronchial β_2-receptor blockade and consequent bronchospastic complications and risk of respiratory failure/death. Practitioners reviewing asthma or COPD therapy should therefore routinely investigate whether there is any ongoing ocular (or systemic) use of β-blockers before formulating a treatment plan

References and further reading

Bellamy D, Booker R (2004). *Chronic Obstructive Pulmonary Disease in Primary Care*. London: Class Publishing Ltd.

Boe, J, Dennis JH, O'Driscoll BR, Bauer TT et al. (2001). European Respiratory Society Guidelines on the use of nebulizers. *Eur Respir J* **18**:228–42.

Boe, J, O'Driscoll BR, Dennis JH (2004). *Practical Handbook of Nebulizer Therapy*. London: Martin Dunitz, Taylor & Francis Group plc.

British Thoracic Society (1997). Current best practice for nebuliser treatment. *Thorax* **52**(Suppl 2):S1–106.

Levy ML, Quanjer PH, Booker R, Cooper BG, Holmes S, Small IR (2009). Diagnostic spirometry in primary care: proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society. *Primary Care Respir J* 18:130–47.

National Institute for Health and Clinical Excellence (2004). Chronic Obstructive Pulmonary Disease: National guideline for management of COPD in adults in primary and secondary care. *Thorax* **59**:(Suppl I).

Primary Care Commissioning (2013). A guide to performing quality assured diagnostic spirometry. Available at: www.pcc-cic.org.uk (accessed 25 May 2013).

Case 4

Paediatric cystic fibrosis

SIÂN BENTLEY

LEARNING OUTCOMES

At the end of this case, you will be able to:

- Outline current knowledge of the aetiology of cystic fibrosis (CF)
- Explain the role of different medications routinely prescribed for a patient with CF
- Describe the presentation and management of allergic bronchopulmonary aspergillosis in a CF patient
- Outline the chemistry and mode of action of omeprazole
- Describe the properties of itraconazole and outline formulation strategies to enhance its bioavailability
- Understand the application of shared-care protocols in prescribing of specialist medication outside the hospital setting

Case study

Charlotte, a 7-year-old girl weighing 21 kg, is admitted to the ward after presenting at her outpatient clinic with increased shortness of breath, increased sputum production (sputum darker than

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

normal), tiredness and generally feeling unwell for the last 3 days.

CASE NOTES

Past medical history
- Cystic fibrosis (CF)
- Pancreatic insufficiency

Allergies
- No known drug allergy (NKDA)

Drug history
- Creon 10 000 with snacks and meals
- Dalivit multivitamin drops 1.2 mL o.d.
- Tocopheryl acetate 100 mg o.d.
- Omeprazole MUPS 20 mg o.d.
- Flucloxacillin 250 mg b.d.
- Colistin (Polymyxin E) 1000 000 units b.d. nebuliser solution
- Salbutamol 100 pMDI two puffs inhaled via a spacer p.r.n. and pre-physiotherapy

On examination

- Temperature 38.5°C

A diagnosis of an infective exacerbation of CF is made. A new sputum sample is taken and sent to microbiology for culture and sensitivity testing. Charlotte is empirically prescribed ceftazidime and gentamicin. The flucloxacillin is increased to a treatment dose:

Ceftazidime: 1000 mg t.d.s. i.v.
Tobramycin: 210 mg o.d. i.v.
Flucloxacillin: 500 mg q.d.s.

- What is CF? Outline the current understanding of its aetiology and symptoms
- Explain what each of Charlotte's medicines on admission are being used for and how they would be administered. Charlotte is unable to take capsules/tablets (Hint: also think about timing with physiotherapy)
- What organisms, common in CF, are the intravenous (i.v.) antibiotics covering?
- Are the doses of the i.v. antibiotics appropriate, and how do they relate to altered pharmacokinetics in CF patients?
- How should the i.v. antibiotics be monitored?

Charlotte receives these antibiotics for a week, but does not improve and becomes progressively more wheezy. Her FEV_1 (% predicted) falls from 65% to 50%. Her blood results show an IgE of 1054 units/mL and Aspergillus fumigatus *RAST (radioallergosorbent test) of 19.8 units/mL, and* Aspergillus *sp. is noted in her recent sputum sample. A diagnosis of ABPA is made and Charlotte is started on prednisolone 30 mg each morning and itraconazole liquid 100 mg twice daily.*

- What does ABPA stand for? What is this? Is the therapy appropriate?
- Comment on the formulation and oral bioavailability of itraconazole in both capsule and liquid form

▼ TABLE 3.2
Blood tests and sputum culture results

Na^+ 136 mmol/L (normal: 134–145 mmol/L)
K^+ 4.5 mmol/L (normal: 3.5–5.2 mmol/L)
Urea 3.3 mmol/L (normal: 2.5–6.5 mmol/L)
Creatinine 35 μmol/L (normal: 32–94 μmol/L)
WBC 17.4 × 10^9/L (normal: 4–13.5 × 10^9/L)
Most recent sputum culture results:
Pseudomonas aeruginosa sensitivity:
Azithromycin R
Ceftazidime S
Chloramphenicol S
Colistin S
Gentamicin S
Tobramicin S
Amikacin S
Temocillin S
Aztreonam R
Timentin S
Meropenem S
Ciprofloxacin R
Staphylococcus aureus sensitivity:
Flucloxacillin S
Penicillin S
Erythromycin R
Gentamicin S

R=resistant; S=sensitive.

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

- How would you counsel Charlotte and her carer to take itraconazole?
- How would you monitor itraconazole therapy?

Charlotte responds well to the itraconazole and prednisolone. However, her sputum remains difficult to expectorate and she is started on DNase 2.5 mg once daily pre-physiotherapy.

She continues to improve and is ready for discharge after 3 weeks. Her discharge medications are as follows:

Creon 10 000: with snacks and meals
Dalivit: 1.2 mL o.d.
Tocopheryl: 100 mg o.d.
Omeprazole: 20 mg o.d.
Flucloxacillin: 250 mg b.d.
Colistin: 1000 000 units b.d. nebuliser solution
Salbutamol 100 pMDI: two puffs via spacer p.r.n. and pre-physiotherapy
Itraconazole: 100 mg b.d.
Prednisolone: 30 mg mane to be reviewed in clinic in 2 weeks
DNase: 2.5 mg o.d. nebuliser solution

- What is DNase (dornase alfa) and how does it work?

The clinical nurse specialist for CF contacts Charlotte's GP to explain the changes to her regimen, to be told that they are not able to prescribe the DNase under the new commissioning arrangements, and the hospital must provide ongoing supplies. They ask if it can be provided as part of a homecare scheme.

- In the NHS, what is meant by 'homecare'? What are the potential benefits of using such a service?

Case discussion

— Causes and symptoms of cystic fibrosis

Cystic fibrosis is an autosomal recessive, life-limiting disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (discovered in 1989), which codes for a Cl^- ion channel normally present in lung epithelial cells. More than 1900 mutations have so far been found in the gene, but only a relatively small number of these mutations (so-called class I–V, with different biological outcomes) can account for most of the CF patients so far characterised with the condition. The most frequent mutation is a deletion of a phenylalanine amino acid residue at position 508 (ΔF508) which results in misfolding of the CFTR channel protein in the cell endoplasmic reticulum (ER), thus preventing it from being trafficked to the plasma membrane. The poorly functioning CFTR channel in CF means that there is an imbalance of chloride and subsequently water across the epithelial cell, leading to accumulation of thick mucus secretions at mucosal surfaces in the lungs that are difficult to clear, and therefore particularly prone to bacterial infection and chronic inflammation. The *CFTR* mutations also affect the exocrine functions of the pancreas, intestine, liver, bile duct, salivary and sweat glands.

There has been extensive research in recent years, with limited success, into the use of gene therapy for the treatment of CF, with delivery of the *CFTR* gene directly to the airways. Transfer of genes into the airway cells requires the use of a vector, which may be viral (e.g. adenoviruses, adeno-associated viruses) or non-viral (e.g. liposomes).

Pharmacological treatment in CF: consideration in this case

— Pancreatic insufficiency

Approximately 90% of CF patients in northern Europe are pancreatic insufficient because of the reduction of pancreatic secretions, which leads to poor digestion of fats and malabsorption of proteins and carbohydrates. Patients have steatorrhoea (fatty stools), decreased absorption of fat-soluble vitamins (A, D, E and K), malnutrition and failure to thrive, and therefore require pancreatic enzyme supplementation. Creon 10 000 is usually administered as delayed-release capsules, which contain enteric-coated microspheres of porcine-derived lipases, proteases and amylases. The microspheres are enteric coated to prevent the breakdown of the enzymes in the acidic environment of the stomach. It is taken with all meals and fat-containing snacks. The capsules should be swallowed whole at the start of a meal and the microspheres not chewed to ensure that adequate enzyme levels reach the duodenum. For young children/babies, capsules can be opened and the microspheres mixed with acidic fluid or soft food. This could be apple sauce or yoghurt or any fruit juice with a pH <5.5, e.g. apple, orange or pineapple juice. If the granules are mixed with fluid or food it is important that they are taken immediately and the mixture not stored, otherwise dissolution of the enteric coating may result. They must not be mixed with the food that requires

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

chewing, because this can cause a sore mouth and put children off eating, as well as reducing efficacy as described previously. The number of capsules taken varies from patient to patient, and the dose and strength are adjusted according to the patient's fat intake, stool consistency/frequency and weight. Dieticians usually advise on the enzyme replacement therapy for each patient. High-strength preparations such as Pancrease HL and Nutrizym 22 are not recommended because of their association with colonic strictures in children. However, no association was found with Creon 25 000. It was also recommended that the total daily dose of lipase should not usually exceed 10 000 units/kg.

It follows that all pancreatic-insufficient patients require supplementation with the fat-soluble vitamins A, D and E. Dalivit is a liquid multivitamin preparation (containing mainly vitamins A, B_2, C and D) available in the form of drops, and tocopheryl acetate (vitamin E acetate: the ester form of tocopherol) is a 100 mg/mL liquid formulation. Levels of vitamins A, D and E are usually checked every year at the annual review and supplement doses amended accordingly.

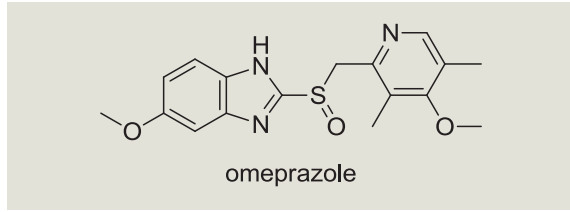
— Gastro-oesophageal reflux

Many CF patients also have gastro-oesophageal reflux which is believed to be due to the hyperacidic gastric secretions and relaxed lower oesophageal sphincter tone. Symptom relief is usually obtained with proton pump inhibitors (PPIs) ± prokinetics such as domperidone and low-dose erythromycin. Long-term treatment is usually required.

PPIs (e.g. omeprazole) and histamine H_2-receptor blockers (e.g. ranitidine) may also be prescribed as adjuvant therapy to enhance the effect of pancreatic enzyme replacement therapy, because pancreatic enzymes are inactivated by gastric acid; therefore, by decreasing acidity, the enzyme efficacy is increased.

— Omeprazole: mode of administration and molecular properties

Omeprazole may be administered to Charlotte as a MUPS (multiple unit pellet system) tablet formulation. The tablets may be dispersed in 10 mL non-carbonated water and then suspended in a small amount of any fruit juice with a pH <5, e.g. apple, orange or pineapple juice, or in apple sauce or yoghurt after gentle mixing. Milk or carbonated water must not be used. The dispersion should be taken immediately or within 30 min. The dispersion is stirred just before drinking and rinsed down with half a glass of water. It is important that the tablets should not be crushed or chewed.



omeprazole

The omeprazole MUPS tablets consist of multiple enteric-coated pellets. The polymeric coating is specifically designed to dissolve only in the higher pH environment of the small intestine, hence the need to disperse the tablets in a slightly acidic medium before administration. On reaching the small intestine, the omeprazole (which itself is inactive) is absorbed into the systemic circulation, from where it reaches the highly acidic environment of the parietal cells, undergoing a pH-dependent chemical rearrangement to its active form. This activated intermediate reacts with the thiol (-SH) group of a cysteine residue present on the H^+/K^+ ATPase (the proton pump), covalently modifying and permanently inactivating it. If the omeprazole were not formulated with an enteric coating, this rearrangement would occur in the contents of the stomach, which would prevent the drug from ever being absorbed and reaching the parietal cells.

— *Staphylococcus aureus* infections

Long-term prophylaxis against *Staphylococcus aureus* is prescribed in order to reduce the frequency of infective exacerbations caused by this organism. The use of anti-staphylococcal prophylaxis from diagnosis until 3 years of age was shown by a Cochrane review to be effective in reducing the incidence of infection with *S. aureus,* although an improvement in clinical outcomes was not shown. Current guidance is to start it in all CF children identified by newborn screening or diagnosed clinically, unless there is a compelling reason not to, i.e. not tolerated, or allergy. Once aged 3 years, flucloxacillin prophylaxis is reviewed. Although policies vary from institution to institution, an example of such a policy is to continue only if *S. aureus* is repeatedly cultured, i.e. more than two isolates of *S. aureus* in a year. Cephalosporins are generally not used for long-term prophylaxis for *S. aureus* because of worries about increased pseudomonas isolation in a US

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

cephalexin trial and also evidence from the European database.

In the case of Charlotte, flucloxacillin is administered as the 250 mg/5 mL preparation, taken on an empty stomach to maximise absorption. As prophylaxis it is administered twice daily to facilitate compliance and to fit better with Charlotte's school day.

— Nebulised colistin

Nebulised antibiotics are prescribed for patients who are chronically colonised with *P. aeruginosa* (grown on three or more isolates in a year) or for eradication of first growth. Long-term nebulised therapy has been shown to reduce the frequency of infective exacerbations and the need for intravenous anti-pseudomonal antibiotics, and to improve lung function. The most frequently used nebulised antibiotics are colistin (colistimethate sodium) and tobramycin. It is currently recommended that colistin be used initially in patients chronically colonised with *P. aeruginosa*. Nebulised colistin achieves low systemic and high local concentrations in the lung, which makes it very useful for long-term therapy, because patients do not have the adverse effects associated with the use of these antibiotics administered intravenously.

Patients must have a bronchoconstriction trial before starting therapy to ensure that the nebulised antibiotic does not cause bronchoconstriction. Colistin nebulisers should be administered post-physiotherapy. This enhances their effects because physiotherapy has removed much of the sputum, enabling better penetration to the site of action.

— Salbutamol

Some patients with CF also have asthma (small airway disease) and therefore benefit from the use of bronchodilators, such as salbutamol (β_2-adrenoreceptor agonist). Before starting treatment, patients should undergo a bronchodilator trial in which their lung function is measured before and after treatment. In patients who demonstrate an improvement, bronchodilator treatment is initiated. Nebulised or pMDI bronchodilators are also used by some patients before nebulising antibiotics, in order to prevent bronchoconstriction.

— Intravenous antibiotics in CF: spectrum of activity, dose and monitoring

Ceftazidime is a third-generation cephalosporin and so has greater activity against Gram-negative bacteria, particularly *P. aeruginosa,* compared with second-generation cephalosporins. However, it is less active against Gram-positive bacteria such as *S. aureus* compared with the second-generation cephalosporins.

Tobramycin is an aminoglycoside that is bactericidal and active against some Gram-positive organisms, including *S. aureus* and many Gram-negative organisms, including *P. aeruginosa.* Tobramycin is the aminoglycoside of choice because there is evidence that it is less nephrotoxic than other aminoglycosides in patients with CF.

Larger doses of many antibiotics are used in CF due to altered pharmacokinetics, notably an increased volume of distribution and increased clearance (renal and non-renal). It is not fully understood why this occurs. In addition, due to the severity of the disease, high concentrations of antibiotics are needed at the site of action.

Both ceftazidime and tobramycin have an increased clearance in CF, so the high doses prescribed are appropriate (ceftazidime 50 mg/kg three times daily and tobramycin 10 mg/kg once daily). There is evidence, from a randomised controlled trial of once versus three times daily tobramycin (the TOPIC study), that once-daily treatment is equally efficacious and associated with less nephrotoxicity in children, although the study showed no difference in ototoxicity between the two regimens. In addition, less money is spent on equipment such as needles and syringes and, importantly for the child with CF, fewer blood tests are needed because only trough serum levels need to be monitored. It also saves on nursing time for drug administration.

The antibiotic therapy must be monitored to ensure that it is effective and not causing adverse effects. Temperature and clinical response (general wellbeing, sputum production and lung function) should be monitored to check efficacy.

In this case, Charlotte's trough serum tobramycin level should be measured 23 hours after administration of the second dose (i.e. shortly before the third dose), 48 hours after any adjustment and weekly thereafter, aiming for a trough level <1 mg/L. This will prevent nephrotoxicity or ototoxicity associated with elevated levels of aminoglycosides. Serum urea and creatinine should be measured at the time of first cannula insertion, and with each trough level.

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

Charlotte's liver function and blood count should also be monitored as ceftazidime can cause disturbances in LFTs (liver function tests) and blood disorders such as leukopenia.

Allergic bronchopulmonary aspergillosis

ABPA is an immune-mediated disease causing bronchiectasis (destruction and widening of the large airways) induced by *Aspergillus fumigatus*, and is not uncommon in CF (occurring in approximately 1–11% of patients). The typical presentation is wheezing, new pulmonary infiltrates on chest radiograph, a rise in serum total IgE and specific IgE to *A. fumigatus*, with a fall in lung function.

The mainstay of treatment is oral corticosteroid therapy to attenuate the inflammatory process, but this may need to be continued for several months and is associated with significant adverse effects. Treatment is with oral prednisolone: an example regimen of 2 mg/kg in the morning (non-enteric coated due to difficulty in absorption of enteric-coated preparations in CF patients as a result of pancreatic insufficiency) for 2 weeks, then 1 mg/kg per day for 2 weeks, and then 1 mg/kg on alternate days for 2 weeks. If an improvement in clinical symptoms, lung function and radiological changes has occurred, and when the IgE levels fall appropriately, prednisolone dose should be tapered to zero over the next 8–12 weeks.

Itraconazole

Itraconazole is used to reduce the antigenic burden of *A. fumigatus* in the respiratory tract. Studies of itraconazole, initially in an uncontrolled setting in CF, and recently in randomised trials in adults with asthma and ABPA, have shown evidence of benefit, including the ability to reduce steroid dosage. It should be given for 3–6 months.

— Formulation, pharmacokinetics and monitoring of oral itraconazole preparations

Itraconazole is a water-insoluble, hydrophobic drug with a log *P* value of 5.66. The poor solubility results in poor bioavailability, particularly from a solid dosage form, because the drug tends to pass through the GI tract without dissolving, ultimately being eliminated in the faeces. As a weakly basic drug, however, dissolution is improved somewhat in acidic conditions. Once in solution, the proportion of drug in the deprotonated (unionised) form can be readily absorbed into systemic circulation. Dissolution and absorption are enhanced in the case of the capsules by forming a solid dispersion of the drug in the rapidly dissolving polymer, hydroxypropyl methylcellulose (HPMC, hypromellose) coated on to sugar spheres. As dissolution requires an acidic environment for dissolution, acid-reducing therapies should be stopped wherever possible and, if not possible, administered at opposite ends of the day to minimise the effects on absorption. Bioavailability from solid dosage forms is approximately 30%, but, if taken with food, bioavailability is increased to about 55%.

Bioavailability is greater from the liquid preparation, which is formulated in cyclodextrin as a solution. Cyclodextrins are cyclic oligosaccharides comprising six (α-cyclodextrin), seven (β-cyclodextrin) or eight (γ-cyclodextrin) glucopyranose units. They have a 'bucket-like' structure with a hydrophilic outer surface and a hydrophobic cavity that can accept a hydrophobic drug molecule, forming an inclusion complex and bringing the drug into solution.

The liquid preparation is much better absorbed, with a bioavailability >70%. However, it is unpalatable and must be taken on an empty stomach. Liver function tests should be monitored at least after 1–2 months, particularly if there is a history of liver dysfunction. ABPA markers will monitor the progress of the disease, e.g. IgE and *Aspergillus fumigatus* RAST, as well as clinical symptoms, e.g. wheeze, lung function and general wellbeing. Itraconazole levels should also be considered when there is a lack of clinical response, or if there is concern about adequate drug absorption or patient compliance.

DNase (dornase alfa)

Patients with CF have thick tenacious sputum, the retention of which contributes to infective exacerbations and reduced pulmonary function. The thick secretions contain a high concentration of extracellular DNA released by degenerating leukocytes, which accumulate in response to infection and add to the viscosity of the secretions. DNase (recombinant human DNase or rhDNase, Pulmozyme) is a genetically engineered version of the naturally occurring enzyme that cleaves extracellular DNA in the sputum; therefore it reduces its viscosity and aids sputum removal. DNase should be administered 1 hour pre-physiotherapy. DNase should be administered only

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

using a jet nebuliser. Ultrasonic nebulisers are not suitable because they may generate heat within the fluid being nebulised, resulting in the degradation of this biopharmaceutical, and indeed others.

Homecare

Homecare medicine delivery and services can be described as a facility that delivers ongoing medicines supplies and, where necessary, associated care, initiated by the hospital prescriber, direct to the patient's home with their consent. Operating as a registered pharmacy, the homecare provider dispenses against the prescription provided by the hospital (with it effectively being a private prescription) for supply to the name patient. Patients that are typically on homecare are those with chronic diseases, such as cystic fibrosis, and stable regimens that do not require acute care input for each supply.

The benefits of using homecare for a medicine such as DNase is that it minimises the inconvenience of patients having to attend outpatient and day care appointments to receive ongoing supplies, thereby releasing appointment slots for other people and increasing efficiency. There is also an opportunity to improve adherence to treatment through regular contact with, and education of, patients. Homecare providers will often be in direct contact with the pataient, and are ideally placed through checking stocks to identify concerns with stockpiling, which can be brought to the attention of the prescribing team to highlight non-adherence and minimise wastage. Equally, the patient has an addtional point of contact in case of difficulties which can be communicated, via the homecare provider, to the prescribing team.

— Medicines management in the home

In addition to shared care between health professionals in the different healthcare sectors, care in the home will be shared between children/young people and their parents/carers. Many CF patients are young. Managing the medication for CF on a daily basis can be a complex task. However, as this is a life-long condition many parents become 'experts' in its management, able to judge symptoms and respond appropriately. However, parents and young people will vary greatly in their confidence in making decisions.

Appropriate use of medicines and good adherence are important for daily wellbeing and longer-term outcomes. Managing medication can be stressful for families. Optimal clinical outcomes depend on optimal use of a wide range of medications: pancreatic enzymes, antibiotics, steroids, vitamins, inhalational therapies. Medicines management activities and ensuring good adherence can be a significant burden for young people and their parents/carers and, when problems and concerns arise, these can be stressful. Shared-care protocols can present additional challenges for parents/carers because formal care is shared between specialists and non-specialists (whose knowledge will be variable and between whom communication can be poor). This can lead to potential inconsistencies in advice and uncertainties for young people and parents with regard to optimal use of medicines.

EXTENDED LEARNING

- Describe recent developments in gene therapy for cystic fibrosis. What are the barriers to successful gene therapy?
- What are biopharmaceuticals? How are they manufactured and formulated into dosage forms? What particular stability problems may they present?
- Liposome delivery of gene therapy is one example of the use of 'nanotechnology' in medicines. What other nano-sized systems have pharmaceutical applications and what benefits do they confer over conventional drug delivery approaches?
- What strategies can formulators employ to enhance the solubility of a drug?

ADDITIONAL PRACTICE POINT

- Consider the particular needs of young people with CF, as they become increasingly responsible for their own medication.

References and further reading

Hanrahan JW, Sampson HM, Thomas DY (2013). Novel pharmacological strategies to treat cystic fibrosis. *Trends Pharmacol Sci* 34:119–25.

Prickett M, Jain M (2013). Gene therapy in cystic fibrosis. *Transl Res* **161**:255–64.

Ryan, G, Mukhopadhyay S, Singh M (2003). Nebulised anti-pseudomonal antibiotics for cystic fibrosis. *Cochrane Database System Rev* **3**:CD001021.

Smyth A, Tan KH, Hyman-Taylor P et al. (2005). Once versus three-times daily regimens of tobramycin treatment for

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

pulmonary exacerbations of cystic fibrosis – the TOPIC study: a randomised controlled trial. *Lancet* **365**:573–8.
Smyth A, Walters S. (2003). Prophylactic antibiotics for cystic fibrosis. *Cochrane Database System Rev* **3**:CD001912.
Stevens DA, Moss RB, Kurup VP et al. (2003) Allergic bronchopulmonary aspergillosis in cystic fibrosis–state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis* **37**(Suppl 3):S225–64.
UK Cystic Fibrosis Trust Antibiotic Working Group (2009). *Antibiotic Treatment for Cystic Fibrosis*, 3rd edn. Bromley: Cystic Fibrosis Trust.
Wark PAB, Gibson PG, Wilson AJ (2004) Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database System Rev* **3**:CD001108.

Case 5
Cough

KATIE GREENWOOD

LEARNING OUTCOMES

At the end of this case you will be able to:

- Outline the pathophysiology, signs, symptoms and diagnosis of different types of cough
- Discuss treatment options for the different types of cough
- Outline the chemistry and mechanism of action of expectorants
- Outline the chemistry and mechanism of action of opiate antitussives
- Know when to refer a patient with a cough to another healthcare professional
- Effectively question a patient to help determine a diagnosis

Case study

John, a 17-year-old student who is one of your regular patient's teenage sons, calls into your pharmacy on the way to college. He has an irritating cough and would like some medicine 'to stop him coughing' so that he can concentrate on his revision and exams. He looks tired and fed up. You notice that John smells of cigarette smoke.

? What questions would you ask the patient?

John explains that he has had the cough for about a week, following a cold. He does not take any other medicines and does not have any medical conditions.

? What is a cough? Explain the pathophysiology
? What are the different types of cough and how would you differentiate between the different types?

You determine that John has a non-productive cough; he has no phlegm and feels that he has an irritation at the back of his throat.

? What are the treatments available for the different types of cough?
? Would there be any restrictions on the products that you could sell due to the patient's age?
? What lifestyle advice, if any, would you provide?

Case discussion

A cough is the most common symptom of upper respiratory tract infection. It may linger after the infection has gone, because the swelling and irritation in the airways can take a while to settle down. The cough can take up to 3 weeks to go completely.

— Pathophysiology of a cough

Coughing is a reflex action initiated by stimulation of sensory nerves in the lining of the respiratory passages. The cough reflex is a vital part of the body's defence mechanisms. Normally, the lungs and the lower respiratory passages are sterile. Coughing usually means that there is something in the respiratory passages that should not be there. This can be caused either by breathing in air-borne dust particles or if a piece of food has gone down the 'wrong way'. If dust or dirt gets into the lungs, it could become a breeding ground for bacteria and cause pneumonia or infection in the airways. It could also be a sign that an infection in the lungs is causing the respiratory passages to produce phlegm.

— Mechanism of cough production

Mechano- and chemosensitive cough receptors (afferent sensory nerve fibres) in the epithelial

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

layer of the pharynx and trachea are fired by the stimuli of excessive mucus or perceived foreign body or irritant (tussigenic) chemical stimulus, and impulses are transmitted to the cough centre in the medulla oblongata of the brain stem via vagal afferent nerve fibres. Impulses are sent back, via efferent neurons, to respiratory muscles of the diaphragm, chest wall and abdomen; these contract, producing a deep inspiration followed by a forced expiration of air, forcing open the glottis and producing a cough.

— Classification of coughs: signs, symptoms and causes

There are two classifications of cough:

- Productive: producing sputum
- Non-productive: dry, with no sputum.

Coughs can further be classified as acute or chronic. This is dependent on their duration and frequency. *Acute coughs* last <3 weeks, whereas *chronic* coughs last >8 weeks. Coughs between 3 and 8 weeks' duration are classified as *subacute*.

Productive cough: a productive, chesty cough, is one in which sputum/phlegm is coughed up. The oversecretion of sputum causes the cough. The appearance of the sputum can often help indicate the underlying cause of the cough: clear or white sputum is usually of little significance; pink/frothy sputum may indicate congestive heart failure, because the blood has congested in the lungs and there has been a leakage of plasma into the air pockets. Coloured sputum can indicate a bacterial infection and lower respiratory tract infection, such as bronchitis or pneumonia, where the sputum is yellow, green, rust coloured (particularly in pneumonia) and/or foul smelling, and thicker. However, it may just represent cell debris being cleared from the air passages. Blood might be present: this is not always a serious sign because capillaries can burst due to violent coughing, but it can be an indication for referral because it might also indicate a pulmonary embolism, tuberculosis (TB), bronchitis or lung cancer. The yellow tinge in allergic cough sputum, as can be seen in asthma, is caused by the presence of large quantities of eosinophils from the blood as part of the allergic response.

Non-productive cough: a non-productive cough may be described as dry, tickly or irritating. It produces no sputum and generally is unlikely to be bacterial, although this should be considered along with other symptoms. Non-productive coughs are irritating to the patient and also to those around them, so the treatment is to try to suppress the cough. A non-productive cough is usually the result of a viral infection, smoking or a dry environment. However, it can also indicate asthma (especially if at night) or lung cancer, or may be due to ongoing medication, e.g. ACE inhibitors.

A cough can be caused by:

- Viral cough associated with a cold (tends to be dry and lasts 7–10 days)
- Postnasal drip
- Allergies
- Croup: viral in origin, affects children aged 9–18 months; barking cough. Occurs commonly in the middle of the night, treated with steam inhalation or referral
- Chronic bronchitis (coughing up mucus on most days for more than 3 months for 2 years) associated with smoking and cough worse on waking
- Asthma can present as just a non-productive cough, especially in young children.

A cough can also be provoked by:

- Smoking
- Sucking material into the airways from the mouth
- Gastro-oesophageal reflux
- Medicines, in particular ACE inhibitors used to treat hypertension and heart failure. Cough may develop within days of starting the course of medicine, or after a few weeks or months. ACE inhibitors, in addition to their main therapeutic effects on the angiotensin production system, inhibit the breakdown of bradykinin and other kinins in the lungs and this triggers the characteristic coughing side effect that is dry, non-productive in type and, in some patients, sufficiently irritating and persistent to warrant a switch in therapy to angiotensin receptor antagonists
- Damage to the nerves that supply the vocal folds (known as vocal fold palsy) and chronic cough can occur.

Rarely, coughing can be provoked by:

- Psychological illness
- Heart failure
- TB
- Pneumonia

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

- Carcinoma of the lung.

— Differential diagnosis

A cough with no serious underlying cause will be self-limiting; however, to confirm this, the patient has to be questioned to ensure that all the relevant information is elicited. Various acronyms can be used as an aide memoire for this questioning process, e.g. WWHAM questions:

Who is the patient?
What are the symptoms?
How long have the symptoms been present?
Action that has been taken to date?
Medication already being taken?

Other useful pharmacy mnemonics include ASMETHOD, ENCORE and SIT DOWN SIR: For further details see: www.resourcepharm.com/pre-reg-pharmacist/pharmacy-mnemonics.html

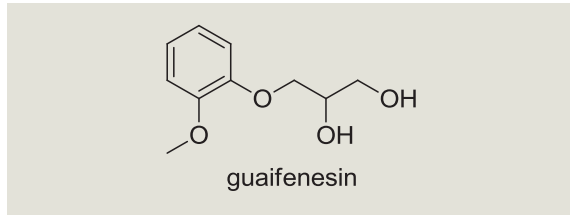
In practice, often a combination or selected questions from these are used depending on the patient's presentation. It is important that you determine the age of the patient, the duration of the cough, whether it is dry or productive and, if productive, the appearance of the sputum. Any associated symptoms such as a cold, or shortness of breath, should be established. The previous history relating to the cough and whether the patient has other medical conditions and medicines should also be established.

— Treatments available for the different types of cough

If in doubt about phlegm production, it is best to regard a cough as productive.

Productive coughs: treatment of a productive cough involves encouraging the removal of the sputum and therefore should be treated with an expectorant cough mixture to help loosen the phlegm and make it easier to cough up from the airways. Expectorants contain ingredients such as guaifenesin (a glycerol derivative), ipecacuanha (derived from the dried root of the Brazilian ipecacuanha plant) and ammonium citrate/chloride or sodium citrate. Two mechanisms of action have been suggested: stimulating bronchial mucus secretion making sputum less viscous, or irritation of the GI tract which subsequently affects the respiratory tract, the former being more probable.

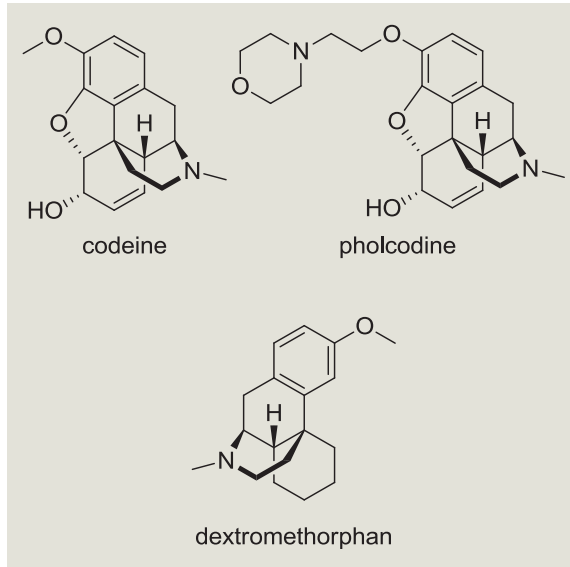
Non-productive coughs: these are irritating to the patient and those around them, so the treatment is a cough suppressant to reduce the cough reflex. Cough suppressants include opiates such as codeine, pholcodine, and dextromethorphan.



guaifenesin

— Chemical properties and actions of opiate antitussives

Codeine, pholcodine and dextromethorphan are all examples of opioid receptor agonists and are all structurally related to the principal opium alkaloid morphine. Each contains a polycyclic four- or five-ring system, which includes a six-membered, nitrogen-containing, aliphatic heterocycle. The nitrogen atom in each is therefore part of a basic, tertiary amino group. Codeine is a naturally occurring analogue of morphine, being methylated at the phenolic hydroxyl group to produce a methyl ether. In pholcodine, a synthetic analogue, the methyl group of the ether is replaced by an extended chain with a morpholine ring at the end, which gives the drug an additional basic centre. The configuration of the ring system in dextromethorphan is opposite to that found in codeine and pholcodine; this can clearly be seen when comparing the structures in the diagram because the ring systems are almost mirror images of each other (opposite relative configurations at each chiral centre).



Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

Opiate antitussives exert their effects centrally by acting primarily on μ- and κ-type (G-protein-coupled) opioid receptors present on relay neurons in the brain-stem medullary cough centre (in or around the nucleus tractus solitarius [NTS]) to inhibit neuronal firing and excitability; they do this through inhibition of excitatory (glutamate) neurotransmitter release and by opening postsynaptic neuronal G-protein, inwardly rectifying K^+ (GIRK) channels. The involvement of δ-opioid receptors in the antitussive action is, however, debatable.

Other treatments: demulcents, e.g. simple linctus and glycerin, lemon and honey linctus, coat and soothe the back of the throat. Antihistamines, e.g. diphenhydramine and promethazine, reduce the cough reflex and also dry up nasal secretions, which can be useful for coughs that are caused by a postnasal drip (mucus running down the back of the throat) or associated with a cold. Some cough remedies also contain sympathomimetics, such as pseudoephedrine, for their airway-relaxing and decongestant effects, and can be useful if the patient has a blocked nose as well as a cough. A practical consideration for patients with diabetes is that the cough medicine be sugar free.

It should be noted that there is limited scientific evidence that cough remedies are effective, although some contain ingredients such as paracetamol which reduce pain or fever. Thus, with the exception of antitussives, cough remedies have for many years not been prescribable on the NHS. However, some patients believe that they get some relief and the products are not considered harmful (Schroeder and Fahey, 2002).

There have been questions asked as to whether pharmacists should promote or recommend products with such a doubtful evidence base.

Legal restrictions on the sale of cough medicines

— Codeine

A UK review of scientific evidence has concluded that the risks associated with OTC oral liquid cough medicines containing codeine outweigh the benefits in children and young people aged <18 years. Consequently, OTC oral liquid medicines containing codeine should not be used to treat cough in children and young people aged <18 years (Medicines and Healthcare products Regulatory Agency [MHRA], 2010).

— OTC cough and cold medicines for children

The Commission on Human Medicines (CHM) has advised on a package of measures to improve safe use of cough and cold medicines for children aged <12 years. The advice is that parents and carers should no longer use OTC cough and cold medicines in children aged <6 years: there is no evidence that they work, and they can cause side effects, such as allergic reactions, effects on sleep or hallucinations (MHRA, 2009).

WHEN TO REFER

- Coughing up phlegm that is green, rusty brown, yellow, blood-stained or foul smelling
- Chest pain
- Shortness of breath or wheezing
- Pain and swelling in the calf (deep vein thrombosis)
- Recurrent night-time cough (asthma)
- Whooping cough or croup
- Worsening smoker's cough
- Sudden weight loss
- Fever and sweating
- Hoarseness of the voice with a chronic cough that doesn't clear up spontaneously.

— Lifestyle advice in this case

Pharmacists have a major role to play in the government's public health agenda. The smell of cigarette smoke should lead to a conversation with John about the benefits of smoking cessation and the products available. Smoking will exacerbate the cough and therefore, even if the patient does not want to stop smoking, he or she should be encouraged to limit the number of cigarettes smoked because this will help to resolve the cough.

EXTENDED LEARNING

- What are the respective roles of the MHRA/EMA (European Medicines Agency) and CHM/CHMP (Committee for Medicinal Products for Human Use) in medicines regulation and guidance for health professionals?

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015

References and further reading

Blenkinsopp A, Paxton P, Blenkinsoppp J (2009). *Symptoms in the Pharmacy*, 6th edn. London: Wiley- Blackwell.

Edwards C, Stillman P (2006). *Minor Illness or Major Disease?*, 4th edn. London: Royal Pharmaceutical Press.

Medicines and Healthcare products Regulatory Agency (2009). *Cough and Colds in Children*. London: MHRA. Available at: www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON038908 (accessed 3 August 2012).

Medicines and Healthcare products Regulatory Agency (2010). *Codeine*. London: MHRA. Available at: www.mhra.gov.uk/SearchHelp/GoogleSearch/index.htm?q=codeine%20over-the-counter%20products (accessed 3 August 2012).

Nathan A (2012). *Managing Symptoms in the Pharmacy*, 2nd edn. London: Pharmaceutical Press.

Rutter P (2009). *Community Pharmacy: Symptoms, Diagnosis and Treatment*, 2nd edn. London: Churchill Livingstone.

Schroeder K, Fahey T (2002). Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults. *BMJ* **324**:329–31.

Sample pages from Integrated Pharmacy Case Studies, published by Pharmaceutical Press, 2015