

# Contents

FOREWORD **xx**

PREFACE **xxi**

EDITORS AND CONTRIBUTORS **xxii**

## **Introduction 1**

## **1 Clinical Pharmacology of Antidiabetic Drugs 2**

*Andrea Llano, Gerry McKay, and Ken Paterson*

Introduction **2**

Clinical Pharmacology **3**

Introduction **3**

Pharmacodynamics **3**

Action on a Receptor **3**

Action on an Enzyme **4**

Membrane Channels **4**

Cytotoxic **4**

Dose–Response Relationship **4**

Pharmacokinetics **5**

Absorption **5**

Distribution/Plasma Protein Binding **5**

Clearance **6**

Drug Metabolism and Elimination **6**

Enzyme Induction and Inhibition **7**

Renal Excretion **7**

Drug Development and Clinical Trials **7**

Introduction **7**

Preclinical Development **8**

Regulatory Approval **9**

Clinical Trials **11**

Microdosing **11**

Phase 1 Trials **11**

Phase 2 Trials **11**

Phase 3 Trials **11**

Phase 4 Trials **12**

Drug Licensing of Antidiabetic Drugs **12**

Cardiovascular Outcome Trials **12**

Marketing Authorisation **14**

Development and Licensing of Insulin **14**

Insulin Regulatory Approval **14**

Development and Approval of Biosimilar Insulin	16
Introduction	16
Insulin Production	16
Biosimilar vs. Generic Drugs	17
Regulatory Considerations for Biosimilars	17
Safety of Biosimilars	18
Interchangeability and Substitution	18
Prescribing Considerations for Biosimilars	18
Pharmacovigilance	19
Passive Pharmacovigilance	19
Active Pharmacovigilance	20
Pharmacoeconomics	21
Introduction	21
Utility Values	23
Health Economic Modelling	23
Sensitivity Analysis	24
Discounting	25
Indirect Comparison and Network Meta-analysis	25
Future Developments in Diabetes Clinical Pharmacology	26
Drug Development	26
Pharmacovigilance	27
Pharmacoeconomics	27

## 2 Metformin 30

*Joseph Timmons and James Boyle*

Introduction	30
History of Biguanides	31
Phenformin and Lactic Acidosis	31
Pharmacology	32
Mechanism of Action	32
Inhibition of Hepatic Glucose Production	33
Reduced Insulin Resistance	34
Intestinal Effects	34
Pharmacokinetics	35
Prescribing in Renal Impairment	35
Prescribing in Liver Disease	35
Prescribing in Heart Failure	35
Prescribing in Pregnancy	35
Glycaemic Efficacy	36
Safety and Side Effects	37
Lactic Acidosis	37
Outcome Trials	38

Cardiovascular Outcome Trials	<b>38</b>
UKPDS	<b>38</b>
HOME Study	<b>39</b>
SPREAD-DIMCAD	<b>41</b>
Renal Effects	<b>42</b>
Prevention of Type 2 Diabetes	<b>42</b>
DPP	<b>42</b>
IDPP	<b>44</b>
CANOE	<b>44</b>
Metformin in Type 1 Diabetes	<b>45</b>
REMOVAL	<b>45</b>
Place of Metformin in Current and Future Practice	<b>46</b>

### **3 Sulfonylureas and Meglitinides 49**

*Joseph Timmons and James Boyle*

Introduction	<b>49</b>
History of Sulfonylureas	<b>50</b>
Pharmacology	<b>51</b>
Insulin Secretion from Beta Cells	<b>51</b>
Mechanism of Action	<b>51</b>
Insulin Secretion	<b>51</b>
Extra-pancreatic Actions	<b>51</b>
Pharmacokinetics	<b>52</b>
Gliclazide	<b>52</b>
Glimepiride	<b>53</b>
Glycaemic Efficacy	<b>53</b>
ADOPT	<b>53</b>
UKPDS	<b>54</b>
GRADE Study	<b>54</b>
Safety and Side Effects	<b>55</b>
Weight Gain	<b>55</b>
Hypoglycaemia	<b>55</b>
Other Side Effects	<b>55</b>
Outcome Trials	<b>56</b>
Cardiovascular Safety and Sulfonylureas	<b>56</b>
UGDP	<b>56</b>
UKPDS	<b>57</b>
ADVANCE	<b>59</b>
CAROLINA	<b>60</b>
TOSCA.IT	<b>60</b>
Meglitinides	<b>61</b>
Nateglinide	<b>61</b>

Repaglinide	61
Outcome Trials	62
NAVIGATOR	62
Place of Sulfonylureas and Meglitinides in Current and Future Practice	65
<b>4 DPP-4 Inhibitors</b>	<b>67</b>
<i>Sharon Mackin and Gemma Currie</i>	
Introduction	67
Pharmacology	68
Structure and Function of Dipeptidyl Peptidase-4	68
Mechanism of Action	68
Pharmacodynamics and Pharmacokinetics	69
Sitagliptin	69
Saxagliptin	70
Vildagliptin	71
Alogliptin	72
Linagliptin	73
Other DPP-4 Inhibitors	73
Glycaemic Efficacy	75
VERIFY	75
GRADE	79
Safety and Side Effects	79
Side Effects	80
Pancreatitis and Pancreatic Cancer	80
Hepatic Side Effects of Alogliptin	82
Outcome Trials	82
Cardiovascular Outcome Trials	82
SAVOR-TIMI 53	84
EXAMINE	85
TECOS	86
CARMELINA and CAROLINA	87
Vildagliptin Meta-analysis	88
Summary of Cardiovascular Outcome Trials	89
Renal Outcomes	89
Saxagliptin	89
Alogliptin	90
Sitagliptin	90
Linagliptin	90
Summary of Renal Effects	91
The Place of DPP-4 Inhibitors in Current and Future Practice	91

**5 SGLT2 Inhibitors 95***Miles Fisher, Andrea Llano, and Gerry McKay***Introduction 96****Pharmacology 96****Physiology of Sodium-dependent Glucose Transporters 96****Mechanism of Action 97****Pharmacodynamics and Pharmacokinetics 97****Dapagliflozin 97****Canagliflozin 98****Empagliflozin 99****Ertugliflozin 99****Sotagliflozin 100****Other SGLT2 Inhibitors 100****Glycaemic Efficacy 100****Comparisons of SGLT2 Inhibitors with GLP-1 Receptor Agonists 101****Additional Effects of SGLT2 Inhibitors 102****Body Weight 102****Blood Pressure 103****Side Effects and Safety 103****Genitourinary Infections 103****Diabetic Ketoacidosis 103****Amputation 104****Other Adverse Effects 105****Outcome Trials 105****Cardiovascular Outcome Trials in Diabetes 105****EMPA-REG OUTCOME 105****The CANVAS Program 108****DECLARE-TIMI 58 108****VERTIS CV 109****Meta-analysis of Cardiovascular Outcome Trials 109****Real-world Evidence of Cardiovascular Benefits 109****Renal Outcome Trials 110****CREDENCE 111****DAPA-CKD 112****SCORED 113****Empagliflozin 113****Ertugliflozin 114****Meta-analysis of Renal Outcomes 114****Real-world Evidence of Renal Benefit 115****Heart Failure Outcome Trials 116**

DAPA-HF	116
The EMPEROR Trials Program	116
SOLOIST-WHF	118
Canagliflozin and Ertugliflozin	118
Meta-analysis of DAPA-HF and EMPEROR-Reduced	118
SGLT2 Inhibitors in Type 1 Diabetes	119
Dapagliflozin in Type 1 Diabetes	119
Sotagliflozin in Type 1 Diabetes	121
Efficacy and Safety of Other SGLT2 Inhibitors in Type 1 Diabetes	121
Diabetic Ketoacidosis	122
Regulatory Approval in Type 1 Diabetes	123
Use of SGLT2 Inhibitors in Other Diseases	123
DARE-19	123
Place of SGLT2 Inhibitors in Current and Future Practice	124
Type 2 Diabetes	124
Chronic Kidney Disease and Heart Failure	124
Type 1 Diabetes	125

## 6 GLP-1 Receptor Agonists 130

*Catherine Russell and John Petrie*

Introduction	130
Pharmacology	131
Glucagon-like Peptide-1 and the Incretin Effect	131
Mechanism of Action	131
Pancreatic Actions	131
Extra-pancreatic Actions	131
Pharmacodynamics and Pharmacokinetics	132
Exenatide	133
Lixisenatide	134
Liraglutide	134
Dulaglutide	135
Semaglutide	135
Other GLP-1 Receptor Agonists	136
Glycaemic Efficacy and Effect on Weight	137
Comparisons within Class	137
Comparisons with Other Antidiabetic Drugs	139
DPP-4 Inhibitors	139
SGLT2 Inhibitors	139
Insulin	139
Other Antidiabetic Drugs	140
Efficacy of Combinations of GLP-1 Receptor Agonists with Insulin	140
Other Effects of GLP-1 Receptor Agonists	141

Cardiovascular System	<b>141</b>
Lipids	<b>142</b>
Side Effects and Safety	<b>142</b>
Side Effects	<b>142</b>
Safety	<b>142</b>
Thyroid Cancer	<b>142</b>
Pancreatitis and Pancreatic Cancer	<b>143</b>
Cholelithiasis	<b>143</b>
Outcome Trials	<b>143</b>
Cardiovascular Outcome Trials	<b>143</b>
ELIXA	<b>143</b>
LEADER	<b>145</b>
SUSTAIN-6	<b>146</b>
EXSCEL	<b>147</b>
REWIND	<b>148</b>
Harmony Outcomes	<b>149</b>
PIONEER 6	<b>149</b>
AMPLITUDE-O	<b>150</b>
Meta-analysis of Cardiovascular Outcome Trials	<b>151</b>
Summary of Cardiovascular Outcome Trials	<b>151</b>
Renal Outcomes	<b>152</b>
Renal Outcomes from Cardiovascular Outcome Trials	<b>152</b>
Meta-analysis of Renal Outcomes from Cardiovascular Outcome Trials	<b>153</b>
Use of GLP-1 Receptor Agonists in Other Diseases	<b>153</b>
Overweight and Obesity	<b>153</b>
Nonalcoholic Fatty Liver Disease	<b>155</b>
Place of GLP-1 Receptor Agonists in Current and Future Practice	<b>155</b>

## **7 Animal and Human Insulins 161**

*Ken Paterson*

Introduction	<b>161</b>
Insulin Structure	<b>161</b>
Insulin Receptors	<b>162</b>
Insulin Physiology	<b>163</b>
Production and Pharmacokinetic Modifications	<b>165</b>
Improved Purification	<b>165</b>
Time Action Prolongation	<b>166</b>
Insulin Zinc Suspension	<b>166</b>
Protamine Zinc Insulin	<b>167</b>
Isophane or Neutral Protamine Hagedorn Insulin	<b>167</b>
Biphasic Insulins	<b>168</b>
Unified Formulation	<b>168</b>

Sources of Insulin	169
Beef Insulin	169
Pork Insulin	169
Human Insulin	169
Hypoglycaemia and Human Insulin	170
Limitations of Older Insulins	170
Short-acting Insulins	171
Intermediate and Long-acting Insulins	171
Time–Action Profile	171
Morning (Fasting) Hyperglycaemia	172
Variability	173
Intensified Insulin Therapy	173
DCCT and EDIC	173
UKPDS	174
Side Effects of Intensified Insulin Therapy	175
Hypoglycaemia	175
Weight Gain	176
Place of Human Insulin in Current and Future Therapy	176
Insulin Therapy in Type 1 Diabetes	176
Insulin Therapy in Type 2 Diabetes	177
<b>8 Short-acting Insulin Analogues</b>	<b>179</b>
<i>Kate Hughes and Gerry McKay</i>	
Introduction	179
Factors Affecting Absorption and Metabolism of Short-acting Insulin	180
Manufacturing Insulin Analogues	180
Short-acting Insulin Analogues	182
Insulin Lispro	182
Insulin Aspart	183
Insulin Glulisine	184
Meta-analysis of Short-acting Insulin Analogues	185
Biosimilar Short-acting Insulin Analogues	186
Second-generation Ultrafast-acting Insulin Analogues	186
Fast-acting Insulin Aspart	186
Ultra-rapid Insulin Lispro	188
Other Attempts to Improve Insulin Absorption and Inhaled Insulin	189
Technosphere Inhaled Insulin	190
Place of Short-acting Insulin Analogues in Current and Future Practice	190
Intensive Insulin Therapy	190
Structured Education	191
Alternative Routes of Insulin Delivery	191



**9 Long-acting Insulin Analogues 194***Robert Lindsay*

- Introduction **195**
  - Older Strategies to Extend the Action of Insulin **195**
  - Factors Affecting the Absorption and Action of Insulin **195**
- Development of Long-acting Insulin Analogues **196**
  - Strategies to Modify the Action of Long-acting Insulin Analogues **196**
- Long-acting Insulin Analogues **197**
  - Insulin Glargine **197**
    - Glycaemic Efficacy and Risk of Hypoglycaemia with Glargine **198**
    - ORIGIN **198**
  - Insulin Detemir **199**
    - Glycaemic Efficacy and Risk of Hypoglycaemia with Detemir **200**
    - 4-T **201**
  - Insulin Degludec **201**
    - Glycaemic Efficacy and Risk of Hypoglycaemia with Degludec **201**
    - DEVOTE **202**
  - U300 Glargine **203**
    - Glycaemic Efficacy and Risk of Hypoglycaemia with U300 Glargine **203**
  - Biosimilar Long-acting Insulin Analogues **205**
  - Other Long-acting Insulin Analogues **205**
  - Combinations of Long- and Short-acting Insulin Analogues **206**
- Meta-analysis of Glycaemic Efficacy of Long-acting Insulin Analogues **207**
  - Type 1 Diabetes **207**
  - Type 2 Diabetes **207**
- Safety of Long-acting Insulin Analogues **209**
- The Place of Long-acting Insulin Analogues in Current and Future Practice **209**
  - Advantages of Insulin Analogues **209**
  - Patterns of Insulin Administration **210**
  - Future Long-acting Insulin Analogues **210**

**10 Devices 214***David Carty*

- Introduction **214**
- Insulin Pens **215**
  - History **215**
  - Modern Insulin Pens **215**
- Insulin Pumps **215**
  - History **215**
  - Modern Insulin Pumps **216**

Glycaemic Efficacy of Insulin Pumps	<b>216</b>
Safety of Insulin Pumps	<b>217</b>
Potential Disadvantages of Pump Therapy	<b>217</b>
Self-monitoring of Blood Glucose	<b>218</b>
Blood Glucose Monitors	<b>218</b>
Continuous Glucose Monitoring	<b>218</b>
Intermittently Scanned (Flash) Continuous Glucose Monitoring	<b>220</b>
Real-time Continuous Glucose Monitoring	<b>221</b>
Accuracy of Continuous Glucose Monitoring	<b>221</b>
Ambulatory Glucose Profiles	<b>221</b>
Time in Range	<b>221</b>
Efficacy of Continuous Glucose Monitoring	<b>223</b>
Linkage of Continuous Glucose Monitoring to Insulin Pumps	<b>223</b>
Low-glucose Suspend	<b>223</b>
Hybrid Closed Loop	<b>224</b>
Efficacy of Closed Loop Systems	<b>225</b>
DIY Closed Loop	<b>225</b>
Guidelines on the Use of Devices	<b>225</b>
Insulin Pumps	<b>225</b>
Continuous Glucose Monitoring	<b>226</b>
Place of Devices in Current and Future Practice	<b>227</b>
<b>11 Acarbose and Alpha Glucosidase Inhibitors</b>	<b>229</b>
<i>Miles Fisher</i>	
Introduction	<b>229</b>
Pharmacology	<b>230</b>
Mechanism of Action	<b>230</b>
Acarbose	<b>230</b>
Other Alpha Glucosidase Inhibitors	<b>231</b>
Glycaemic Efficacy	<b>231</b>
Safety and Side Effects	<b>232</b>
Outcome Trials	<b>232</b>
Prevention of Type 2 Diabetes	<b>232</b>
STOP-NIDDM	<b>232</b>
Voglibose Ph-3 Study	<b>234</b>
Cardiovascular Outcome Trials	<b>235</b>
Meta-analysis of Cardiovascular Events with Acarbose	<b>235</b>
ACE	<b>236</b>
Meta-analysis of Cardiovascular Events with Alpha Glucosidase Inhibitors	<b>237</b>
Place of Alpha Glucosidase Inhibitors in Current and Future Practice	<b>237</b>

**12 Glitazones and Glitazars 239***Miles Fisher*Introduction **239**Pharmacology **240**Mechanism of Action **240**Pharmacokinetics **241**Pioglitazone **241**Glycaemic Efficacy **241**ADOPT **241**Other Effects of Glitazones **242**Safety and Side Effects **242**Side Effects **242**Safety **243**Cardiovascular Safety **243**Heart Failure **244**Bone Fractures **244**Bladder Cancer **245**Outcome Trials **245**Cardiovascular Outcome Trials **245**RECORD **245**TIDE **247**PROactive **247**IRIS **249**TOSCA.IT **250**Prevention of Type 2 Diabetes **251**DREAM **251**Other Trials on the Prevention of Diabetes **251**Glitazars **252**Aleglitazar **253**Saroglitazar **253**Place of Glitazones and in Current and Future Practice **253**Type 2 Diabetes **253**Prevention of Diabetes **254****13 Other Antidiabetic Drugs 257***Maroria Oroko, Andrea Llano, and Miles Fisher*Introduction **257**Pramlintide **258**Pharmacology **258**Glycaemic Efficacy **259**Efficacy in Type 1 Diabetes **259**

Efficacy in Type 2 Diabetes	259
Safety	260
Colesevelam	260
Pharmacology	260
Glycaemic Efficacy	261
Cardiovascular Safety	262
Bromocriptine	262
Pharmacology	262
Glycaemic Efficacy	263
Cylcoset Safety Trial	263
Hydroxychloroquine	264
Pharmacology	265
Glycaemic Efficacy	265
Antiobesity Drugs	265
Orlistat	266
Pharmacology	266
Glycaemic Efficacy	266
XENDOS	267
Naltrexone/Bupropion	268
Pharmacology	268
Efficacy	268
Cardiovascular Safety	268
Phentermine and Phentermine/Topiramate	269
Pharmacology	269
Efficacy	269
Cardiovascular Safety	270
Place of Other Drugs in Current and Future Practice	270
Type 1 Diabetes	270
Type 2 Diabetes	271
<b>14 Future Antidiabetic Drugs</b>	<b>274</b>
<i>Emma Johns and Miles Fisher</i>	
Introduction	274
Dual and Triple Agonists	275
Physiology	275
GLP-1	275
GIP	275
Glucagon	277
Pharmacology of Multiagonist Therapies	277
GLP-1/GIP Receptor Dual Agonists	278
Tirzepatide	278
NNC0090-2746	285

GLP-1/Glucagon Receptor Dual Agonists	<b>285</b>
Cotadutide	<b>285</b>
Bamadutide	<b>286</b>
GLP-1/Glucagon Receptor Dual Agonists in Non-alcoholic Fatty Liver Disease	<b>287</b>
Triple Agonists	<b>287</b>
Imeglimin	<b>288</b>
Pharmacology	<b>288</b>
Mechanism of Action	<b>288</b>
Pharmacokinetics	<b>288</b>
Glycaemic Efficacy and Safety	<b>288</b>
Regulatory Status	<b>290</b>
Place of New Antidiabetic Drugs in Future Practice	<b>291</b>

## **15 Guidelines on Antidiabetic Drugs 294**

*Miles Fisher and Russell Drummond*

Introduction	<b>295</b>
Evidence-based Guidelines	<b>295</b>
Consensus Reports	<b>295</b>
Common Approaches and HbA1c Targets	<b>295</b>
Guidelines on the Use of Antidiabetic Drugs in Type 2 Diabetes	<b>298</b>
NICE	<b>298</b>
SIGN	<b>300</b>
ICGP	<b>300</b>
EASD and ADA Consensus Reports	<b>302</b>
ESC	<b>305</b>
IDF	<b>307</b>
Guidelines on the Management of Type 1 Diabetes	<b>308</b>
NICE	<b>308</b>
SIGN	<b>308</b>
ADA	<b>310</b>
ADA/ESD Consensus Report on the Management of Type 1 Diabetes in Adults	<b>310</b>
Special Patient Groups	<b>311</b>
Use of Antidiabetic Drugs in Pregnancy	<b>311</b>
Use of Antidiabetic Drugs in Patients with Kidney Disease	<b>313</b>
KDIGO	<b>313</b>
ABCD	<b>314</b>
Use of Antidiabetic Drugs during Ramadan	<b>315</b>
Use of Antidiabetic Drugs in Under-resourced Countries	<b>316</b>
Place of Guidelines in Current and Future Practice	<b>318</b>

## **16 Prescribing Antidiabetic Drugs 322**

*Andrea Llano, Gerry McKay, Frances McManus, Catriona McClements, Joyce McKenzie, and Deborah Morrison*

### **Introduction 322**

#### **Why Prescribe? 323**

### **Therapeutic Inertia 323**

#### **Introduction 323**

#### **Causes of Therapeutic Inertia 324**

##### **Clinician-related Factors 324**

##### **Patient-related Factors 325**

##### **Healthcare System Factors 326**

#### **Overcoming Inertia 326**

### **Polypharmacy 326**

#### **Introduction 326**

#### **Detecting and Managing Polypharmacy 327**

### **Nonadherence 329**

#### **Introduction 329**

#### **Improving Adherence 330**

### **The Patient with Problematic Hypoglycaemia 330**

#### **Introduction 330**

#### **Problematic Hypoglycaemia 331**

#### **Management of Problematic Hypoglycaemia 331**

##### **Identify and Characterise Hypoglycaemia 332**

##### **Review Risk Factors for Problematic Hypoglycaemia 332**

##### **Review Patient Education and Behaviour 332**

##### **Review Insulin 333**

### **Prescribing in Renal Impairment 333**

#### **Introduction 333**

##### **Reduced Absorption 335**

##### **Increased Bioavailability 335**

##### **Reduced Renal Clearance 335**

#### **Metformin 335**

#### **Pioglitazone 335**

#### **Acarbose 336**

#### **Sulfonylureas and Meglitinides 336**

#### **Incretin-based Therapies 336**

#### **SGLT2 Inhibitors 336**

#### **Insulin 336**

### **Prescribing in Liver Disease 337**

#### **Introduction 337**

#### **Liver Disease and Diabetes 337**

##### **Reduced Drug Absorption 338**

Increased Volume of Distribution	<b>339</b>
Altered Protein Binding	<b>339</b>
Reduced Metabolism	<b>339</b>
Hepatic Blood Flow	<b>339</b>
Reduced Excretion	<b>339</b>
Metformin	<b>339</b>
Pioglitazone	<b>339</b>
Sulfonylureas and Meglitinides	<b>339</b>
Incretin-based Therapies	<b>340</b>
SGLT2 Inhibitors	<b>340</b>
Insulin	<b>340</b>
Acarbose	<b>340</b>
Prescribing in Cardiovascular Disease	<b>340</b>
Diabetes and Coronary Artery Disease	<b>340</b>
Glycaemic Control	<b>342</b>
Choosing Antidiabetic Drugs with Cardiovascular Benefit	<b>345</b>
Management of Other Cardiovascular Risk Factors	<b>345</b>
Blood Pressure Management	<b>345</b>
Lipid Management	<b>345</b>
Antiplatelet Therapy	<b>345</b>
Acute Coronary Syndromes	<b>345</b>
Diabetes and Heart Failure	<b>346</b>
Pioglitazone	<b>346</b>
Saxagliptin	<b>346</b>
GLP-1 Receptor Agonists	<b>346</b>
SGLT2 Inhibitors	<b>347</b>
Prescribing in Pregnancy	<b>347</b>
Introduction	<b>347</b>
Antidiabetic Drugs in Pregnancy	<b>347</b>
Other Drugs Used in Pregnancy	<b>348</b>
Breastfeeding	<b>348</b>
Prescribing in the Young	<b>348</b>
Prescribing in the Elderly	<b>349</b>
Introduction	<b>349</b>
Hypoglycaemia in the Elderly	<b>350</b>
The Patient with Type 1 Diabetes: a Therapeutic Journey (an Illustrative Case)	<b>350</b>
The Patient with Type 2 Diabetes: a Therapeutic Journey (an Illustrative Case)	<b>351</b>
Future Developments in Prescribing in Diabetes	<b>353</b>

APPENDIX	<b>357</b>
----------	------------

INDEX	<b>359</b>
-------	------------