2. McCormick PA, *et al.* COX 2 inhibitor and fulminant hepatic failure. *Lancet* 1999; **353:** 40–1.
3. Sbeit W, *et al.* Nimesulide-induced acute hepatitis. *Ann Pharmacother* 2001; **35:** 1049–52.
4. Maciá MA, *et al.* Hepatotoxicity associated with nimesulide: data from the Spanish pharmacovigilance system. *Clin Pharmacol Ther* 2002; **72:** 596–7.
5. Traversa G, *et al.* Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. *BMJ* 2003; **327:** 18–22.
6. Irish Medicines Board. Immediate suspension of the marketing of medicines containing nimesulide (issued 15th May, 2007). Available at: http://www.imb.ie/EN/Safety--Quality/Advisory-Warning--Recall-Notices/Human-Medicines/Nimesulide-Suspension.aspx?page=1&noticetypeid=-1&year=2007 (accessed 08/11/07)
7. EMEA. Questions and answers on the CHMP recommendation on nimesulide-containing medicines (issued 21st September, 2007). Available at: http://www.emea.europa.eu/pdfs/human/opinion/43098807en.pdf (accessed 08/11/07)
8. Lateo S, Boffa MJ. Localized toxic pustuloderma associated with nimesulide therapy confirmed by patch testing. *Br J Dermatol* 2002; **147:** 624–5.
9. Teixeira M, *et al.* Acute generalized exanthematous pustulosis induced by nimesulide. *Dermatol Online J* 2006; **12:** 20. Available at: http://dermatology.cdlib.org/126/case_presentations/agep/teixeira.html (accessed 08/11/07)
10. Malheiro D, *et al.* Nimesulide-induced fixed drug eruption. *Allergol Immunopathol (Madr)* 2005; **33:** 285–7.
11. Yapakci E, *et al.* Hypoglycaemia and hypothermia due to nimesulide overdose. *Arch Dis Child* 2001; **85:** 510.

Pregnancy. Irreversible *end-stage renal failure* has been reported in a neonate born to a mother who received nimesulide as a tocolytic from the 26th to the 32nd week of pregnancy.[1] Others have reported neonatal renal failure associated with nimesulide.[2] *Premature closure of the ductus arteriosus* leading, in some cases, to *persistent pulmonary hypertension* has also been seen in 10 neonates whose mothers self-medicated with nimesulide during the third trimester of pregnancy.[3]

1. Peruzzi L, *et al.* Neonatal end-stage renal failure associated with maternal ingestion of cyclo-oxygenase-type-2 selective inhibitor nimesulide as tocolytic. *Lancet* 1999; **354:** 1615. Correction. *ibid*. 2000; **355:** 238.
2. Balasubramaniam J. Nimesulide and neonatal renal failure. *Lancet* 1999; **355:** 575.
3. Paladini D, *et al.* Severe ductal constriction in the third-trimester fetus following maternal self-medication with nimesulide. *Ultrasound Obstet Gynecol* 2005; **25:** 357–61.

Premature labour. Nimesulide has been tried as an alternative to indometacin to delay labour in patients with a history of preterm delivery (p.2003). Nimesulide was given from 16 to 34 weeks of gestation and a successful delivery started 6 days after withdrawal.[1] There appeared to be no adverse effect on fetal renal function or the ductus arteriosus. The authors suggested that fetal prostaglandin synthesis might be mainly mediated through cyclo-oxygenase-1 (COX-1) and that a relatively selective COX-2 inhibitor such as nimesulide might produce fewer adverse effects on the fetus than other non-selective NSAIDs. However, in a small study short-term effects on the fetus were similar for nimesulide, indometacin, and sulindac.[2]

Adverse effects have been reported in some neonates whose mothers received nimesulide during their pregnancies, see above.

1. Sawdy R, *et al.* Use of a cyclo-oxygenase type-2-selective non-steroidal anti-inflammatory agent to prevent preterm delivery. *Lancet* 1997; **350:** 265–6.
2. Sawdy RJ, *et al.* A double-blind randomized study of fetal side effects during and after the short-term maternal administration of indomethacin, sulindac, and nimesulide for the treatment of preterm labor. *Am J Obstet Gynecol* 2003; **188:** 1046–51.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aldoron; Aulin†; Doloctaprin†; Flogovital NF; Metaflex†; Virobron; ***Austria:*** Aulin; Mesulid; ***Belg.:*** Mesulid; ***Braz.:*** Antiflogil†; Cimelide; Deflogen; Deltaflan; Fasulide; Flogilid†; Inflalid; Maxsulid; Neosulida; Nimalgex†; Nimedalin†; Nimeflan†; Nimesilam; Nimesubal; Nimesulin; Nimesulix; Nimesulon; Nisalgen†; Nisoflan; Nisuflex; Nisulid; Optaflan†; Scaflam; Scalid; Sintalgin; ***Chile:*** Áinex; Aulin†; Doloc; Nimepast; Nimesyl; Nimex†; Nisulid; Nisural; ***Cz.:*** Aulin; Coxtral; Mesulid; Nimed; Nimesil; ***Fin.:*** Nimed†; ***Fr.:*** Nexen; ***Gr.:*** Aflogen; Alencast; Algosulid; Algover; Amocetin; Aulin; Auromelid; Chemisulide†; Cliovyl; Discorid; Dolostop; Edrigyl; Elinap; Erlecit; Fladalgin; Flogostop; G-Revm; Kartal; Lalide; Lasazin; Lemesil; Lizepat; Londopon†; Lovirem; Melicate; Melimont; Mesulid; Mesupon; Min-A-Pon; Mosuolit; Multiformil; Myxina; Naofid; Niberan; Nimegel; Nimelide; Nimesul; Omnibus; Rhemid; Ristolzit; Ritamine; Rolaket; Scaflam†; Specilid; Sudinet; Tranzicalm; Ventor; Volonten; ***Hong Kong:*** Mesulid; Nidol; Nimm; ***Hung.:*** Mesulid; Nidol; Nimelid; Xilox; ***India:*** Beta Nicip; Mesulid; Nicip; Nilide; Nimcet; Nimfast; Nimica; Nimodol; Nimulid; Nimusyp; Nimutab; Nimvista; Nise; Willgo†; ***Indon.:*** Arnid; Aulin; Nicox; Nimed; Nimost; Sohoflam; Ximede; ***Irl.:*** Aulin†; Mesine†; Mesulid†; ***Israel:*** Mesulid; ***Ital.:*** Algimesil; Algolider; Antalgo; Areuma; Aulin; Biosal†; Delfos; Dimesul; Doleside†; Doloxtren†; Domes; Edemax†; Efridol; Erreflog; Eudolene; Fansidol†; Fansulide; Flolid; Idealid; Isodol; Laidor†; Ledolid†; Ledoren; Lidenix†; Mesulid; Migraless; Nerelid; Nide†; Nimedex; Nimenol; Nimesil; Nimesulene; Nimexan†; Nims; Noalgos; Noxalide; Pantames; Remov; Resulin; Solving; Sulidamor; Sulide; ***Malaysia:*** Nidol†; ***Mex.:*** Apolide; Cargespril; Defam; Degorflan; Dexlin; Eskaflam; Fenoxil; Flamide; Flamozin; Inim; Lesiden; Lusemin; Meliden; Mesulid; Minus†; Nimepis; Nizurin; Quidofril; Redaflam; Severin; Sidel; Sindel; Sulidek; Sundir; Ul-Flam; ***Philipp.:*** Aulin; Flamesul; Mesulid; Nidolid; Sorini; ***Pol.:*** Aulin; Minesulin; Nimesil; ***Port.:*** Aulin; Donulide; Gerilide; Jabasulide; Nimalge; Nimartin; Nimed; Nimesulene; Reumolide; Sulidor; Sulimed; Vitolide; ***Rus.:*** Actasulid (Актасулид); Aponil (Апонил); Coxtral (Кокстрал); Nimesil (Нимесил); Nimica (Нимика); Nise (Найз); ***Singapore:*** Nidol†; Nise†; ***Switz.:*** Aulin; Nisulid; ***Thai.:*** Neptide; Nidol; Nilide; Nimes†; Nimind; Nimulid; ***Turk.:*** Mesulid; Motival; Nimes; Sulidin; ***Venez.:*** Ainex; Aulin; Drexel; Nimecox; Nimelid; Nimepirex†; Niprolide†; Nise†; Normosilen†; Reduben; Scaflan.

Multi-ingredient: ***Arg.:*** Doloctaprin Plus†; Metaflex Plus†; Mio Aldoron; Mio-Virobron; ***India:*** Cipzen N; Niciflex-T; Nicip Cold; Nicip D; Nicip MR; Nicip Plus; Nicip Super; Nicip T; Nicispas; Nimica Plus; Nimulid MR; Nimulid Nugel; Nimulid SP; Nimvista Plus; Nizer; ***Mex.:*** Amoxiclide; Zithroflam.

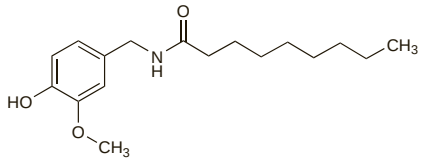
Nonivamide *(rINN)*

Nonivamida; Nonivamidum; Noniwamid; Nonylvanillamide; PAVA; Pelargonyl Vanillylamide; Pseudocapsaicin. *N*-Vanillylnonamide; *N*-[(4-Hydroxy-3-methoxyphenyl)methyl]nonanamide.

Нонивамид

$C_{17}H_{27}NO_3$ = 293.4.

CAS — 2444-46-4.



NOTE. Use of the term 'synthetic capsaicin' to describe nonivamide has arisen from the use of nonivamide as an adulterant for capsaicin and capsicum oleoresin.

Profile

Nonivamide is a synthetic analogue of capsaicin (p.32) that is used in topical preparations for the relief of muscular and rheumatic pain.

Nonivamide has also been used as a food flavour and in 'pepper sprays' for law enforcement and self defence.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: ABC Hydrogel-Warmepflaster; ***Ger.:*** ABC Warme-Pflaster Sensitive†; Gothaplast Capsicum-Warmepflaster; Hansaplast ABC Warme-Pflaster Sensitive†.

Multi-ingredient: ***Austral.:*** Finalgon; ***Austria:*** Finalgon; Rubriment; ***Canad.:*** Finalgon†; ***Cz.:*** Pain Expeller†; ***Ger.:*** Finalgon; Infrotto Ultra†; Lomazell forte N†; Ostochont†; Rheumasalbe†; Rubriment; Vertebralon N†; ***NZ:*** Finalgon†; ***Port.:*** Finalgon; ***Rus.:*** Betalgon (Беталгон); Betanicomylon (Бетаникомилон); Capsicam (Капсикам); Finalgon (Финалгон); ***Spain:*** Finalgon; ***Switz.:*** Forapin†; Histalgane; Radalgin; Thermocutan†; ***Thai.:*** Ammeltz.

Nonsteroidal Anti-inflammatory Drugs

AINE; AINS; Fármacos antiinflamatorios no esteroideos; NSAIDs; NSAİİ'ler.

НПВП; НПВС; НСПВП; Нестероидные Противовоспалительные Препараты

Adverse Effects and Treatment

The commonest adverse effects of NSAIDs are generally gastrointestinal disturbances, such as gastrointestinal discomfort, nausea, and diarrhoea; these are usually mild and reversible but in some patients peptic ulceration and severe gastrointestinal bleeding may occur. It is generally agreed that inhibition of cyclo-oxygenase-1 (COX-1) plays an important role in the gastrointestinal effects of NSAIDs; the selective inhibition of COX-2 improves gastrointestinal tolerance.

CNS-related adverse effects include headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally and include fever, angioedema, bronchospasm, and rashes. Hepatotoxicity and aseptic meningitis, which occur rarely, may also be hypersensitivity reactions. Some patients may experience visual disturbances.

Haematological adverse effects of NSAIDs include anaemias, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis. Unlike aspirin, inhibition of platelet aggregation is reversible with other NSAIDs.

Some NSAIDs have been associated with nephrotoxicity such as interstitial nephritis and nephrotic syndrome; renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment. Haematuria has also occurred. Long-term use or abuse of analgesics, including NSAIDs, has been associated with nephropathy.

Fluid retention may occur, rarely precipitating heart failure in susceptible patients. Other cardiovascular adverse effects of NSAIDs, including those selective for COX-2 inhibition, are discussed in detail below.

Other adverse effects include photosensitivity. Alveolitis, pulmonary eosinophilia, pancreatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare adverse effects. Induction or exacerbation of colitis has also been reported.

Further details concerning the adverse effects of the individual NSAIDs may be found under their respective monographs.

Incidence of adverse effects. The relative toxicity of NSAIDs is a subject of debate.[1] Attempts have been made to rank these drugs according to their toxicity on various body systems.[2] The toxicity of selective cyclo-oxygenase-2 (COX-2) inhibitors has also been reviewed.[3] For further details see below under individual headings.

1. Skeith KJ, *et al.* Differences in NSAID tolerability profiles: fact or fiction? *Drug Safety* 1994; **10:** 183–95.
2. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
3. Chaiamnuay S, *et al.* Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. *Am J Health-Syst Pharm* 2006; **63:** 1837–51.

Effects on the blood. The UK CSM has provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them NSAIDs for which there were 133 reports of agranulocytosis (45 fatal) and 187 of neutropenia (15 fatal). The most frequently implicated NSAID was phenylbutazone with 74 reports of agranulocytosis (39 fatal) and 40 of neutropenia (4 fatal).

1. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)

Effects on bone. Prostaglandins have been shown to play an important role in the bone-healing process and, consequently, the decrease in prostaglandin levels produced by NSAID use may impair the healing process.[1] Under experimental conditions, many NSAIDs including the cyclo-oxygenase-2 (COX-2) inhibitors have been shown to reduce healing.[1] However, clinical evidence of such an effect is rare.[2] There is also concern that some NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis.[3,4]

1. Harder AT, An YH. The mechanisms of the inhibitory effects of nonsteroidal anti-inflammatory drugs on bone healing: a concise review. *J Clin Pharmacol* 2003; **43:** 807–15.
2. Glassman SD. *et al.* The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. *Spine* 1998; **23:** 834–8.
3. Rashad S, *et al.* Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989; **ii:** 519–22.
4. Huskisson EC, *et al.* Effects of antiinflammatory drugs on the progression of osteoarthritis of the knee. *J Rheumatol* 1995; **22:** 1941–6.

Effects on the cardiovascular system. ***BLOOD PRESSURE.*** A meta-analysis[1] of 50 randomised studies of the effects of NSAIDs on blood pressure in a total of 771 patients found that NSAIDs had elevated mean supine blood pressure by 5 mmHg. Piroxicam, indometacin, and ibuprofen had produced the greatest increase but the effect was only found to be statistically significant for piroxicam. Aspirin, sulindac, and flurbiprofen produced the smallest elevation in blood pressure while the effect of tiaprofenic acid, diclofenac, and naproxen was intermediate. The increase was more marked in studies in which patients had received antihypertensive therapy than in those where such treatment had not been used. NSAIDs had antagonised all antihypertensive therapy but the effect had been greater against beta blockers and vasodilators than against diuretics. An earlier meta-analysis of intervention studies had produced similar results.[2] Of the 1324 patients who had received NSAIDs, increases in mean arterial pressure were greatest in hypertensive patients who had taken either indometacin, naproxen, or piroxicam, although results were only significant for indometacin and naproxen. Sulindac and aspirin had minimal effects on mean arterial pressure.

It has been suggested that the use of NSAIDs in the elderly may increase the risk of the need for antihypertensive therapy.[3] A study[3] of 9411 patients aged 65 years or older who had just started treatment with antihypertensives found that 41% had used NSAIDs in the previous year compared with 26% of 9629 control patients not being treated with antihypertensives.

1. Johnson AG, *et al.* Do nonsteroidal anti-inflammatory drugs affect blood pressure? *Ann Intern Med* 1994; **121:** 289–300.
2. Pope JE, *et al.* A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; **153:** 477–84.
3. Gurwitz JH, *et al.* Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. *JAMA* 1994; **272:** 781–6.

HEART FAILURE. The recent use of NSAIDs has been associated with an increased risk of developing heart failure in elderly patients.[1] A case-control study[2] found that the use of an NSAID in the previous week doubled the odds of being admitted to hospital with heart failure; this risk was increased tenfold in those with a history of heart disease. The study also suggested an association between both high-dose and long drug plasma half-life and an increased risk of heart failure.

1. Bleumink GS, *et al.* Nonsteroidal anti-inflammatory drugs and heart failure. *Drugs* 2003; **63:** 525–34.
2. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognised public health problem. *Arch Intern Med* 2000; **160:** 777–84.

THROMBOTIC EVENTS. After the introduction of the selective cyclo-oxygenase-2 (COX-2) inhibitors, concerns arose that the risk of thrombotic events such as myocardial infarction and stroke might be increased in patients treated with these selective NSAIDs, and their safety was continuously reviewed by some regulatory bodies. Subsequently, clinical study data confirmed that there was a small increased risk of these events with the COX-2 inhibitors which prompted the general world-wide withdrawal of rofecoxib (see p.121) and valdecoxib (see p.132). For those selective NSAIDs that remained, prescribing restrictions were imposed (for further details, see under Celecoxib, p.34).

Concerns have also been raised that the increased risk of thrombotic events seen with the selective COX-2 inhibitors may also apply to the non-selective NSAIDs. After a review of data available at the time, the FDA[1] reported in April 2005 that the use of non-selective NSAIDs may potentially increase cardiovascular risk. In August 2005, the UK CSM advised that any cardiovascular risk with the non-selective NSAIDs was likely to be small and associated with continuous long-term treatment and higher doses;[2] no changes to current prescribing practices were recommended. This advice was endorsed a few months later by the EMEA in Europe.[3] However, new information has since become available and, in October 2006, the EMEA updated its advice.[4] Based on data which included the MEDAL programme[5] and reviews of several important epidemiological studies[6-8] the following points were made:

- the results from the MEDAL programme suggest that *diclofenac* (150 mg daily) has a risk of thrombotic events similar to that of etoricoxib (60 mg or 90 mg daily); however, further issues need to be considered before this can be considered conclusive
- based on study and epidemiological evidence, diclofenac, particularly at a high dose (150 mg daily), may be associated with an increased risk of thrombotic events
- clinical study data suggest that high-dose *ibuprofen* (2.4 g daily) is associated with an increased risk of thrombotic events; however, overall, epidemiological studies do not support an increased risk with low-dose ibuprofen (1.2 g daily or less)
- *naproxen* (1 g daily) may be associated with a lower risk for thrombotic events than the COX-2 inhibitors, but a small risk cannot be excluded; overall, there is no evidence of a cardioprotective effect
- for all *other non-selective NSAIDs* there are insufficient data to assess the thrombotic risk and consequently an increased risk cannot be excluded; a small increase in absolute risk seems most likely when used in high doses and for long-term treatment

It has been suggested that NSAIDs may reduce the cardioprotective effect of aspirin, but see under Interactions of Aspirin, p.23.

1. FDA. FDA announces series of changes to the class of marketed non-steroidal anti-inflammatory drugs (NSAIDs) (issued 7th April, 2005). Available at: http://www.fda.gov/bbs/topics/news/2005/NEW01171.html (accessed 08/11/07)
2. CSM. Cardiovascular safety of NSAIDs: review of evidence. Message from Professor G Duff, Chairman of CSM (issued August 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con1004303&RevisionSelectionMethod=Latest (accessed 08/11/07)
3. EMEA. European Medicines Agency update on non-selective NSAIDs (issued 17th October, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/29896405en.pdf (accessed 29/08/08)
4. EMEA. Opinion of the Committee for Medicinal Products for Human Use pursuant to article 5(3) of regulation (EC) no 726/2004, for non-selective non steroidal anti-inflammatory drugs (NSAIDs) (issued 18th October, 2006). Available at: http://www.emea.europa.eu/pdfs/human/opiniongen/nsaids.pdf (accessed 08/11/07)
5. Cannon CP, *et al.* Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006; **368:** 1771–81.
6. Kearney PM, *et al.* Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; **332:** 1302–8.
7. Hernández-Díaz S, *et al.* Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol* 2006; **98:** 266–74.
8. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; **296:** 1633–44.

Effects on the CNS. A literature review[1] revealed that headache, hearing loss, and tinnitus are the most frequent CNS adverse effects in patients taking NSAIDs. Aseptic meningitis had occurred rarely in patients using NSAIDs such as naproxen, sulindac, or tolmetin, but the most common reports were in patients with SLE who were receiving ibuprofen (see also p.64).

Reports of psychosis appear to be rare[1,2] and have involved indometacin or sulindac, but in some reviewers' experience it was probably under-reported and was typically seen in elderly patients given indometacin.[1]

Adverse CNS effects have also been reported with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[2]

The role of NSAIDs in the development of cognitive decline in the elderly is unclear. They have been associated with memory impairment and attention deficits in elderly patients,[1,3] especially when given in high doses;[4] however, some authors have also reported that long-term NSAID use may reduce the rate of cognitive decline[4,5] or the risk of developing Alzheimer's disease[6-8] (see also Dementia, under Uses and Administration, below).

1. Hoppmann RA, *et al.* Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991; **151:** 1309–13.
2. Onder G, *et al.* NSAID-related psychiatric adverse events: who is at risk? *Drugs* 2004; **64:** 2619–27.
3. Saag KG, *et al.* Nonsteroidal antiinflammatory drugs and cognitive decline in the elderly. *J Rheumatol* 1995; **22:** 2142–7.
4. Karplus TM, Saag KG. Nonsteroidal anti-inflammatory drugs and cognitive function - do they have a beneficial or deleterious effect? *Drug Safety* 1998; **19:** 427–33.
5. Rozzini R, *et al.* Protective effect of chronic NSAID use on cognitive decline in older persons. *J Am Geriatr Soc* 1996; **44:** 1025–9.
6. Stewart WF, *et al.* Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997; **48:** 626–32.
7. in 't Veld BA, *et al.* Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med* 2001; **345:** 1515–21.
8. Vlad SC, *et al.* Protective effects of NSAIDs on the development of Alzheimer disease. *Neurology* 2008; **70:** 1672–7.

Effects on electrolytes. See Effects on the Kidneys, below.

Effects on the eyes. Ocular effects such as blurred vision occur rarely in patients taking NSAIDs. Other more serious effects on the eyes associated with NSAIDs also appear to be rare. In the USA the National Registry of Drug-Induced Ocular Side Effects analysed 144 reports they received of possible adverse optic nerve reactions associated with the use of NSAIDs.[1] Of the 24 cases of papilloedema with or without pseudotumor cerebri more than half were associated with propionic acid derivatives, but it was considered that the data indicated that, on rare occasions, most NSAIDs could cause this effect; the number of reports for individual drugs was: 7 for ibuprofen, 5 each for indometacin and naproxen, 3 for meclofenamate, and 1 each for diflunisal, ketoprofen, sulindac, and tolmetin. Almost two-thirds of the 120 cases of optic or retrobulbar neuritis were also associated with propionic acid derivatives; the number of reports for individual drugs was: ibuprofen 43, naproxen 17, indometacin 9, benoxaprofen 8, phenylbutazone 8, piroxicam 8, zomepirac 7, sulindac 6, fenoprofen 5, oxyphenbutazone 3, meclofenamate 2, tolmetin 2, diflunisal 1, and ketoprofen 1.

Ocular adverse effects have also been reported with the selective Cyclo-oxygenase-2 (COX-2) inhibitors.[2]

There have been reports of severe corneal toxicity associated with the use of some topical NSAIDs, such as diclofenac and ketorolac, in the eye (see p.45).

1. Fraunfelder FT, *et al.* Possible optic nerve side effects associated with nonsteroidal anti-inflammatory drugs. *J Toxicol Cutan Ocul Toxicol* 1994; **13:** 311–16.
2. Coulter DM, *et al.* Celecoxib, rofecoxib, and acute temporary visual impairment. *BMJ* 2003; **327:** 1214–15.

Effects on fertility. Reversible infertility has been reported in women on long-term NSAIDs.[1-3] Prostaglandins are considered to be involved in the processes of ovulation and it is thought that NSAIDs may compromise ovulation via inhibition of cyclo-oxygenase-2 (COX-2). Women trying to become pregnant may need to avoid treatment with NSAIDs.

1. Mendonça LLF, *et al.* Non-steroidal anti-inflammatory drugs as a possible cause for reversible infertility. *Rheumatology (Oxford)* 2000; **39:** 880–2.
2. Norman RJ. Reproductive consequences of COX-2 inhibition. *Lancet* 2001; **358:** 1287–8.
3. Stone S, *et al.* Nonsteroidal anti-inflammatory drugs and reversible female infertility: is there a link? *Drug Safety* 2002; **25:** 545–51.

Effects on the gastrointestinal tract. NSAIDs can cause clinically important damage of the gastrointestinal tract, increasing the incidence of bleeding in the upper gastrointestinal tract and of perforation, although serious complications and death are relatively infrequent. They have also been associated with damage to the distal small intestine and colon.[1-3]

The complex **mechanisms** involved are not fully understood, although it is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in gastrointestinal toxicity and that the selective COX-2 inhibitors are less gastrotoxic than the traditional NSAIDs (see below).[4-8] The gastric mucosa is damaged both by local and systemic effects of NSAIDs.[5] The local effect is pH-dependent and varies between individual drugs. The systemic effect is pH-independent, can occur with any route of administration, and is less drug specific; it is this effect that is thought to involve COX-1 inhibition.

Risk factors continue to be studied and so far the most important patient-related factors for upper gastrointestinal toxicity are old age, a history of peptic ulcers or bleeding of the gastrointestinal tract, and concomitant use of corticosteroids.[9] It has also been suggested that risk is increased in children.[10] *Helicobacter pylori* infection exacerbates the risk of ulceration, but patients remain at increased risk even if infection is eradicated.[11] Duration of therapy is not thought to influence the risk for serious events; a cohort study[12] found that the risk of gastrointestinal bleeding or perforation with NSAIDs was constant throughout treatment, and risk quickly declines after NSAID withdrawal.[13]

Several studies[14-17] have been conducted on the **relative toxicity** of oral NSAIDs on the upper gastrointestinal tract and various rankings of these drugs have been discussed.[18-22] The UK CSM[20] examined 10 epidemiological studies for 7 oral non-aspirin NSAIDs and also examined the spontaneous reports they had received of gastrointestinal effects associated with NSAIDs. The CSM concluded that:

- azapropazone was associated with the *highest* risk of gastrointestinal reactions
- ibuprofen carried the *lowest* risk (but this may be related to dose, see below)
- piroxicam, ketoprofen, indometacin, naproxen, and diclofenac had an *intermediate* risk; it was considered that the risk for piroxicam might be higher than for the other NSAIDs with intermediate toxicity

A later update[23] by the CSM confirmed these findings.

The relative gastrointestinal toxicity of NSAIDs has also been reviewed by the EMEA[21] using data from epidemiological studies and spontaneous adverse drug reaction reports. Available evidence suggested that piroxicam and ketoprofen, particularly in high doses, were associated with the greatest risk of gastrointestinal toxicity when compared to diclofenac, etodolac, ibuprofen, indometacin, meloxicam, nabumetone, naproxen, and nimesulide. No firm conclusions were made for the other NSAIDs although there was weak evidence to suggest that the risk of toxicity was slightly higher for indometacin and naproxen than for diclofenac and ibuprofen. As a result of this review the EMEA carried out a full benefit-risk assessment for piroxicam and subsequently placed restrictions on its systemic usage (see p.118).

In a systematic review[24] of controlled epidemiological studies that found a relation between NSAID use and hospital admission for gastric haemorrhage or perforation, the low risk of serious gastric toxicity with ibuprofen appeared to be attributable mainly to the low doses used clinically; higher doses of ibuprofen were associated with a similar risk to indometacin and naproxen. For reference to an association between aspirin and the most severe gastric lesions compared with other NSAIDs, see p.21.

Results from controlled studies have confirmed that the **selective COX-2 inhibitors** are associated with a lower incidence of serious gastrointestinal effects, such as bleeding, perforation, and obstruction, than the traditional NSAIDs[25] (see also Celecoxib, p.35 for further details). However, since the risk of such effects is inherently low in those with no history of peptic ulcer disease, the general prescribing of selective COX-2 inhibitors to all patients requiring an NSAID is questioned, particularly in the light of concerns about their cardiovascular effects (see Thrombotic Events, above). In the UK, the use of selective COX-2 inhibitors is limited to patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID. High-risk patients include the elderly, those already receiving gastrotoxic drugs, and those with existing gastrointestinal disorders.

There has been concern that **topical** use of NSAIDs may also be associated with gastrointestinal toxicity but a case-controlled study[26] concluded that this route was not associated with significant upper gastrointestinal bleeding or perforation.

Apart from the selection of an NSAID with a lower risk for gastrointestinal toxicity, other methods used for the **prevention** or **treatment** of NSAID-associated ulceration are discussed under the treatment of peptic ulcer disease on p.1702.

1. Kwo PY, Tremaine WJ. Nonsteroidal anti-inflammatory drug-induced enteropathy: case discussion and review of the literature. *Mayo Clin Proc* 1995; **70:** 55–61.
2. Gleeson MH, *et al.* Non-steroidal anti-inflammatory drugs, salicylates, and colitis. *Lancet* 1996; **347:** 904–5.
3. Evans JMM, *et al.* Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut* 1997; **40:** 619–22.
4. Hayllar J, Bjarnason I. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; **346:** 521–2.
5. Bjorkman DJ. Nonsteroidal anti-inflammatory drug-induced gastrointestinal injury. *Am J Med* 1996; **101** (suppl 1A): 25S–32S.
6. Soll A. Pathogenesis of nonsteroidal anti-inflammatory drug-related upper gastrointestinal toxicity. *Am J Med* 1998; **105** (suppl 5A): 10S–16S.
7. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; **353:** 307–14. Correction. *ibid.* 1440. [dose]
8. Wolfe MM, *et al.* Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999; **340:** 1888–99.
9. Seager JM, Hawkey CJ. ABC of the upper gastrointestinal tract: indigestion and non-steroidal anti-inflammatory drugs. *BMJ* 2001; **323:** 1236–9.

10. Mulberg AE, *et al.* Identification of nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children with juvenile rheumatoid arthritis. *J Pediatr* 1993; **122:** 647–9.
11. Pounder RE. Helicobacter pylori and NSAIDs—the end of the debate? *Lancet* 2002; **358:** 3–4.
12. MacDonald TM, *et al.* Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997; **315:** 1333–7.
13. Mellemkjaer L, *et al.* Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. *Br J Clin Pharmacol* 2002; **53:** 173–81.
14. Kaufman DW, *et al.* Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clin Pharmacol Ther* 1993; **53:** 485–94.
15. García Rodríguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 769–72.
16. Langman MJS, *et al.* Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 1075–8.
17. Lewis SC, *et al.* Dose–response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. *Br J Clin Pharmacol* 2002; **54:** 320–6.
18. Bateman DN. NSAIDs: time to re-evaluate gut toxicity. *Lancet* 1994; **343:** 1051–2.
19. Smith CC, *et al.* NSAIDs and gut toxicity. *Lancet* 1994; **344:** 56–7.
20. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
21. EMEA. Public CHMP assessment report of medicinal products containing non-selective non steroidal anti-inflammatory drugs (NSAIDs) (issued 7th November, 2006). Available at: http://www.emea.europa.eu/pdfs/human/opiniongen/44213006en.pdf (accessed 08/11/07)
22. Laporte J-R, *et al.* Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. *Drug Safety* 2004; **27:** 411–20.
23. CSM/MCA. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and gastrointestinal (GI) safety. *Current Problems* 2002; **28:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
24. Henry D, *et al.* Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996; **312:** 1563–6.
25. Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; **345:** 433–42.
26. Evans JMM, *et al.* Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case-control study. *BMJ* 1995; **311:** 22–6.

Effects on the kidneys. NSAIDs can produce renal disorders on systemic or topical use,[1] some of which are due to their inhibition of prostaglandin synthesis.[2,3] In the presence of renal vasoconstriction the vasodilator action of prostaglandins increases renal blood flow and thereby helps to maintain renal function.[4,5] Patients whose renal function is being maintained by prostaglandins are therefore at risk from NSAIDs. Such patients include those with impaired circulation, the elderly, those on diuretics, and those with heart failure or renal vascular disease.[2,4] Other risk factors for renal impairment with NSAIDs include dehydration, cirrhosis, surgery, sepsis,[6] and a history of gout or hyperuricaemia.[6,7] The half-life of an NSAID may be a more important determinant of the risk of developing functional renal impairment than the ingested dose.[7] Evidence of renal toxicity due to cyclo-oxygenase-2 (COX-2) selective inhibitors is less extensive; however, such NSAIDS appear to have effects on renal function similar to those of the non-selective NSAIDs.[8,9]

ACE inhibitors and angiotensin receptor antagonists can also produce renal impairment and combined use with NSAIDs should be undertaken with great care.[10,11] The Australian Adverse Drug Reactions Advisory Committee[10] stated in August 2003 that over 50% of cases of renal failure reported to the committee were associated with use of NSAIDs, ACE inhibitors, or diuretics (alone or together); where all these were taken together the fatality rate for reported cases of renal failure was 10%.

Prostaglandin inhibition may also lead to salt and water retention particularly when there is pre-existing hypertension or sodium depletion.[4] NSAIDs, therefore, tend to counteract the action of diuretics and antihypertensives.[2,4] There have been isolated reports of severe hyponatraemia and other symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion in patients taking NSAIDs.[12,13]

Potassium homoeostasis is less dependent on prostaglandins and hyperkalaemia occurs infrequently with NSAIDs.[3] It is more likely to occur in patients with specific risk factors such as those receiving potassium supplements or potassium-sparing diuretics.[3] Indometacin appears to be the main NSAID implicated.

NSAIDs may cause acute interstitial nephritis, perhaps involving an allergic response,[2,3,14] and it may progress to interstitial fibrosis or papillary necrosis.[3,15]

Analgesic abuse or prolonged excessive use can produce nephropathy, a condition characterised by renal papillary necrosis and chronic interstitial nephritis, and, eventually, renal failure.[16] Phenacetin, a para-aminophenol derivative, has long been recognised as being one of the main drugs responsible for analgesic nephropathy,[17,18] but nephropathy has also been associated with the long-term use of NSAIDs and paracetamol without phenacetin.[19]

1. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.
2. Kendall MJ, Horton RC. Clinical pharmacology and therapeutics. *Postgrad Med J* 1990; **66:** 166–85.
3. Whelton A, Hamilton CW. Nonsteroidal anti-inflammatory drugs: effects on kidney function. *J Clin Pharmacol* 1991; **31:** 588–98.
4. Harris K. The role of prostaglandins in the control of renal function. *Br J Anaesth* 1992; **69;** 233–5.
5. Kenny GNC. Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. *Drugs* 1992; **44** (suppl 5): 31–7.
6. MacDonald TM. Selected side-effects: 14. non-steroidal anti-inflammatory drugs and renal damage. *Prescribers' J* 1994; **34:** 77–80.
7. Henry D, *et al.* Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects: results of a case-control study. *Br J Clin Pharmacol* 1997; **44:** 85–90.
8. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; **111:** 64–7.
9. Noroian G, Clive D. Cyclo-oxygenase-2 inhibitors and the kidney: a case for caution. *Drug Safety* 2002; **25:** 165–72.
10. Adverse Drug Reactions Advisory Committee (ADRAC). ACE inhibitor, diuretic and NSAID: a dangerous combination. *Aust Adverse Drug React Bull* 2003; **22:** 14–15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0308.htm (accessed 08/11/07)
11. Loboz KK, Shenfield GM. Drug combinations and impaired renal function – the 'triple whammy'. *Br J Clin Pharmacol* 2005; **59:** 239–43.
12. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.
13. Cheung NT, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by diclofenac. *BMJ* 1993; **306:** 186.
14. Ravnskov U. Glomerular, tubular and interstitial nephritis associated with non-steroidal antiinflammatory drugs. Evidence of a common mechanism. *Br J Clin Pharmacol* 1999; **47:** 203–10.
15. Sandler DP, *et al.* Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. *Ann Intern Med* 1991; **115:** 165–72.
16. De Broe ME, Elseviers MM. Analgesic nephropathy. *N Engl J Med* 1998; **338:** 446–52.
17. Sandler DP, *et al.* Analgesic use and chronic renal disease. *N Engl J Med* 1989; **320:** 1238–43.
18. Dubach UC, *et al.* An epidemiologic study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). *N Engl J Med* 1991; **324:** 155–60.
19. Perneger TV, *et al.* Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994; **331:** 1675–9.

Effects on the liver. A retrospective study involving over 220 000 adults who were either using, or had used, NSAIDs identified a small excess risk of serious, acute non-infectious liver injury; in current users there was a twofold increase in risk and there was a predominance of the cholestatic type of liver injury among such patients. Nonetheless, admissions to hospital for liver injury had been rare.[1] In a review[2] of cohort and case-control studies describing an association between NSAIDs and liver disease, the strongest evidence emerged for sulindac. There were also a significant number of reports of hepatotoxicity on rechallenge with diclofenac. Evidence of hepatotoxicity for other NSAIDs was weak, although the risk appeared to be high when they were used with other hepatotoxic drugs. However, the overall incidence of liver disease with NSAIDs was very low.

A later review has also concluded that NSAID-induced hepatotoxicity is an uncommon event.[3] Nevertheless, an increased risk of hepatotoxicity has been associated with the selective cyclo-oxygenase-2 (COX-2) inhibitor lumiracoxib which led to its subsequent withdrawal in many countries (see p.78). For similar reasons, nimesulide has been withdrawn in some countries and its use is limited in others (see p.95).

1. García Rodríguez LA, *et al.* The role of non-steroidal anti-inflammatory drugs in acute liver injury. *BMJ* 1992; **305:** 865–8. Correction. *ibid.*: 920.
2. Manoukian AV, Carson JL. Nonsteroidal anti-inflammatory drug-induced hepatic disorders. *Drug Safety* 1996; **15:** 64–71.
3. O'Connor N, *et al.* Hepatocellular damage from non-steroidal anti-inflammatory drugs. *Q J Med* 2003; **96:** 787–91.

Effects on the lungs. Adverse pulmonary effects such as pneumonitis, alveolitis, pulmonary infiltrates, and pulmonary fibrosis, often suggestive of an allergic or immune reaction, have been reported with a number of NSAIDs. For references, see under individual monographs.

Effects on the pancreas. A review[1] of drug-induced pancreatitis considered that sulindac was amongst the drugs for which a definite association with pancreatitis had been established. There had been isolated reports of pancreatitis with ketoprofen, mefenamic acid, and piroxicam but any association was considered to be questionable. A more recent population-based, case-controlled study found a substantial variation in the risk of pancreatitis between individual NSAIDs.[2] The increase in risk was highest for diclofenac and ketoprofen (adjusted odds ratios of 5.0 and 4.8, respectively), with indometacin and ibuprofen showing smaller but nonetheless significant increases (odds ratios of 3.6 and 1.5, respectively). Of the other NSAIDs studied (celecoxib, etodolac, naproxen, and rofecoxib), all showed a small but non-significant increase in risk of pancreatitis in current NSAID users.

For further references see under individual monographs.

1. Underwood TW, Frye CB. Drug-induced pancreatitis. *Clin Pharm* 1993; **12:** 440–8.
2. Sørensen HT, *et al.* Newer cyclo-oxygenase-2 selective inhibitors, other non-steroidal anti-inflammatory drugs and the risk of acute pancreatitis. *Aliment Pharmacol Ther* 2006; **24:** 111–16.

Effects on the skin. The diverse cutaneous reactions to NSAIDs including those selective for cyclo-oxygenase-2 (COX-2) inhibition have been reviewed.[1-3]

Of 250 children attending a rheumatology clinic 34 (13.6%) were found to have 4 or more facial scars of unknown origin.[4] This number of scars was found in 22.2% of the 116 children who had received naproxen and in 9.2% of the 87 who had received other NSAIDs. Children affected were more likely to have light skin and blue or green eyes. It was not known whether this was a form of phototoxic reaction but pseudoporphyria-like eruptions associated with NSAIDs, and naproxen in particular (see p.93), have been reported.[5,6]

Concern by the EMEA over the serious nature of skin reactions associated with piroxicam has led to restrictions on the systemic use of piroxicam in the EU (see p.118).

See also Hypersensitivity, below.

1. Bigby M, Stern R. Cutaneous reactions to nonsteroidal anti-inflammatory drugs. *J Am Acad Dermatol* 1985; **12:** 866–76.
2. La Grenade L, *et al.* Comparison of reporting of Stevens-Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. *Drug Safety* 2005; **28:** 917–24.
3. Layton D, *et al.* Serious skin reactions and selective COX-2 inhibitors: a case series from prescription-event monitoring in England. *Drug Safety* 2006; **29:** 687–96.
4. Wallace CA, *et al.* Increased risk of facial scars in children taking nonsteroidal antiinflammatory drugs. *J Pediatr* 1994; **125:** 819–22.
5. Checketts SR, *et al.* Nonsteroidal anti-inflammatory-induced pseudoporphyria: is there an alternative drug? *Cutis* 1999; **63:** 223–5.
6. Al-Khenaizan S, *et al.* Pseudoporphyria induced by propionic acid derivatives *J Cutan Med Surg* 1999; **3:** 162–6.

Hypersensitivity. NSAIDs have produced a wide range of hypersensitivity reactions in susceptible individuals; the most common include skin rashes, urticaria, rhinitis, angioedema, bronchoconstriction, and anaphylactic shock. Hypersensitivity to NSAIDs appears to occur more frequently in patients with asthma or allergic disorders but other risk factors have been identified (for further details see under Aspirin, p.21). The occurrence of aspirin sensitivity in patients with asthma and nasal polyps has been referred to as the 'aspirin triad'. There is considerable cross-reactivity between aspirin and other NSAIDs and it is generally recommended that patients who have had a hypersensitivity reaction to aspirin or any other NSAID should avoid all NSAIDs. For references to hypersensitivity reactions associated with NSAIDs, see under individual monographs. See also Effects on the Skin (p.73) for a report suggesting that ketoprofen is more allergenic than other topical NSAIDs.

Overdosage. In general, symptoms of NSAID poisoning are mild, and usually include nausea and vomiting, headache, drowsiness, blurred vision, and dizziness. There have been isolated case reports of more serious toxicity, including seizures, hypotension, apnoea, coma, and renal failure, although usually after ingestion of substantial quantities. Seizures are a particular problem with mefenamic acid overdosage.

Treatment of NSAID overdosage is entirely supportive. Gastric lavage and activated charcoal may be of benefit within 1 hour of ingestion of a potentially toxic amount. Multiple doses of activated charcoal may be useful in enhancing elimination of NSAIDs with long half-lives such as piroxicam and sulindac. Forced diuresis, haemodialysis, or haemoperfusion are unlikely to be of benefit for NSAID overdosage, although haemodialysis may be required if oliguric renal failure develops.

Precautions

All NSAIDs are contra-indicated in patients with active peptic ulceration; in addition, the non-selective NSAIDs should be used with caution, if at all, in patients with a history of such disorders. To reduce the risk of gastrointestinal effects, NSAIDs may be taken with or after food or milk. Histamine H_2-antagonists, proton pump inhibitors such as omeprazole, or misoprostol may be used for a similar purpose in high-risk patients taking non-selective NSAIDs (see Peptic Ulcer Disease, p.1702). However, food, milk, and such measures may reduce the rate and extent of drug absorption. The UK CSM recommends that NSAIDs associated with the lowest risk of gastrointestinal toxicity (see Effects on the Gastrointestinal Tract, under Adverse Effects, above) should be tried first in the lowest recommended dose, and not more than one oral NSAID should be used at a time; selective inhibitors of cyclo-oxygenase-2 (COX-2) should be reserved for patients at highest risk of ulcer, perforation, or bleeding, and after assessment of cardiovascular risk. There is no evidence to justify the use of gastroprotective

drugs with selective inhibitors of COX-2 to further reduce the risk of gastrointestinal effects.

All NSAIDs are contra-indicated in severe heart failure; furthermore selective COX-2 inhibitors should not be used in patients with moderate heart failure, ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. NSAIDs should be used with caution in patients with hypertension; the selective COX-2 inhibitors should also be used with caution in patients with left ventricular failure, oedema, or a history of cardiac failure, and in patients with risk factors for developing heart disease.

NSAIDs should be used with caution in patients with infections, since symptoms such as fever and inflammation may be masked (for the suggestion that they should not be used in children with varicella see below). They should also be used with caution in patients with asthma or allergic disorders. NSAIDs (including topical NSAIDs) are contra-indicated in patients with a history of hypersensitivity reactions to such drugs, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.

Other general precautions to be observed include use in patients with haemorrhagic disorders or impaired renal or hepatic function. Patients undergoing therapy with some NSAIDs may need to be monitored for the development of blood, kidney, liver, or eye disorders. NSAIDs should be used with caution in the elderly and may need to be given in reduced doses.

Some NSAIDs can interfere with thyroid function tests by lowering serum-thyroid hormone concentrations.

Further details concerning the precautions of the individual NSAIDs may be found under their respective monographs.

Pregnancy. Most licensed product information recommends avoidance of NSAIDs during pregnancy, unless the proposed benefit outweighs the risks, but in many cases published data on use of the drugs in pregnancy is scanty or absent, making an informed decision difficult. Use of NSAIDs during pregnancy may delay the onset of labour and increase its duration.

Use of NSAIDs during the third trimester of pregnancy may result in the *premature closure of fetal ductus arteriosus*. A recent meta-analysis[1] suggested that the short-term use of NSAIDs was associated with a fifteen fold increase in the risk of premature closure when compared to either placebo or other non-NSAIDs. There was insufficient data to predict the outcome of long-term NSAID treatment in late pregnancy; however, it seemed likely that the risk of premature closure would be even greater with such treatment.

Results from a case-control interview study[2] suggested that prenatal ingestion of aspirin or other NSAIDs might be implicated in *persistent pulmonary hypertension* of the newborn. The authors suggested that these drugs may be responsible for gestational structural or functional alterations of the pulmonary vasculature. However, the primary cause might also have been the underlying disorder for which the NSAIDs or aspirin were ingested. They were unable to pinpoint in which trimester the drugs might have their proposed action. A more recent study[3] has found that persistent pulmonary hypertension of the newborn is significantly associated with *in-utero* NSAID exposure, particularly to aspirin, ibuprofen, and naproxen. Fetal exposure to an NSAID was confirmed by meconium analysis.

The risk of *miscarriage* may be increased with NSAID use;[4,5] however, this observation remains to be confirmed. One study[4] also found no association between NSAID use and congenital abnormalities, low birth weight, or preterm birth.

1. Koren G, *et al.* Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother* 2006; **40:** 824–9.
2. Van Marter LJ, *et al.* Persistent pulmonary hypertension of the newborn and smoking and aspirin and nonsteroidal antiinflammatory drug consumption during pregnancy. *Pediatrics* 1996; **97:** 658–63.
3. Alano MA, *et al.* Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. *Pediatrics* 2001; **107:** 519–23.
4. Nielsen GL, *et al.* Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. *BMJ* 2001; **322:** 266–70.
5. Li D-K, *et al.* Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003; **327:** 368–71.

Renal impairment. The *BNF* recommends that NSAIDs in general should be given at the lowest effective dose in patients with mild renal impairment and that renal function should be carefully monitored; they should be avoided if possible in patients with moderate to severe renal impairment.

See also under individual monographs.

Thyroid function tests. References[1,2] to the interference with thyroid function tests by some NSAIDs.

1. Bishnoi A, *et al.* Effect of commonly prescribed nonsteroidal anti-inflammatory drugs on thyroid hormone measurements. *Am J Med* 1994; **96:** 235–8.
2. Samuels MH, *et al.* Variable effects of nonsteroidal antiinflammatory agents on thyroid test results. *J Clin Endocrinol Metab* 2003; **88:** 5710–16.

Varicella. The French regulatory authorities noted in July 2004 that after the report of 3 cases of septic shock, 1 fatal, in children treated with NSAIDs for fever and pain, pharmacovigilance studies had discovered a number of other cases of severe complications relating to infection of the skin lesions of chickenpox in NSAID-treated children.[1] Although these, and a few reports in the literature[2,3] could not establish a causal relation, it was considered prudent to avoid the use of NSAIDs in children with chickenpox, and licensed product information for the relevant drugs was to be modified appropriately.[1] More recently, a nested case-control study[4] of nearly 250 000 patients with chickenpox or shingles in the UK General Practice Research Database found an increased risk of severe skin and soft tissue complications associated with the use of NSAIDs, mostly in children with chickenpox.

1. Agence Française de Sécurité Sanitaire des Produits de Santé. L'utilisation d'anti-inflammatoires nonstéroïdiens (AINS), dans le traitement de la fièvre et/ou de la douleur, n'est pas recommandée chez l'enfant atteint de varicelle (issued 15th July, 2004). Available at: http://www.agmed.sante.gouv.fr/htm/10/filltrpsc/lp040701.htm (accessed 08/11/07)
2. Zerr DM, *et al.* A case-control study of necrotizing fasciitis during primary varicella. *Pediatrics* 1999; **103:** 783–90.
3. Lesko SM, *et al.* Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. *Pediatrics* 2001; **107:** 1108–15.
4. Mikaeloff Y, *et al.* Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease. *Br J Clin Pharmacol* 2008; **65:** 203–9.

Interactions

Interactions involving NSAIDs include enhancement of the effects of oral anticoagulants (especially by azapropazone and phenylbutazone) and increased plasma concentrations of lithium, methotrexate, and cardiac glycosides. The risk of nephrotoxicity may be increased if given with ACE inhibitors, ciclosporin, tacrolimus, or diuretics. Effects on renal function may lead to reduced excretion of some drugs. There may also be an increased risk of hyperkalaemia with ACE inhibitors and some diuretics, including potassium-sparing diuretics. The antihypertensive effects of some antihypertensives including ACE inhibitors, beta blockers, and diuretics may be reduced. Convulsions may occur due to an interaction with quinolones. NSAIDs may increase the effects of phenytoin and sulfonylurea antidiabetics.

Use of more than one NSAID together (including aspirin) should be avoided because of the increased risk of adverse effects. The risk of gastrointestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids, the SSRIs, the SNRI venlafaxine, the antiplatelets clopidogrel and ticlopidine, iloprost, erlotinib, sibutramine, or, possibly, alcohol, bisphosphonates, or pentoxifylline. There may be an increased risk of haematotoxicity if zidovudine is used with NSAIDs. Ritonavir may increase the plasma concentrations of NSAIDs. Licensed product information for mifepristone advises of a theoretical risk that prostaglandin synthetase inhibition by NSAIDs or aspirin may alter the efficacy of mifepristone. There have been occasional reports of increased adverse effects when NSAIDs were given with misoprostol although such combinations have sometimes been used to *decrease* the gastrointestinal toxicity of NSAIDs.

Further details concerning the interactions of the individual NSAIDs may be found under their respective monographs.

◊ References.

1. Brouwers JRBJ, de Smet PAGM. Pharmacokinetic-pharmacodynamic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1994; **27:** 462–85.

Antihypertensives. For reference to the relative effects of NSAIDs in antagonising different types of antihypertensive drugs, see Effects on the Cardiovascular System and Effects on the Kidneys under Adverse Effects, above.

Aspirin. It has been suggested that NSAIDS such as ibuprofen may reduce the cardioprotective effect of aspirin but see under Interactions of Aspirin, p.23.

Pharmacokinetics

Details of the pharmacokinetics of individual NSAIDs may be found under their respective monographs.

◊ General reviews.

1. Woodhouse KW, Wynne H. The pharmacokinetics of non-steroidal anti-inflammatory drugs in the elderly. *Clin Pharmacokinet* 1987; **12:** 111–22.
2. Walson PD, Mortensen ME. Pharmacokinetics of common analgesics, anti-inflammatories and antipyretics in children. *Clin Pharmacokinet* 1989; **17** (suppl 1): 116–37.
3. Simkin PA, *et al.* Articular pharmacokinetics of protein-bound antirheumatic agents. *Clin Pharmacokinet* 1993; **25:** 342–50.
4. Lapicque F, *et al.* Protein binding and stereoselectivity of nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1993; **25:** 115–25.
5. Day RO, *et al.* Pharmacokinetics of nonsteroidal anti-inflammatory drugs in synovial fluid. *Clin Pharmacokinet* 1999; **36:** 191–210.

Uses and Administration

Given as single doses or in short-term intermittent therapy NSAIDs can relieve mild to moderate pain. However, it may take up to 3 weeks of use before their anti-inflammatory effects become evident. The combined analgesic and anti-inflammatory effects make them particularly useful for the symptomatic relief of painful and/or inflammatory conditions including rheumatic disorders such as rheumatoid arthritis, osteoarthritis, and the spondyloarthropathies, and also in peri-articular disorders, and soft-tissue rheumatism. Some NSAIDs are used in the management of dental or post-operative pain. Some NSAIDs, but not aspirin or other salicylates, are also used to treat acute gouty arthritis.

Generally, it is felt that there are only small differences in anti-inflammatory activity between the various NSAIDs and choice is largely empirical. Responses of individual patients vary widely. Thus, if a patient fails to respond to one NSAID, another drug may be successful. However, it has been recommended that NSAIDs associated with a low risk of gastrointestinal toxicity should generally be preferred and the lowest effective dose used. Treatment with NSAIDs that are selective inhibitors of cyclo-oxygenase-2 (COX-2), such as celecoxib, is limited in the UK to those patients with a history of serious gastrointestinal problems or considered to be at high risk of developing such problems if given a non-selective NSAID (see Effects on the Gastrointestinal Tract, above).

NSAIDs are usually given orally, with or after food, although some such as diclofenac, ketoprofen, ketorolac, parecoxib, piroxicam, and tenoxicam can be given intramuscularly; diclofenac, ketorolac, parecoxib, and tenoxicam can also be given intravenously. Some NSAIDs are applied topically or given rectally as suppositories.

Several NSAIDs are used in ophthalmic preparations for the inhibition of intra-operative miosis, control of postoperative ocular inflammation, and prevention of cystoid macular oedema.

Action. Cyclo-oxygenases play an important role in the biosynthesis of prostaglandins (p.2374). Non-selective NSAIDs inhibit both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2); the idea that inhibition of COX-1 is associated with adverse gastrointestinal effects while inhibition of COX-2 is associated with anti-inflammatory activity,[1-6] led to the development[7] of preferential or selective inhibitors of COX-2. Meloxicam and nimesulide are preferential inhibitors of COX-2, (i.e. they have a higher selectivity for COX-2 than COX-1 but are not exclusive COX-2 inhibitors); etodolac and nabumetone are also claimed to have preference for COX-2 although there is less evidence for this. Drugs with a very high selectivity for COX-2 are also available; celecoxib and parecoxib are two examples. Although the selective inhibition of COX-2 may be associated with reduced gastrointestinal toxicity, adverse effects associated with such inhibition have been noted in other body systems, see Thrombotic Events under Effects on the Cardiovascular System, and Effects on the Kidneys, above.

There is evidence that NSAIDs may also have a central mechanism of action that augments the peripheral mechanism.[6]

Many NSAIDs possess centres of chirality within their molecular structure, with different chiral forms (enantiomers) having different degrees of pharmacological activity.[8,9] For example, in-

dometacin, its analogues, and some arylpropionic acids are chiral drugs with the S(+)-enantiomer in most cases showing the dominant pharmacological activity. However, the ratio of S/R activity varies between drugs and between *animal* species. NSAIDs are generally used clinically as the racemate with only a few currently being given as the (S)-enantiomer (for example, dexibuprofen and dexketoprofen). The chirality of a drug may have subtle effects on its toxicity and interactions, and it may be more desirable to use a drug as its active enantiomer.[9]

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Colic pain. Prostaglandins have been implicated in the aetiology of biliary colic (p.5), and some NSAIDs such as diclofenac, indometacin, and ketoprofen have been used to relieve such pain.

Dementia. A systematic review[1] of observational studies suggested that the risk of developing dementia (p.362) is lower in patients who are taking NSAIDs. However, a randomised trial[2] found no benefit from treatment with naproxen or rofecoxib in patients with existing mild to moderate Alzheimer's disease. Another systematic review[3] has suggested that the beneficial effects of NSAIDs seen in some studies are likely to be due to biases such as recall introduced by the study's design; the benefit of NSAIDs in preventing dementia or cognitive impairment was 50% in studies with prevalent (pre-existing) dementia cases, which decreased to 20% in studies of incident dementia cases (those developing during the study period), and was absent in those which used cognitive decline as an end-point. Further studies are needed to determine the role of NSAIDs in dementia.[4,5]

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Diabetes insipidus. NSAIDs such as indometacin have been used in the treatment of diabetes insipidus; for some references, see p.68.

Ectopic ossification. Ectopic ossification (heterotopic ossification) is a condition in which mature bone develops in non-skeletal tissues, commonly the connective tissue of muscles. It occurs after local trauma, for example after joint dislocation or surgery such as total hip replacement, and also after neurological damage such as severe head or spinal cord injuries.[1,2] Ectopic bone formation usually starts about 2 weeks after the injury, though symptoms, which include localised pain, fever, swelling, erythema, and restriction of movement, may not appear for 8 to 12 weeks.[1,3] Neurogenic ectopic ossification may develop even several years after spinal cord injury.[3] A congenital form of ectopic ossification, myositis ossificans progressiva (fibrodysplasia ossificans progressiva), also occurs but is rare. The principal complications of ectopic ossification are loss of joint mobility and function.[1,2]

Ectopic ossification should be distinguished from the calcification of soft tissue which may occur in connective tissue disorders or in parathyroid disorders as a result of high circulating concentrations of calcium and or phosphate; in these conditions calcification occurs without bone formation.

Surgical resection can improve joint motion[1,3] in patients with ectopic ossification, but may be associated with severe complications and poor outcome, and ossification may recur postoperatively.[3] Delaying surgery as long as possible until bone formation has decreased may lessen the likelihood of these complications,[1] although earlier surgery may prevent fibrous ankylosis and muscle contracture.[3] Although there is no consensus on treatment, early, regular and cautious physiotherapy is recommended to mobilise joints;[1-3] aggressive manipulation may cause further ossification.

Prophylactic measures include radiotherapy or drug therapy. While prophylaxis does not always prevent the development of ectopic ossification, it can decrease its occurrence and severity. Prophylactic measures should be begun as early as possible and with regard to orthopaedic surgery may be started before the operation. Prophylaxis is also required if mature ectopic bone is to be surgically excised in order to minimise the rate of recurrence. Low-dose radiotherapy is as effective as high-dose, and pre-operative irradiation is as effective as postoperative.[4] Studies suggest that NSAID prophylaxis is of similar efficacy to radiotherapy.[4] NSAIDs appear to significantly reduce the incidence of ectopic bone formation,[2-5] possibly by inhibiting inflammation and suppressing mesenchymal cell proliferation.[3] While controversy exists as to duration and doses, indometacin is considered the NSAID of choice by some; naproxen, tenoxicam, and diclofenac may also be of benefit.[4] Ibuprofen has been tried; however, a recent study[6] has found that, although it significantly reduced the rate of ectopic bone formation, there were no clinical benefits 6 to 12 months after surgery. Bisphosphonates that inhibit the mineralisation of the deposited bone, such as etidronate, have also been used but they do not prevent the formation of the osteoid matrix. Also when etidronate is stopped, some mineralisation can occur, resulting in delayed ectopic or rebound ossification, though it is usually less severe. Prolonged treatment may be needed.[2,3] A systematic review,[7] however, found insufficient evidence to recommend the use of etidronate for the treatment of acute ectopic ossification.

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Eye disorders. Miosis resistant to conventional mydriatics often develops during ocular surgery, possibly due to release of prostaglandins and other substances associated with trauma. NSAIDs, which are prostaglandin synthetase inhibitors, are therefore used prophylactically as eye drops before ocular surgery to ameliorate intra-operative miosis but there has been some doubt that the effect they produce is of clinical significance. Those commonly used include diclofenac, indometacin, and flurbiprofen. These drugs do not possess intrinsic mydriatic properties.

Some NSAIDs are used topically or systemically in inflammatory ocular disorders, including inflammation and cystoid macular oedema following ocular surgery (see below). Topical NSAIDs are also effective analgesics when used in the management of corneal abrasions. However, their role in the treatment of macular oedema associated with uveitis (p.1515) is less clear. NSAIDs are also used in the treatment of scleritis (see p.1512). Diclofenac and ketorolac have also both been used in the management of seasonal allergic conjunctivitis (see p.564).

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POSTOPERATIVE INFLAMMATORY OCULAR DISORDERS. Corticosteroids are used topically for the control of **postoperative ocular inflammation** but caution is required as they can delay wound healing and mask postoperative infection. They should only be used for short periods as they can cause glaucoma in susceptible individuals. Topical NSAIDs have also been tried and appear to be as effective as corticosteroids in controlling signs of inflammation after ocular surgery,[1] but there has been some concern about reports of corneal toxicity (see p.45).

Cystoid macular oedema may follow cataract or retinal detachment surgery due to a disturbance of the blood-retinal barrier. A number of NSAIDs,[1-7] including diclofenac, flurbiprofen, indometacin, and ketorolac are used topically with or without corticosteroids to prevent or relieve cystoid macular oedema. NSAIDs such as indometacin are also used systemically in its management. However, a recent systematic review[6,7] has found insufficient evidence for the efficacy of NSAIDs (topical and oral) in acute or chronic cystoid macular oedema after cataract surgery although topical ketorolac may have a positive effect in chronic disease.

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6. Sivaprasad S, *et al.* Non-steroidal anti-inflammatory agents for cystoid macular oedema following cataract surgery: a systematic review. *Br J Ophthalmol* 2005; **89:** 1420–2.
7. Sivaprasad S, *et al.* Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 31/10/07).

Fever. Paracetamol, salicylates, and some other NSAIDs are the main antipyretics used to control fever (p.10). Paracetamol is usually the antipyretic of choice in infants and children but ibuprofen is an effective alternative; alternation of the two may be better than either alone, although this is controversial. Salicylates are generally contra-indicated in these patients because of the possible link between their use and the development of Reye's syndrome (see under Adverse Effects of Aspirin, p.22).

Gout. NSAIDs are the drugs usually used first for the treatment of acute attacks of gout (p.552). Since the drug treatment of chronic gout can lead to the mobilisation of urate crystals from established tophi to produce acute attacks, NSAIDs may also be used for the prophylaxis of acute gout during the first few months of urate-lowering therapy.

Headache. An NSAID is often tried first for the symptomatic treatment of various types of headache including migraine (p.616) and tension-type headache (p.617). NSAIDs may also be effective prophylactic drugs for migraine, although propranolol is generally preferred. Paroxysmal hemicrania, a rare variant of cluster headache (p.616), responds to indometacin.

Kidney disorders. Although NSAIDs can produce adverse effects on the kidney (see above) they may have a role in the management of some types of glomerular kidney disease (p.1504). They may be of use for the control of proteinuria due to nephrotic syndrome except when there is overt renal failure.

Malignant neoplasms. An early study by the American Cancer Society[1] suggested that regular use of aspirin might reduce the risk of developing fatal cancer of the oesophagus, stomach, colon, or rectum. Death rates due to other gastrointestinal cancers did not appear to be affected. Some studies[2-11] appear to support this reduced risk of colorectal cancer (see Prophylaxis, under Malignant Neoplasms of the Gastrointestinal Tract, p.666) in regular users of aspirin or other NSAIDs, particularly in high-risk patients, conclusions that were cautiously endorsed by a systematic review.[12] However, other studies[13,14] have found no evidence of an association between the use of aspirin or NSAIDs and the incidence of colorectal cancer, although the authors suggest that these results may be explained by the short treatment period and the low dose of aspirin used. Although a subsequent review[15] prepared for the US Preventive Services Task Force (USPSTF) indicated that cyclo-oxygenase-2 (COX-2) inhibitors and NSAIDs reduce the incidence of colonic adenomas and that NSAIDs also reduce the incidence of colorectal cancer, the USPSTF issued a statement[16] that, because of the adverse cardiovascular and gastrointestinal effects associated with these agents, their use to prevent colorectal cancer could not be recommended in those at average risk of colorectal cancer.

The potential role that inhibition of COX-2 may play in the management of cancer has been discussed[17,18] and a recent study[19] has found that regular use of aspirin appears to reduce the risk of colorectal cancers that overexpress COX-2 but not those with weak or absent expression of COX-2.

A large case-control study,[20] using data held on the UK general practice research database, has examined information on NSAID use and the development of common cancers. This study also found that the use of NSAIDs (including aspirin) may protect against cancer of the oesophagus, stomach, colon, and rectum. However, the study failed to show any decrease in risk of non-gastrointestinal cancers. More recently, 2 meta-analyses[21,22] have also suggested that aspirin and NSAID use reduce the risk of other gastrointestinal cancers such as oesophageal or stomach cancer. In addition, one analysis[21] considered the effect of NSAID and aspirin use on non-gastrointestinal cancers: aspirin use showed a chemoprotective effect in pancreatic cancer although this was not significant statistically; there was also a slight, but nonetheless significant, reduction in the risk of breast cancer associated with both aspirin and NSAID use. The results for other sites, namely ovary, lung, bladder, and prostate, suggested no effect or possibly a slight reduced risk. The authors considered that it was unclear if any potential benefit in non-gastrointestinal cancers may be offset by the known adverse effects associated with the long-term use of these drugs particularly in those cancers with a low incidence.

Treatment with sulindac (see Gastrointestinal Disorders, p.127) has been found to reduce the number of polyps in patients with familial adenomatous polyposis, a condition which predisposes to development of colorectal cancer. Celecoxib has similar effects (see p.36) and it is now licensed for use in such patients.

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22. Wang WH, *et al.* Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2003; **95:** 1784–91.

Menstrual disorders. Menorrhagia (p.2126) is thought to be associated with abnormalities of prostaglandin production. Treatment with NSAIDs such as ibuprofen, mefenamic acid, or naproxen during menstruation, can reduce uterine blood loss by an average of 30% in women with menorrhagia. There does not appear to be any evidence that one NSAID is more effective than another.

NSAIDs are usually the first choice for the pain of dysmenorrhoea (p.6). Mefenamic acid may have a theoretical advantage over other NSAIDs in being able to inhibit both the synthesis and the peripheral action of prostaglandins, but clinical studies have not shown fenamates to be more effective, and systematic review has suggested that ibuprofen may have the best risk/benefit ratio.

Migraine. See Headache, above.

Orthostatic hypotension. Fludrocortisone is usually the first drug tried in the treatment of orthostatic hypotension (p.1530) when nonpharmacological treatment has failed. NSAIDs such as flurbiprofen, ibuprofen, or indometacin may be used alone or added to treatment if the response is inadequate.

Pain. NSAIDs have a similar analgesic effect to aspirin and paracetamol in single doses but, in regular full dosage, they have both a lasting analgesic and an anti-inflammatory effect. They are used in the management of mild to moderate pain (see Choice of Analgesic, p.2) and are of particular value in pain due to inflammation. NSAIDs may be of benefit for inflammatory pain in infants and children (p.3), although paracetamol is generally the preferred non-opioid analgesic in this age group. NSAIDs may be used in the treatment of acute low back pain (p.7) if paracetamol fails to provide adequate pain relief. NSAIDs may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p.5) and are particularly effective in bone pain of malignant origin. NSAIDs may be used for postoperative analgesia (p.4), and are of particular value after day-case surgery because of their lack of sedative effects. They are not usually considered to be strong enough as the sole analgesic after major surgery, but may be used with stronger analgesics and may allow dosage reduction of opioids. The pain of mild sickle-cell crises (p.9) may be controlled by analgesics such as NSAIDs or less potent opioids, for example codeine or dihydrocodeine; NSAIDs may be used with more potent opioids such as morphine for severe crises.

Dependence and tolerance are not a problem with non-opioid analgesics such as NSAIDs, but there is a ceiling of efficacy, above which, increasing the dose has no further therapeutic effect.

Rheumatic disorders. NSAIDs provide symptomatic relief for rheumatic disorders such as rheumatoid arthritis (p.11) and spondyloarthropathies (p.13), but they do not alter the course of the disease and additional antirheumatic drugs may need to be given to prevent irreversible joint damage. NSAIDs may also be used as an alternative to paracetamol for osteoarthritis (p.11). Short-term use of oral NSAIDs may help to relieve pain and reduce inflammation of soft-tissue rheumatism (p.13); topical formulations of some NSAIDs are also used.

Scleroderma. NSAIDs should be used with caution in scleroderma (p.1817) because of the risk of exacerbating renal and other problems.

Opioid Analgesics

Analgésicos opioides u opiáceos; Analgésiques Opioïdes; Opioid-analgetika.

Опиоидные Аналгетики

Dependence and Withdrawal

Repeated use of opioids is associated with the development of psychological and physical dependence. Although this is less of a problem with legitimate therapeutic use, dependence may develop rapidly when opioids are regularly abused for their euphoriant effects. Drug dependence of the opioid type is characterised by an overwhelming need to keep taking the drug (or one with similar properties), by a physical requirement for the drug in order to avoid withdrawal symptoms, and by a tendency to increase the dose owing to the development of tolerance.

Abrupt withdrawal of opioids from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose, and the duration of drug use. Withdrawal symptoms may also follow the use of an opioid antagonist such as naloxone or a mixed agonist and antagonist such as pentazocine in opioid-dependent persons. Neonatal abstinence syndrome may occur in the offspring of opioid-dependent mothers and these infants can suffer withdrawal symptoms at birth.

Opioid analgesics can be classified according to the receptors at which they act (see Uses and Administration, below) and withdrawal syndromes are characteristic for a receptor type. Cross-tolerance and cross-dependence can be expected between opioids acting at the same receptors. Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than those associated with κ-receptor agonists. Onset and duration of withdrawal symptoms also vary according to the duration of action of the specific drug. With morphine and diamorphine *withdrawal symptoms* usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside; they develop more slowly with methadone. Withdrawal symptoms include yawning, mydriasis, lachrymation, rhinorrhoea, sneezing, muscle tremor, weakness, sweating, anxiety, irritability, disturbed sleep or insomnia, restlessness, anorexia, nausea, vomiting, loss of weight, diarrhoea, dehydration, leucocytosis, bone pain, abdominal and muscle cramps, gooseflesh, vasomotor disturbances, and increases in heart rate, respiratory rate, blood pressure, and temperature. Some physiological values may not return to normal for several months after the acute withdrawal syndrome.

Withdrawal symptoms may be terminated by a suitable dose of the original or a related opioid. Tolerance diminishes rapidly after withdrawal so that a previously tolerated dose may prove fatal.

For a discussion of the treatment of opioid dependence and neonatal abstinence syndrome, see below.

◊ Review.

1. Van Ree JM, *et al.* Opioids, reward and addiction: an encounter of biology, psychology, and medicine. *Pharmacol Rev* 1999; **51:** 341–96.

Diagnosis. Naloxone (p.1455) and other opioid antagonists have been used to diagnose opioid dependence.

Treatment of opioid dependence. The treatment of opioid dependence has been the subject of a number of reviews and discussions.[1-10]

Planned withdrawal (**detoxification**) may be effected slowly or rapidly. The usual method in many countries is to replace the drug of dependence with *methadone* (an opioid agonist) given as a liquid oral preparation, and then gradually withdraw the methadone if possible. Methadone is suitable for withdrawal therapy because it can be given orally and its long half-life allows once daily use. Oral *diamorphine* has been used similarly to methadone; reefers containing diamorphine have also been used in some centres. *Dihydrocodeine* tablets have been used successfully. The partial opioid agonist *buprenorphine*, given sublingually, is another alternative to methadone in the treatment of opioid dependence, and withdrawal symptoms may possibly resolve more quickly than with methadone.[11] However, it should only be given to patients with moderate dependence; those dependent on high doses of opioids may experience withdrawal symptoms when given buprenorphine. The methadone derivative *levacetylmethadol* was a more recent introduction but its proarrhythmic effects have led to its use being suspended.

Iatrogenic opioid dependence may occur in patients receiving μ-agonists such as morphine, fentanyl, or pethidine for the management of acute pain or in an intensive care setting for more than 5 to 10 days. Methadone has been used successfully to manage opioid withdrawal in adult intensive care patients.[12] However, some[13] avoid using methadone to manage withdrawal in children because of the stigma of its associations with managing withdrawal in drug addicts. In physically dependent but non-addicted patients, gradual weaning using the same opioid that was used therapeutically is preferred where possible, although in some cases, it may be necessary to change to a different opioid because of ease of use, duration of action, and ability to taper the dose; virtually any opioid can be used.[13]

Other drugs used in the management of opioid withdrawal include alpha$_2$-adrenoceptor agonists such as *clonidine* and opioid antagonists such as *naltrexone* and *naloxone*. Clonidine may help to suppress symptoms of opioid withdrawal, such as anxiety, insomnia, and muscle aches. It appears to be more effective when used in the control of symptoms after abrupt withdrawal than when used during gradual withdrawal of methadone. Hypotension may limit its usefulness in some patients. The clonidine analogue *lofexidine* may produce similar results to those obtained with clonidine and appears to be less sedating and hypotensive.[14]

Naltrexone and naloxone block the euphoriant effects of opioids although their use as monotherapy in detoxification is limited by unacceptable opioid withdrawal effects. Naltrexone may be used with alpha$_2$-adrenoceptor agonists such as clonidine or lofexidine to ameliorate symptoms but there are insufficient data to determine whether such combinations reduce the duration of withdrawal treatment or increase the rate of transfer to maintenance therapy with an opioid antagonist.[15] Naloxone and naltrexone are also being used in the relatively new technique of rapid or ultra rapid opioid detoxification,[16-18] which is achieved while the patient is heavily sedated or under *general anaesthesia* and hence unaware of any unpleasant withdrawal symptoms. However, although detoxification may be achieved within 24 hours and has a high initial success rate, the technique itself is not without risks and it does not obviate the need for maintenance treatment (see below).

Concomitant counselling and other psychosocial services have been shown to be important in the outcome of withdrawal therapy.[19,20] Detoxification alone does not ensure long-term abstinence.

A number of other drugs may be of use as **adjuncts** in the management of withdrawal symptoms. *Diphenoxylate* with atropine or *loperamide* may be used for the control of diarrhoea. *Promethazine* has been used for its antiemetic and sedative actions. Beta blockers such as *propranolol* may be of use for patients with pronounced somatic anxiety symptoms. *Benzodiazepines* or *clomethiazole* can be given to relieve anxiety and associated insomnia but only short courses should be used in order to minimise the risk of dependence and abuse.

Long-term **maintenance** treatment (stabilisation treatment) with an opioid is sometimes used, in conjunction with psychosocial support, to enable the patient to acquire some form of social stability. *Methadone* is most commonly used; the use of *diamorphine* although feasible[21,22] is controversial[23] and is advocated by only a few individual centres. *Buprenorphine* is another possibility.[24] The use of methadone for maintenance has been reviewed.[25-27] *Naltrexone* can be effective in maintaining abstinence in opioid addicts after detoxification, especially after rapid or ultra rapid detoxification. It is considered that naltrexone would probably be of most use in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids.[1,28,29]

The problems associated with the management of the **pregnant** patient with opioid dependence have been discussed.[30] The aim should be to stabilise the patient first using *methadone* since acute withdrawal can result in fetal death. Drug withdrawal is best done slowly during the second trimester. It has been suggest-