

FFPRHC Guidance (April 2005)

Drug interactions with hormonal contraception

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This Guidance provides information for clinicians and women using hormonal contraception applicable when concurrent medications are prescribed. A key to the grades of recommendations, based on levels of evidence, is given at the end of this document. Details of the methods used by the Clinical Effectiveness Unit (CEU) in developing this Guidance and evidence tables summarising the research basis of the recommendations are available on the Faculty website (www.ffprhc.org.uk). Abbreviations (in alphabetical order) used include: CEU, Clinical Effectiveness Unit; COC, combined oral contraceptive/contraception; DMPA, depot medroxyprogesterone acetate; EE, ethinylestradiol; ENG, etonorgestrel; IUD, copper-bearing intrauterine contraceptive device; LNG, levonorgestrel; LNG-IUS, levonorgestrel-releasing intrauterine system; POC, progestogen-only contraceptive/contraception; POP, progestogen-only pill; SJW, St John's Wort; WHO, World Health Organization; WHOMEC, WHO Medical Eligibility Criteria for Contraceptive Use; WHOSPR, WHO Selected Practice Recommendations for Contraceptive Use.

Background

This Guidance updates a Faculty Aid to Continuing Professional Development Topic (FACT) on drug interactions with hormonal contraception.¹ This Guidance does not consider the effects on hormonal contraception of the underlying condition that necessitated concurrent medication.

Potential drug interactions should be considered when prescribing any medication for women of reproductive age. Concentrations of contraceptive hormones may be increased or decreased by concomitant drug use. Contraceptive hormones may themselves increase or decrease serum concentrations of concomitant drugs. Drug interactions that result in a reduction in contraceptive efficacy are clinically relevant. Factors that influence the clinical significance of interactions include: narrow therapeutic ranges of drugs or hormones, wide individual variation in serum concentrations of drugs or hormones, and poor compliance.

There is a lack of good quality, robust evidence on the effects of drugs on hormonal contraception. Most data have been obtained from case reports, which provide limited evidence. Pregnancy has been reported in women using hormonal contraception following use of concomitant drugs.^{2–6} Nevertheless, this does not prove that the drug was responsible for contraceptive failure leading to pregnancy.

The *British National Formulary (BNF)* provides clinicians with information on potential drug interactions. Nevertheless, the BNF uses information from Summaries of Product Characteristics (SPCs), which may not reflect current evidence. This evidence-based Guidance summarises evidence on interactions between hormonal contraception and liver enzyme-inducing drugs, non-liver enzyme-inducing antibiotics, drugs which may be toxic if serum concentrations increase, and on commonly used drugs (prescription and non-prescription) which do and do not affect contraceptive efficacy.

Further research into drug interactions and hormonal contraception is needed to guide clinical practice and should be encouraged.

How might concomitant drugs affect contraceptive hormones?

Drug interactions may result from alterations in pharmacodynamics or pharmacokinetics.⁷

Pharmacodynamic interactions occur when one drug directly influences the action of another by synergy or antagonism. There are no important pharmacodynamic interactions relevant for hormonal contraception.

Pharmacokinetic interactions occur during the processes of drug absorption, distribution, metabolism or elimination. Pharmacokinetic interactions are relevant to contraceptive hormones (as summarised in Figure 1).

Bioavailability is the amount of hormone available to have clinical effect (e.g. inhibition of ovulation or cervical mucus thickening). There are wide inter- and intra-individual variations in the bioavailability of ethinylestradiol (EE) and progestogens.⁸ Bioavailability of contraceptive hormones depends primarily on absorption (including secondary absorption via the enterohepatic circulation) and metabolism.

Absorption

Orally administered EE and progestogens are absorbed from the small intestine. Drugs that affect the absorption of hormones may theoretically reduce bioavailability but no evidence was identified to support this. Drugs that induce vomiting may indirectly affect hormone absorption. If vomiting occurs less than 2 hours after ingesting hormonal contraception, women are advised to take a further dose.^{9–11} It is unclear whether crushing or chewing contraceptive pills can affect absorption. A chewable combined oral contraceptive (COC) is available in the USA. This should be taken with a glass of water to ensure all of the dose reaches the stomach.¹²

Both EE and progestogens can be absorbed directly into the systemic circulation (thus bypassing first-pass metabolism in the intestinal mucosa and liver). Progestogens and EE are absorbed transdermally via the combined contraceptive patch¹³ or vaginally via a contraceptive ring.¹⁴

When progestogen is administered as an etonorgestrel (ENG) subdermal implant, almost 100% is bioavailable.

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Table 1 Drugs that induce liver enzymes and relevant associated drugs that do not induce liver enzymes

Type of drug	Liver enzyme induction	Effect	No liver enzyme induction	Effect
Anti-epileptic	Carbamazepine Oxcarbazepine Phenytoin Phenobarbital Primidone Topiramate	Reduction in ethinylestradiol (EE) and progestogens ^{28–31}	Ethosuximide Gabapentin Lamotrigine Levetiracetam Valproate Vigabatrin	No reduction in EE or progestogens ^{32–36}
Antibiotic	Rifampicin Rifabutin	Reduction in EE and progestogen, breakthrough bleeding ^{27,58,59}	All other antibiotics narrow- and broad-spectrum	Potential reduction in EE due to effect on gut flora
Antifungal	Griseofulvin	Known to be a potent liver enzyme-inducer, pregnancies documented ⁴⁵	Fluconazole Itraconazole Ketoconazole	No alterations in EE or progestogens ^{55,56} Breakthrough bleeding, no ovulation ^{51–54}
Antiretroviral	<i>Protease inhibitors</i> Amprenavir Atazanavir Nelfinavir Lopinavir Saquinavir Ritonavir <i>Non-nucleoside reverse transcriptase inhibitors</i> Efavirenz Nevirapine	Reduction in EE and progestogen but additional or alternative contraceptive methods advised with hormonal contraception ⁷⁹ EE reduced ⁸⁰ Reduction in EE and progestogen. Additional or alternative contraceptive methods advised with hormonal contraception ⁷⁹	<i>Protease inhibitors</i> Indinavir <i>Nucleoside reverse transcriptase inhibitors</i> Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir Zalcitabine Zidovudine	No clinically significant interaction ⁷⁹ No evidence for pharmacokinetic interactions with EE and progestogens identified
Gastrointestinal	Lansoprazole	Can induce liver enzymes but no reduction in EE ^{83,84}		
Immunosuppressant	Tacrolimus	Can induce liver enzymes but no published evidence of reduced contraceptive efficacy		
Respiratory	Bosentan	Induces liver enzymes but no evidence published for efficacy of hormonal contraception	Anti-asthmatic drugs	No effect on hormonal contraception
Central nervous system	Modafinil	Known liver enzyme-inducer ^{27,86}	Selective serotonin reuptake inhibitors	No effect on contraceptive efficacy suspected

Serum ENG concentrations increase rapidly within 8 hours of insertion and peak after 4 days.^{15,16} Levels reach steady state (200 pg/ml) after 4–6 months. These low concentrations are sufficient to inhibit ovulation for 3 years.¹⁶

Following a single intramuscular injection of medroxyprogesterone acetate (MPA), progestogen is absorbed from its injection site and metabolised in the liver. Serum concentrations of MPA are relatively constant for 2–3 months (1 ng/ml).¹⁷ Repeat injections at 12-weekly intervals maintain serum concentrations of MPA. If not repeated, serum concentrations gradually decline and by 6 months reach concentrations (0.2 ng/ml) that cannot inhibit ovulation. MPA has been identified in serum 9 months after a single injection.¹⁸

Following a single intramuscular injection of norethisterone enanthate, serum concentrations of norethisterone and norethisterone enanthate peak at 7 days¹⁹ and the injection is repeated after 8 weeks to maintain serum concentrations. Anovulation has been demonstrated even after 12 weeks.²⁰

Distribution

Once absorbed, EE and progestogens are transported to the liver in blood, bound to albumin or sex hormone-binding globulin, or free (unbound).⁷

Metabolism

Orally administered EE and progestogens undergo extensive ‘first-pass metabolism’ in the small intestinal mucosa and liver before reaching the systemic circulation.^{21,22} As much as 60% of orally administered EE undergoes first-pass metabolism and thus only 40% is bioavailable. The bioavailability of progestogens varies. Some hormones are ingested in inactive forms (prodrugs) and are active only after metabolism. For example, mestranol is metabolised to EE; desogestrel is metabolised to 3-ENG; norgestimate is in part metabolised to levonorgestrel; and ethynodiol diacetate is metabolised to norethisterone.¹

EE is metabolised in the mucosa of the small intestine and in the liver, forming sulphate and glucuronide conjugates (Figure 1).

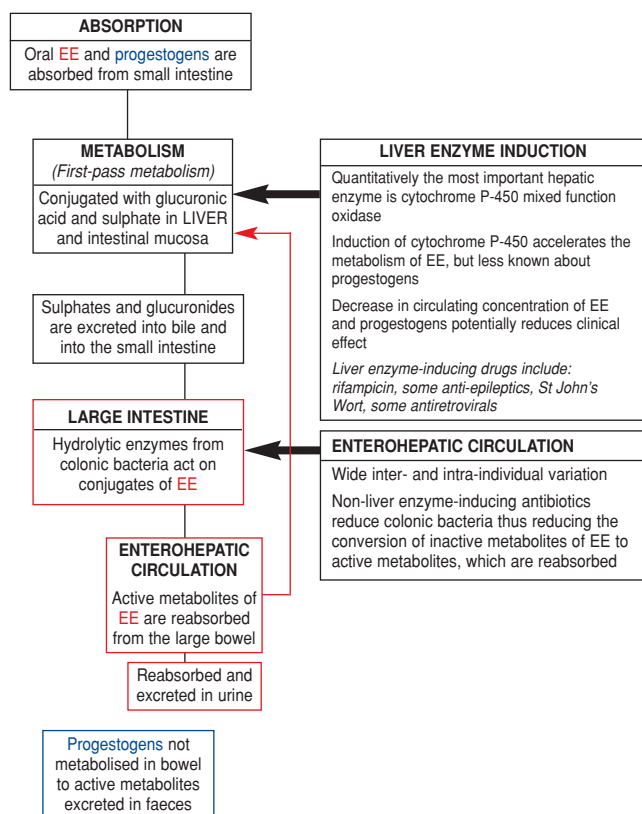


Figure 1 Pharmacokinetics of ethinylestradiol (EE) and progestogens and interaction with liver enzyme-inducing drugs and antibiotics

Microsomal enzymes involved in metabolism of contraceptive hormones and other drugs are found in liver and intestinal mucosal cells. There are two types of microsomal enzymes: Phase I enzymes (mixed-function oxidases), which catalyse oxidation, reduction and hydrolysis; and Phase II enzymes, which catalyse glucuronidation, sulphation and acetylation.^{21–23} Cytochrome P-450 is the most important family of enzymes in drug metabolism and CYP3A4 is the major subtype found in adult hepatocytes and intestinal mucosal cells. There is marked interindividual variation in the activity of cytochrome P-450. Drugs that inhibit or induce cytochrome P-450 may affect concurrent medications.

If cytochrome P-450 is *induced*, the metabolism of concomitant drugs is increased, potentially reducing the clinical effect. Drugs known to be potent inducers of liver enzymes are listed in Table 1. Once started, these drugs may induce liver enzymes within 2 days and the effects are maximal within 1 week. After cessation, liver enzymes return to their normal functionality in 4 weeks.

If cytochrome P-450 is *inhibited*, the metabolism of concomitant drugs is decreased, potentially leading to toxicity. Inhibition of liver enzymes is less relevant for women using hormonal contraceptives, as toxicity with EE or progestogens rarely occurs. Inhibition occurs as soon as the inhibitor appears in the liver and is maximal within 24 hours.

Excretion and the enterohepatic circulation

After metabolism, conjugates of EE, unaltered EE and progestogens are excreted into bile and subsequently released into the small intestine. Conjugates cannot be absorbed from the small intestine.

In the large intestine, conjugates are broken down by hydrolytic enzymes released from colonic bacteria (clostridia, *Bacteroides* species, lactose-fermenting coliforms and some staphylococci). Conjugates are broken down into free (active) metabolites, which can be reabsorbed. These are eventually excreted in urine.

The degree of reabsorption of EE via the enterohepatic circulation may vary between individuals. The importance of this reabsorption of EE, in terms of contraceptive efficacy, is unclear. For some women it may be important, especially if contraceptive pills are missed. Women who have had a colectomy and ileostomy have no enterohepatic circulation of EE. The efficacy of combined oral contraception (COC) does not appear to be reduced in this situation.²⁴

There is no enterohepatic circulation of progestogens and therefore antibiotics that eliminate colonic bacteria do not affect progestogen-only contraceptives (POCs).

What should be discussed when prescribing drugs to women using hormonal contraception?

- 1 Clinicians should consider the possibility of a drug interaction when prescribing contraception and when prescribing other medicines to women using hormonal contraception (Good Practice Point).**
- 2 Clinicians giving women information on contraceptive options should enquire about: current and previous drug use; prescription, non-prescription and herbal drug use; and specifically about use of drugs which induce liver enzymes and non-liver enzyme-inducing antibiotics (Good Practice Point).**
- 3 Women should be informed that some drugs might reduce the effectiveness of hormonal contraception and should be advised where to seek advice if other drugs are taken (Good Practice Point).**
- 4 After counselling, women using short courses of drugs that interact with hormonal contraception may choose to continue their current hormonal method even if additional contraception, such as condoms, is required. However, women on long-term courses of drugs that continue to interact with hormonal contraception should be encouraged to consider a contraceptive method that is unaffected by the interacting drug (Good Practice Point).**

The contraceptive efficacy of hormonal contraception [with the exception of the progestogen-only injectable or the levonorgestrel-releasing intrauterine system (LNG-IUS)] is reduced by liver enzyme-inducing drugs. Non-liver enzyme-inducing antibiotics are used relatively frequently. The enterohepatic circulation of EE may be reduced and therefore the efficacy of combined contraception may be reduced. Evidence for this will be provided in the following sections.

Women using hormonal contraception should be advised that some drugs could reduce contraceptive efficacy. Women should be advised to seek advice about interacting medication from their general practitioner, local family planning service, local pharmacy or the fpa (Family Planning Association) in the first instance when a new drug is used.

The length of time a woman has to take a drug that interacts with her hormonal contraception may influence her contraceptive choices. For example, a woman using COC and given a short course of non-liver enzyme-inducing antibiotic (e.g. treatment of urinary tract infection) or a liver enzyme-inducing antibiotic (e.g. prophylaxis against meningitis) may continue with COC with additional contraception, such as condoms, until contraceptive efficacy is restored. A woman using COC

who requires long-term treatment of epilepsy or tuberculosis (with liver enzyme-inducing drugs) or frequent courses of antibiotics (e.g. cystic fibrosis) should be advised to consider another method of contraception that is unaffected by concomitant drug use.

The underlying condition for which drugs are being used can also affect contraceptive choices and should be taken into consideration when counselling women. For example, women with epilepsy using drugs which induce liver enzymes may choose to continue with an increased dose of COC and condoms.²⁵ For women with epilepsy who have associated memory problems, a contraceptive method that avoids daily pill taking and is unaffected by drug use may be preferred. Full discussion of other underlying conditions is outside the scope of this Guidance.

Which drugs may reduce the efficacy of hormonal contraception?

Drugs that induce liver enzymes (Table 1) are used to treat a number of conditions and may reduce the efficacy of hormonal contraception by increasing the metabolism of EE and progestogens. The use of antibiotics that do not induce liver enzymes may also reduce the efficacy of some hormonal contraceptives by altering colonic bacteria. Evidence on interactions between these two types of drugs and hormonal contraception are summarised in this section.

Liver enzyme-inducing drugs

5 Women should be informed that drugs which induce liver enzymes can reduce the efficacy of combined hormonal contraception, progestogen-only pills (POPs), and implants but do not appear to reduce the efficacy of progestogen-only injectables or the LNG-IUS (Grade C).

Liver enzyme-inducing drugs increase the metabolism of EE and progestogens.^{21–24,26} EE and progestogens have a narrow therapeutic range, and a decrease in bioavailability may lead to decreased contraceptive efficacy. Table 1 lists those drugs that induce liver enzymes and relevant associated drugs that do not. Details on all liver enzyme-inducing drugs can be found in the *BNF* and readers are referred to the most recent version for further details.²⁷

Anti-epileptic drugs

Epilepsy is a common disorder and clinicians are likely to see women using anti-epileptic drugs and contraception. Some drugs used in the management of epilepsy are liver enzyme-inducers. Guidelines on the management of women with epilepsy recommend use of drugs that are safer in pregnancy.²⁵ Monotherapy is advised where possible.²⁵ When initiating or changing anti-epileptic drugs, the implications for women using hormonal contraception should be considered.²⁵ Some anti-epileptic drugs are also used in the management of conditions other than epilepsy, but the interactions are the same.

Combined hormonal contraception. Evidence concerning concurrent use of anti-epileptic liver enzyme-inducing drugs and hormonal contraception is variable and of poor quality. Most evidence relates to the use of COC. Studies are inconsistent and measure different outcomes: pharmacokinetics of EE and progestogens, serum concentration of EE and progestogens, ovulation assessed by ultrasound or progesterone levels, gonadotrophin concentrations, breakthrough bleeding, and (rarely) pregnancy rates.

Anti-epileptic drugs that induce liver enzymes affect hormonal contraception by increasing the metabolism of EE and progestogens. A randomised, controlled, double-blind, crossover study in women using a 30 µg EE COC showed that *oxcarbazepine* reduced serum concentrations of EE and progestogen.²⁸ A case series of women using *phenobarbital* found a significant decrease in EE concentrations and increase in sex hormone-binding globulin.²⁹ A prospective study of women using a 35 µg EE COC showed increased clearance of EE with *topiramate*.³⁰ A pharmacokinetic study showed reduced EE concentrations in women using a 50 µg EE COC and *carbamazepine* and *phenytoin*.³¹

Some anti-epileptic drugs do not induce liver enzymes and therefore do not affect hormonal contraception. A small, randomised, double-blind, crossover trial of women using a 30 µg EE COC and *levetiracetam* found no decrease in EE and progestogen. In addition, gonadotrophin and progesterone concentrations were not increased.³² A small, randomised, double-blind, controlled trial in women using a 30 µg EE COC showed that the use of *vigabatrin* did not appear to affect COC and liver enzymes were not induced.³³ A prospective crossover study found that *gabapentin* did not affect EE and progestogen concentrations.³⁴ Case reports provide lower quality evidence.^{35,36} *Sodium valproate*³⁵ and *lamotrigine*³⁶ do not appear to affect the pharmacokinetics of oral contraceptives.

Progestogen-only contraception (POC). A small study investigated nine women using a levonorgestrel (LNG) implant (Norplant®) with phenytoin and/or other anti-epileptic medication.³⁷ Serum concentration of LNG decreased and two pregnancies were reported.

An observational study of women on anti-epileptic liver enzyme-inducing drugs using the LNG-IUS showed one true failure giving a failure rate of 1.1 per 100 woman-years (95% CI 0.03–6.25).³⁸ The dose of progestogen released into the uterine cavity from the LNG-IUS is 1000 times greater than the uterine concentration seen following progestogen-only implants. Most of the contraceptive effect of the LNG-IUS is mediated via this direct release into the uterine cavity and is unaffected by metabolism in the liver.

Little evidence was identified for efficacy of POPs with anti-epileptic drugs.³⁹ However, the efficacy is likely to be reduced as for other oral hormonal methods. Manufacturers of POPs do not recommend their continued use for women taking liver enzyme-inducing drugs.^{40–43}

The SPC for depot medroxyprogesterone acetate (DMPA) suggests that the efficacy of DMPA is *unaffected* by liver enzyme-inducing drugs.⁴⁴

Antifungals

Griseofulvin is a liver enzyme-inducer that may decrease the serum concentration, and hence efficacy, of drugs also metabolised by CYP3A4.⁴⁵ The contraceptive efficacy of hormonal contraception may be decreased and additional contraceptive protection is advised with *griseofulvin*.⁴⁵ Case reports have described pregnancy in women using COC and *griseofulvin*.^{46–49} The *BNF* suggests that *griseofulvin* and other antifungals (fluconazole, itraconazole, ketoconazole) reduce the efficacy of oestrogen and progestogen contraception.²⁷ Nevertheless, these other antifungals do not appear to induce liver enzymes. The SPC for *itraconazole* states there is no associated increase in metabolism of EE or progestogen.⁵⁰ Unintended pregnancy has been reported in women using *ketoconazole*⁵¹ and *itraconazole*. Breakthrough bleeding has been reported in COC users taking *itraconazole*^{52,53} and *ketoconazole*⁵⁴ but no pregnancies were identified in these studies. Evidence from

small, randomised, crossover trials has been reassuring with regard to *fluconazole*.^{55,56} Oral fluconazole (150 mg) given for two or three consecutive cycles did not reduce serum concentrations of progestogens and EE. A case series showed lower serum EE concentrations in women using COC with fluconazole compared to COC alone.⁵⁷ No ovulation or breakthrough bleeding was reported. Data for POC and these antifungals are unavailable.

Liver enzyme-inducing antibiotics

Rifampicin and rifabutin (used in the treatment of tuberculosis or meningococcal meningitis prophylaxis) are potent liver enzyme-inducers and case series have identified pregnancies in women using COC and rifampicin.^{58,59} The evidence to support rifampicin and rifabutin decreasing the efficacy of hormonal contraception is of poor quality.^{60–62}

Combined hormonal contraception. Evidence for reduced efficacy of COC with rifampicin and rifabutin is from one non-blind, randomised, controlled trial.⁶⁰ This trial showed that the pharmacokinetics of EE and the progestogen, norethisterone, were affected by both rifampicin and rifabutin (300 mg/day for 10 days). Serum concentrations of EE and norethisterone were decreased; irregular bleeding was more common; and serum concentrations of follicle-stimulating hormone and luteinising hormone were increased. Nevertheless, ovulation was not identified. Other small studies have shown evidence of ovulation in women using oral contraception and rifampicin.^{63–65}

Progestogen-only contraception. Evidence for reduced efficacy of POPs with rifampicin is obtained from one small prospective study of nine women using antitubercular treatment (rifampicin and ethambutol).⁶⁶ The half-life of norethisterone increased following the cessation of rifampicin. There are no direct data on the efficacy of progestogen-only injectables with rifampicin or rifabutin but the SPCs suggest they are unaffected.⁴⁴ Evidence on the efficacy of the LNG-IUS with rifampicin or rifabutin is poor. An observational study found a low failure rate for LNG-IUS users taking liver enzyme-inducing drugs (anti-epileptics and rifampicin).³⁸ Evidence for rifampicin or rifabutin decreasing the efficacy of progestogen-only implants is poor. A case report of a woman using an LNG implant with a liver enzyme-inducing drug (phenytoin) suggested decreased serum concentrations of LNG during treatment associated with ovulatory cycles.⁶⁷

Although evidence showing that rifampicin and rifabutin decrease the efficacy of hormonal contraception is of poor quality, this does not imply no association. These drugs are potent liver enzyme-inducers and therefore are likely to reduce efficacy of hormonal contraception.

St John's Wort

Evidence that St John's Wort (SJW) decreases the efficacy of hormonal contraception is of poor quality.⁶⁸ A prospective cohort study in male volunteers showed an increase in intestinal P-glycoprotein and intestinal and hepatic CYP3A4.⁶⁹ Evidence exists that other medicines (such as rifampicin) which induce these same microsomal enzymes are associated with contraceptive failure.⁵⁹ Evidence exists that SJW increases the metabolism of other medications.^{70–72} Case reports show that concentrations of cyclosporin decrease with SJW use, leading to transplanted organ rejection.^{73–76}

A small, randomised, non-blinded, non-crossover trial found no evidence of ovulation when a 20 µg COC was

used with SJW.⁷⁷ This trial aimed to detect ovulation by both serum progesterone and ultrasound scan. COC compliance was assessed with electronic monitoring. The study was limited by its small size and short duration (three cycles). Bleeding occurring on one or two occasions between withdrawal bleeds was common in Cycle 1 for all groups (treatment and control). In Cycles 2 and 3, bleeding settled in most COC users. However, with the addition of SJW, bleeding continued into Cycles 2 and 3. A further non-randomised study of women using COC (Ortho-Novum®) has shown an increase in breakthrough bleeding with SJW use; but no evidence of ovulation.⁷⁸ No data were identified on SJW and progestogen-only methods.

Although there is a lack of good quality evidence to show a reduction in efficacy of hormonal contraception with SJW, this does not imply no association. As SJW is a liver enzyme-inducer, the Clinical Effectiveness Unit (CEU) upholds advice from the Committee on Safety of Medicines (CSM) that women using hormonal contraception should be cautious when using SJW. The use of SJW may need to be reconsidered and even stopped.⁷⁰ The CEU suggests that advice for women using hormonal contraception and SJW is as for other liver enzyme-inducing drugs.

Antiretroviral drugs

Some antiretroviral drugs may reduce the efficacy of hormonal contraception. Antiretroviral drugs such as protease inhibitors (e.g. lopinavir, ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) are metabolised by the CYP3A4 liver enzyme system and can affect liver enzymes (Table 1). Women with HIV may use combination therapy where one or more drugs may induce liver enzymes. Readers should refer to the most recent *BNF*²⁷ or to a useful website⁷⁹ for further information on interactions with antiretrovirals. Few studies have been published which investigated the pharmacokinetics of EE and progestogens with antiretroviral drugs and none on the efficacy of hormonal contraception. Serum concentrations of EE were reduced when women using a 50 µg EE COC were also taking ritonavir but no pregnancies have been documented.⁸⁰ Further information is given in Table 1.

Other drugs

Tacrolimus is an immunosuppressant used in the prevention of donor organ rejection.²⁷ Tacrolimus is extensively metabolised via CYP3A4 isoenzyme. Tacrolimus has an inhibitory effect on CYP3A4-dependent metabolism and therefore the concomitant use of drugs metabolised via CYP3A4 may be affected by tacrolimus.⁸¹ The SPC on tacrolimus is unclear regarding hormonal contraception.⁸² Nevertheless, the *BNF* suggests that concurrent use of tacrolimus and contraceptive hormones may increase levels of tacrolimus and decrease contraceptive hormones, potentially reducing efficacy.²⁷ No randomised trials were identified on use of tacrolimus and hormonal contraception.

Lansoprazole is a proton pump inhibitor. The SPC suggests lansoprazole is a weak inducer of cytochrome P-450.⁸³ The effects of lansoprazole on a 30 µg EE COC were investigated in a randomised placebo-controlled study.⁸⁴ No significant changes were identified in the serum concentration of EE and progestogens with lansoprazole use. The *BNF* does not suggest that lansoprazole, or any other proton pump inhibitor, affects the efficacy of hormonal contraception.²⁷

Bosentan is used in the management of pulmonary hypertension.⁸⁵ Bosentan can induce cytochrome P-450.

No studies were identified which investigated hormonal contraceptive use and bosentan. The SPC, however, suggests the avoidance of hormonal contraception in patients on this drug as a main method of contraception, as does the BNF.^{27,85}

Modafinil, used in the management of narcolepsy, has been shown *in vitro* to induce liver enzymes.^{27,86} Its use may decrease the efficacy of hormonal contraception.

Non-liver enzyme-inducing antibiotics

6 Women should be informed that non-liver enzyme-inducing antibiotics can reduce the efficacy of combined hormonal contraception but there is no reduction in the efficacy of progestogen-only methods (Grade C).

Antibiotics that do not induce liver enzymes may reduce contraceptive efficacy in other ways. Non-liver enzyme-inducing antibiotics temporarily decrease colonic bacteria and thus inhibit the enterohepatic circulation of EE. Three weeks after the initiation of antibiotics, gut flora have recovered. Many studies investigating the pharmacokinetics of antibiotics and hormonal contraceptives are of short duration and only investigate effects in the initial weeks of antibiotic use. Antibiotics do not affect progestogens, as metabolites are inactive.

Pregnancies have been documented following the use of antibiotics.^{3,46–48,87–94} Nevertheless, case series reporting inadvertent pregnancy following antibiotic use do not identify *causation* and the potential for bias and confounding is high. The influence of antibiotics on the risk of pregnancy for individual women is unclear, even from data reported to the CSM.⁹⁵ All trials investigating the use of antibiotics in women using hormonal contraception are limited by their sample size, short duration, inconsistent assessment of ovulation, and failure to eliminate bias. These limitations were highlighted in a systematic review on antibiotics and hormonal contraception.⁹⁶

Three small randomised trials suggest that *ciprofloxacin* and *ofloxacin* may not affect COC.^{97–99} A small, randomised, placebo-controlled, crossover study of women using a variety of COCs found no differences in serum concentrations of gonadotrophins or oestradiol with concomitant use of ciprofloxacin 500 mg twice daily.⁹⁷ No data were collected on ovarian follicular activity or serum progesterone to identify ovulation. A more recent Phase I double-blind placebo-controlled trial investigated the interactions between ciprofloxacin and a 30 µg EE COC.⁹⁸ No significant ovarian follicular activity was identified (low serum concentrations of oestradiol) and progesterone levels indicated anovulation. A small, randomised, double-blind, crossover study investigated the effect of ofloxacin 200 mg twice daily on ovulation in women using a 30 µg EE COC.⁹⁹ No evidence of ovulation, by ultrasound scan and serum progesterone, was found.

Small prospective non-randomised studies have failed to show that *ampicillin* has any effect on gonadotrophin concentration or progesterone in women using a COC with ≥30 µg EE.^{100–102}

A retrospective cohort study of women attending dermatology clinics suggested an increased risk of pregnancy in COC users with concomitant use of antibiotics *minocycline* and *cephalosporins*.⁶ However, the potential for bias in this study was high.

A small, non-randomised trial suggested *tetracycline* did not affect the pharmacokinetics of EE or progestogens.¹⁰³ One study has investigated the effect of

tetracycline on the pharmacokinetics of transdermal combined contraception.¹⁰⁴ No effect was seen on serum concentrations of EE and progestogens.

A non-randomised trial investigated the use of *doxycycline* 100 mg twice daily for 7 days in women using a 35 µg EE COC and did not identify any changes in the pharmacokinetics of EE or progestogens.¹⁰⁵

It is clear that although many studies of variable quality have investigated the pharmacokinetics of EE and progestogens in women using antibiotics, no studies have reliably investigated the efficacy of hormonal contraception.

Antimalarial drugs

Neither *chloroquine* nor *primaquine* have an effect on serum concentrations of EE or LNG in women using a 30 µg EE COC.¹⁰⁶ *Doxycycline* is commonly used in the management of malaria. Although the pharmacokinetics of EE and progestogens appear unaffected by *doxycycline*,¹⁰⁵ advice regarding additional contraceptive protection while taking the antibiotic and for 7 days after cessation is as for other antibiotics.

What advice should be given to women using hormonal contraception and liver enzyme-inducing drugs?

Combined hormonal contraception

7 Women taking liver enzyme-inducing drugs who wish to use COC should choose a regimen containing at least 50 µg EE daily. Additional contraceptive protection, such as condoms, should be used until 4 weeks after the liver enzyme-inducing drug has been stopped. Information should be given on the use of alternative methods of contraception if liver enzyme-inducing drugs are to be used long term (Grade C).

8 Breakthrough bleeding does not necessarily indicate low serum EE concentrations and risk of ovulation. Nevertheless, women using liver enzyme-inducing drugs with breakthrough bleeding may increase their dose of EE above 50 µg daily (Good Practice Point).

9 No evidence was identified that supports omitting or reducing the pill-free interval to reduce the risk of ovulation in women using liver enzyme-inducers (Good Practice Point).

10 Women using liver enzyme-inducing drugs may use a combined contraceptive patch with additional contraceptive protection, such as condoms, until 4 weeks after the liver enzyme-inducing drug has been stopped. Information should be given on the use of alternative methods of contraception (Grade C).

11 Women using even short courses of rifampicin (for prophylaxis) should be advised to use additional contraception during the course and for 4 weeks afterwards (Grade C).

Based on limited evidence (but due to the consequences should an unintended pregnancy ensue), the CEU recommends that women using combined hormonal contraception should be advised that the efficacy of these methods might be reduced with liver enzyme-inducing drugs.

Table 2 Advice regarding contraceptive use for women using liver enzyme-inducing drugs

Contraceptive method	Advice for women using liver enzyme-inducing drugs
Combined hormonal contraception	
Combined oral contraception (COC)	<p>Use a COC with at least 50 µg ethinylestradiol daily. This can be taken as a 30 µg COC plus a 20 µg COC or as two 30 µg COCs.</p> <p>Additional contraceptive protection, such as condoms, is required when taking liver enzyme-inducers and for 4 weeks after they are stopped.</p> <p>Information should be given on the use of alternative methods which are unaffected by liver enzyme-inducers.</p> <p>If additional contraception fails or is not used emergency contraception may be indicated.</p>
Combined contraceptive patch	<p>Use one patch per week as for women not using liver enzyme-inducers.</p> <p>Additional contraceptive protection, such as condoms, is required when taking liver enzyme-inducers and for 4 weeks after they are stopped.</p> <p>Information should be given on the use of alternative contraceptive methods if liver enzyme-inducers are to be used long term.</p> <p>If additional contraception fails or is not used emergency contraception may be indicated.</p>
Progestogen-only contraception	
Progestogen-only pills (POPs)	<p>Advise alternative contraceptive methods.</p>
Progestogen-only implants	<p>May continue with progestogen-only implants with additional contraceptive protection, such as condoms, when taking liver enzyme-inducers and for 4 weeks after they are stopped.</p> <p>Information should be given on the use of alternative contraceptive methods if liver enzyme-inducing drugs are to be used long term.</p>
Progestogen-only injectables	<p>Progestogen-only injectables are unaffected by liver enzyme-inducers. Continue with the usual injection interval of 12 weeks for depot medroxyprogesterone acetate and 8 weeks for norethisterone enanthate.</p>
Progestogen-only emergency contraception	<p>Take a total dose of 2.25 mg levonorgestrel as a single dose as soon as possible and within 72 hours of unprotected sex.</p> <p>Consider the use of a copper IUD, which is unaffected.</p>
Levonorgestrel-releasing intrauterine system	<p>No additional contraceptive protection required.</p>
Non-hormonal methods	
Copper-bearing intrauterine contraceptive device (IUD), barrier methods	<p>No additional contraceptive protection required.</p>

It has been established UK practice to start a COC with at least 50 µg EE daily for women taking liver enzyme-inducing drugs (Table 2).^{1,11,25,107,108} Despite lack of evidence, in the light of the potentially serious sequelae of unintended pregnancy, women are advised to use additional contraception, such as condoms, during use of a liver enzyme-inducing drug and for 28 days after the liver enzyme-inducer is stopped.^{25,11} The most commonly used COC containing 50 µg EE (Ovran®) was discontinued in 2002. An alternative preparation containing 50 µg mestranol (Norinyl-1®) is available. Two studies have provided conflicting evidence on the bioequivalence of 50 µg EE and mestranol.^{109,110} The CEU suggests an alternative regimen using two low-dose COCs providing a total daily dose of 50–60 µg EE (e.g. Loestrin 20® plus Loestrin 30®, or Marvelon® plus Mercilon®, or two Microgynon 30®). No trials have compared the bioavailability to that of a single tablet. This use of COCs is outside product licence.

Breakthrough bleeding has been suggested as an indicator of low serum hormone concentrations and risk of ovulation; however, no evidence was identified to support this. Nevertheless, it may be prudent to increase the dose of EE if breakthrough bleeding occurs in women using liver enzyme-inducers. This may also control the breakthrough bleeding. Omitting or reducing the pill-free interval has also been advised for women using liver enzyme-inducing

drugs. No evidence was identified as to whether this outside licence use improves contraceptive efficacy.

Additional contraceptive protection, such as condoms, is advised when women using liver enzyme-inducers are using combined contraceptive patches.¹¹¹ Using more than one patch at a time is not recommended.¹¹¹ Consideration should be given to the alternative use of progestogen-only injectables, the LNG-IUS or an intrauterine device (IUD), which are unaffected by liver enzyme-inducing drugs.

Progestogen-only contraception

- 12 Women using liver enzyme-inducing drugs should be advised that progestogen-only injectables are unaffected and can be continued with the usual injection interval (Grade C).**
- 13 Women using liver enzyme-inducing drugs in the short term may choose to continue with progestogen-only implants. Additional contraceptive protection, such as condoms, should be used until 4 weeks after the liver enzyme-inducing drug has stopped. Information should be given on the use of alternative contraception if liver enzyme-inducing drugs are to be used long term (Good Practice Point).**

14 Women using POPs should be advised to consider alternative contraception if liver enzyme-inducing drugs are used (Grade C).

15 Women can be advised that the LNG-IUS appears to be unaffected by liver enzyme-inducing drugs (Grade B).

16 Women using liver enzyme-inducing drugs who require progestogen-only emergency contraception (POEC) should be advised: to take a total of 2.25 mg LNG as a single dose as soon as possible and within 72 hours of unprotected sex; that this use is outside the product licence; and about the alternative use of an IUD (Grade C).

Based on limited evidence (but due to the consequences should an unintended pregnancy ensue), the CEU recommends that women using POPs and progestogen-only implants should be advised that the efficacy of these methods is reduced with liver enzyme-inducing drugs (Table 2).

Although no good evidence for reduced efficacy of POPs was identified, the SPCs for POPs advise against continued use with liver enzyme-inducing drugs.^{40–42,112} The SPC for DMPA advises that the contraceptive efficacy is *unaffected* by liver enzyme-inducing drugs and injections should be given at the usual 12-week interval.⁴⁴ Similar advice (no need to reduce the 8-week injection interval) is given for norethisterone enanthate. The SPC for the only progestogen-only implant (Implanon®) available in the UK suggests additional contraceptive protection while women are using a liver enzyme-inducing drug and for 28 days after its cessation.¹¹³

Women not using liver enzyme-inducing drugs who require POEC are advised to take a single 1.5 mg dose of LNG as soon as possible and within 72 hours of unprotected intercourse.¹¹⁴ There are no data on the use of POEC by women using liver enzyme-inducing drugs. Clinical practice in the UK has been to increase the dose by 50% (1.5 mg LNG at first presentation and 0.75 mg 12 hours later).¹⁰ The most recent *BNF*, however, supports taking 2.25 mg LNG as a single dose at first presentation.²⁷ The CEU was unable to identify any new data to support a single dose of 2.25 mg LNG for women taking liver enzyme-inducers. Some clinicians currently use a 1.5 mg LNG dose and repeat it 12 hours later. There is no evidence on efficacy, compliance or side effects with any of these regimens. The CEU advises that women should be informed about the lack of data on efficacy of POEC when using liver enzyme-inducers and be offered an IUD as an alternative. These regimens of POEC are outside the product licence.¹¹⁴ Clinicians may consider using the regimen that is most acceptable to an individual woman. Pharmacies should have a supply of a new single tablet 1.5 mg dose of LNG (Levonelle One Step®) early in 2005. This may also be available for National Health Service supplies later in 2005. Women who are using liver enzyme-inducing drugs attending pharmacies for POEC should be referred to a prescribing clinician.

What advice should be given to women using hormonal contraception and non-liver enzyme-inducing antibiotics?

17 Women should be advised that pregnancies have been reported in COC users taking non-liver enzyme-inducing antibiotics, but the evidence does not generally support reduced COC efficacy and causation (Grade B).

18 A COC user taking a short course (<3 weeks) of non-liver enzyme-inducing antibiotics should be advised to use additional contraceptive protection, such as condoms, during the treatment and for 7 days after the antibiotic has been stopped. If fewer than seven active pills are left in the pack after antibiotics have stopped, she should omit the pill-free interval (or discard any inactive pills) (Grade C).

19 A combined contraceptive patch user taking a short course (<3 weeks) of non-liver enzyme-inducing antibiotics (except tetracycline) should be advised to use additional contraceptive protection, such as condoms, during the treatment and for 7 days after the antibiotic is stopped. If there are <7 days remaining before her usual patch-free week, another patch should be applied when due for changing and the patch-free week delayed by 7 days (Grade C).

20 A woman who is an established user of non-liver enzyme-inducing antibiotics (≥3 weeks) does not require additional contraceptive protection when starting combined hormonal contraception unless she changes to a different antibiotic (Grade C).

21 Women should be informed that the efficacy of progestogen-only methods of contraception is not reduced by non-liver enzyme-inducing antibiotics and additional contraceptive protection is not required (Grade C).

22 Women using non-liver enzyme-inducing antibiotics (short- or long-term) who require POEC may be advised that the usual dose (1.5 mg within 72 hours of unprotected intercourse) is appropriate (Grade C).

It has been established practice in the UK to advise additional contraceptive protection for women using combined hormonal contraception with broad-spectrum antibiotics. Based on published low-quality evidence, antibiotics (broad-spectrum and narrow-spectrum) appear to have a limited effect on serum concentrations of EE and progestogens. Some studies show no alteration in pharmacokinetics of EE and progestogens and continued anovulation. No study has reliably investigated whether combined hormonal contraceptive efficacy is reduced. Case reports have described pregnancies in women using hormonal contraception and antibiotics. Although this does not confirm direct causation, the consequences of an unplanned pregnancy are such that the CEU suggests a cautious approach when advising women. Additional contraceptive protection, such as condoms, is advised when COC users start or change any non-enzyme-inducing antibiotic (Table 3). Additional contraceptive protection is advised during the antibiotic treatment and after the antibiotics have stopped until seven consecutive pills have been taken. If there are fewer than seven active pills remaining in the pack, the pill-free interval should be omitted.¹¹ Traditionally, such advice on additional contraceptive precautions has been restricted to broad-spectrum antibiotics. The CEU recognises that there is confusion and lack of clarity regarding what constitutes a broad-spectrum antibiotic. For simplicity, on pragmatic grounds, the CEU recommends that this advice is applied to all non-liver enzyme-inducing antibiotics.

The efficacy of progestogen-only methods is not reduced with non-liver enzyme-inducing antibiotics.

Table 3 Advice regarding contraceptive use for women using non-liver enzyme-inducing antibiotics

Contraceptive method	Advice for women using non-liver enzyme-inducing antibiotics
Combined hormonal contraception	
Combined oral contraception (COC)	<i>Established COC user</i>
	When taking a short course (<3 weeks) of any non-liver enzyme-inducing antibiotic additional contraceptive protection, such as condoms, is advised during the treatment and for 7 days after the antibiotic has been stopped.
	If fewer than seven pills are left in the packet after antibiotics have stopped the pill-free interval should be omitted or any inactive pills discarded.
	When any non-liver enzyme-inducing antibiotic is taken for ≥ 3 weeks additional contraceptive protection is no longer required. If a new antibiotic is prescribed, however, advice is as for short courses.
	<i>New COC user</i>
	When starting a COC if currently taking a short course (<3 weeks) of any non-liver enzyme-inducing antibiotic additional contraceptive protection, such as condoms, is advised during the treatment and for 7 days after the antibiotic is stopped.
	When starting a COC if any non-liver enzyme-inducing antibiotic has been taken for ≥ 3 weeks additional contraceptive protection is not required.
Combined contraceptive patch	<i>Established contraceptive patch users</i>
	If taking a short course (<3 weeks) of any non-liver enzyme-inducing antibiotic (except tetracycline) additional contraceptive protection, such as condoms, is advised during the treatment and for 7 days after the antibiotic is stopped.
	If there are fewer than 7 days remaining before the usual patch-free week another patch should be applied (when due for changing) so that the patch-free week is delayed by 7 days.
	When any non-liver enzyme-inducing antibiotic is taken for ≥ 3 weeks additional contraceptive protection is no longer required. If a new antibiotic is prescribed, however, advice is as for short courses.
	<i>New patch user</i>
	When starting a contraceptive patch if currently taking a short course (<3 weeks) of any non-liver enzyme-inducing antibiotic additional contraceptive protection, such as condoms, is advised during the treatment and for 7 days after the antibiotic is stopped.
	When starting a contraceptive patch if any non-liver enzyme-inducing antibiotic has been taken for ≥ 3 weeks additional contraceptive protection is not required.
Progestogen-only methods	Efficacy of progestogen-only methods (including emergency contraception) is not reduced by non-liver enzyme-inducing antibiotics.
Non-hormonal contraception	Efficacy unaffected.

Which drugs increase serum levels of contraceptive hormones and what are the resulting clinical effects?

Liver enzyme inhibitors

Concentrations of EE can be increased with use of the non-steroidal anti-inflammatory drugs, *etoricoxib* and *valdecoxib*.²⁷ The antilipid medication, *rosuvastatin*, can increase serum concentrations of both EE and progestogens. The clinical effect of increased EE and progestogens is unclear. No evidence was identified of increased risk of venous thromboembolism with these concurrent medicines.

Which drugs can be increased or decreased by concomitant use of contraceptive hormones?

The bioactive pool of some drugs can be increased by concomitant hormonal contraceptive use (e.g. corticosteroids, ciclosporin, theophylline and ropinirole) (Table 4). Depending on the nature and clinical effect of the drug, potentially toxic effects can result.

An increase in *corticosteroid* concentrations has little if any clinical effect.

Ciclosporin is a potent immunosuppressant. Neurotoxicity and nephrotoxicity have been demonstrated. Sex steroid hormones may increase plasma levels of ciclosporin leading to toxic effects.²⁷

Theophylline is a bronchodilator with a narrow

therapeutic index and toxicity (arrhythmia and convulsions) if serum concentrations increase.²⁷ Sex steroid hormones may increase plasma levels of theophylline leading to toxic effects.²⁷

Ropinirole is used in the management of Parkinson's disease and serum concentrations may increase with hormonal contraceptive use.²⁷

The use of oestrogen and/or progestogen is suspected to have an antagonistic effect on the clinical effect of some concurrent medication (Table 4). Little evidence to support this was identified. It is suspected that the antihypertensive effects of a variety of medications, the anticoagulant effect of *warfarin* and *phenidione*, and the antidiabetic effects of a variety of medications may be antagonised by use of oestrogens.²⁷ It must be remembered, however, that the risks of oestrogen-containing contraception for women with uncontrolled hypertension, diabetes with small vessel disease, or with venous thromboembolic disease being actively treated outweigh any benefits (WHO Category 3)¹¹⁵ or pose an unacceptable health risk (WHO Category 4). Therefore this clinical situation should not arise.

Miscellaneous drugs

Sibutramine hydrochloride (Reductil®), a centrally acting serotonin and noradrenaline reuptake inhibitor, is used as an anti-obesity agent. A small, single-blind, placebo-

Table 4 Drugs whose effects may be decreased or increased by use of hormonal contraception²⁷

Type of drug	Clinical effect
<i>Decreased clinical effect</i>	
All antihypertensives	Hypotensive effect may be antagonised by combined hormonal contraception.
Antidiabetics	Hypoglycaemic effects maybe antagonised by combined hormonal contraception.
Anticoagulants <i>Phenidione</i> <i>Warfarin</i>	Anticoagulant effect reduced by ethinylestradiol (EE) and progestogens.
Antidepressants <i>Tricyclics</i>	Antidepressant effects of tricyclics can be reduced by EE but side effects of tricyclics may be increased because serum concentration is increased. No evidence identified.
<i>Increased clinical effect</i>	
Immunosuppressants <i>Ciclosporin</i>	Serum concentrations of ciclosporin increased by EE and progestogens potentially leading to toxicity
Corticosteroid	Serum concentrations of corticosteroid increased by EE and progestogens but no significant clinical effect.
Bronchodilators <i>Theophylline</i>	Serum concentrations of theophylline increased by EE and progestogens potentially leading to toxicity.
Dopaminergics <i>Ropinirole</i>	Serum concentrations of ropinirole increased by EE and progestogens but no significant clinical effect.
Potassium-sparing diuretics	Potentially lead to hyperkalaemia when used with the progestogen drospirenone.

controlled trial showed that sibutramine did not impair efficacy of concomitantly administered COC.¹¹⁶

Terbinafine has been associated with breakthrough bleeding in women using POC.²⁷ Despite extensive searching, no further evidence on the use of terbinafine in women using hormonal contraception was identified. It is unclear if this drug induces liver enzymes; but it is unlikely to do so.

Retinoids do not appear to induce liver enzymes and no reduction in hormonal contraceptive efficacy has been demonstrated. A pharmacokinetic study showed a reduction in serum concentrations of EE and norethisterone when women taking COC (Ortho-Novum) were also taking *isotretinoin*.¹¹⁷

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This Guidance was developed by the Clinical Effectiveness Unit (CEU) of the Faculty of Family Planning and Reproductive Health Care (FFPRHC): Dr Gillian Penney (Director), Dr Susan Brechin (Co-ordinator) and Ms Gillian Stephen (Research Assistant) in consultation with the Clinical Effectiveness Committee, which includes service user representation and a multidisciplinary expert group of health care professionals involved in family planning and reproductive health care. The multidisciplinary group comprised: Dr Andrea Brockmeyer (Subspecialty Trainee in Sexual and Reproductive Health Care, Abacus Clinics, Liverpool), Mr Craig Rore (Lead Pharmacist, Grampian Medicines Information Centre, Aberdeen Royal Infirmary, Aberdeen), Dr Alyson Elliman (Lead Associate Specialist, Family Planning Service, Croydon Primary Care Trust/FFPRHC Clinical Standards Committee Member), Dr James McClay (Senior Lecturer in Clinical Pharmacology, Department of Medicine and Therapeutics, Aberdeen Royal Infirmary, Aberdeen), Ms Susan Stewart (Helpline and Information Manager, Epilepsy Scotland, Glasgow), Dr Kate Weaver (Staff Grade, Family Planning and Reproductive Health Service, Dean Terrace, Edinburgh). Written feedback was provided by: Professor David Back (Professor of Pharmacology, University of Liverpool, Liverpool), Ms Toni Belfield (Director of Information, fpa, London), Ms Sheena Bevan (Epilepsy Fieldworker, Links Resource Centre, Aberdeen), Dr Rachel Westwick (Career Grade Trainee in Family Planning and Reproductive Health Care/Trainee Member of the FFPRHC Education Committee).

This guidance is also available online at www.ffprhc.uk Evidence tables are available on the FFPRHC website. These summarise relevant published evidence on drug interactions with hormonal contraception, which was identified and appraised in the development of this Guidance. The clinical recommendations within this Guidance (i.e. the text appearing within the blue and red boxes) are based on evidence whenever possible.

Grades of Recommendations	
A	Evidence based on randomised controlled trials (RCTs)
B	Evidence based on other robust experimental or observational studies
C	Evidence is limited but the advice relies on expert opinion and has the endorsement of respected authorities
	Good Practice Point where no evidence exists but where best practice is based on the clinical

Electronic searches were performed for: MEDLINE (CD Ovid version) (1990–2004), EMBASE (1990–2004), PubMed (1990–2004), The Cochrane Library (to November 2004) and the US National Guideline Clearing House. The searches were performed using relevant medical subject headings (MeSH), terms and text words. The Cochrane Library was searched for systematic reviews, meta-analyses and controlled trials relevant to drug interactions with hormonal contraception. Previously existing guidelines from the FFPRHC, the Royal College of Obstetricians and Gynaecologists (RCOG), the World Health Organization (WHO) and reference lists of identified publications were also searched. Similar search strategies have been used in the development of other national guidelines. Selected key publications were appraised according to standard methodological checklists before conclusions were considered as evidence. Evidence was graded as above, using a scheme similar to that adopted by the RCOG and other guideline development organisations.