

PRESCRIBING and CLINICAL EFFECTIVENESS NEWSLETTER



Supporting the
Derbyshire Health Community

Volume 8: Issue 9

December 2009



Merry Christmas to all our readers

Further in this issue	Page 2	Statins: updated product information. Silver dressings
	Page 3	More on aspirin for primary prevention
	Page 4	St John's Wort and hormonal contraceptives
	Page 5	Oral contraceptives and venous thromboembolism
	Page 6	Positive effects of vitamin D. Website of the month

JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and NHS Derby. It provides recommendations on drugs and medicines management issues.

RED drugs are those where prescribing responsibility lies with a hospital consultant or a specialist. AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a GP under a shared care agreement. GREEN drugs are regarded as suitable for primary care prescribing. BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

The most recent updates are in the table below; the full list is available at

<http://www.derbyshiremedicinesmanagement.nhs.uk/home>

The guidelines, formulary chapters, newsletters, etc can now be found via this link.

Drug	Date considered	Decision
Prasugrel	December 2009	GREEN (after consultant initiation)
Fentanyl nasal spray / tablet / lozenge	November 2009	BROWN
Saxagliptin	November 2009	BROWN
Mercaptamine	November 2009	RED
Trientine	November 2009	RED
Voriconazole	November 2009	RED
Ulipristal acetate (ellaOne)	November 2009	GREEN (between 72 and 120 hours)
Full Marks solution spray	October 2009	BROWN

Ulipristal

Ulipristal (ellaOne®) is a new prescription-only emergency contraceptive pill licensed for use up to 5 days after unprotected intercourse. Currently used methods of emergency contraception are levonorgestrel 1.5mg, which is licensed for up to 72 hours following unprotected intercourse, or a copper intra-uterine device, which can be inserted up to 120 hours after unprotected intercourse. This is an unlicensed indication of the IUD¹. Ulipristal is the first emergency hormonal contraception that is licensed for up to 120 hours after unprotected intercourse.

Ulipristal has been shown to have equivalent efficacy to levonorgestrel in large randomised and single-arm open studies. Its safety profile also appears similar to that of levonorgestrel, with mild gastrointestinal symptoms and disruption of normal menses common².

The Newsletter is produced by Peter Burrill - Specialist Pharmaceutical Adviser for Public Health
peter.burrill@derbyshirecountypct.nhs.uk

Ulipristal is more than three times as costly as levonorgestrel and JAPC has decided that levonorgestrel is still recommended for patients who present up to 72 hours following unprotected intercourse and ulipristal is the preferred drug treatment option for patients who present between 72 and 120 hours following unprotected intercourse. Being new, ulipristal is a black triangle drug and all suspected adverse reactions to black triangle drugs should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk).

1. London New Drugs Group APC/DTC Briefing Document, September 2009
2. Wolfson Unit Regional Drug and Therapeutics Centre, [New drug evaluation, October 2009](#)

Statins: updated product information

The 'Hot topic' section of the November issue of 'Drug Safety Update' highlights that new product information in patient leaflets will shortly be coming into the packs of all statins.

"In February 2008, we reported a European-wide review on statins. New advice and information on side effects have been agreed, and healthcare professionals should be aware of the updated information so they can discuss it appropriately with new and existing patients.

The headline message from the review was that the balance of risks and benefits of statins as a class remains positive. Statins are one of the most important and widely used medicines in patients with lipid disorders and in the prevention of cardiovascular events. The efficacy and safety of statins have been studied in a number of large trials for both primary and secondary prevention of cardiovascular disease showing that overall, statins can reduce heart attacks and the need for bypass surgery and similar types of operation, and even save lives for certain patient groups. Trials have also shown that statins are generally well tolerated by most people who use them.

However, the review also identified the need for the product information for all statins to reflect the issues identified from analyses of clinical trials and post-marketing data from case reports of adverse drug reactions. These included sleep disturbance, memory loss, sexual disturbances, depression, and interstitial pneumopathy. The review also considered published and unpublished data and relevant clinical guidelines, and concluded that it was important that prescribers and patients alike are aware of the potential for these adverse reactions.

- Patients should be made aware that treatment with any statin may be associated with depression, sleep disturbances, memory loss and sexual dysfunction.
- Statins may very rarely be associated with interstitial lung disease. Patients should seek help from their doctor if they develop presenting features of interstitial lung disease such as dyspnoea, non-productive cough, and deterioration in general health (eg, fatigue, weight loss, and fever)

On the basis of the data examined for individual statins and the class as a whole, the review concluded that there is sufficient evidence to support a possible causal relationship between statin use and the above adverse reactions. Summaries of Product Characteristics and Patient Information Leaflets are being amended to include the potential for these reactions. Prescribers will wish to be aware of these changes coming through so that they can discuss them with patients."¹

1. [Drug Safety Update, November 2009](#)

Silver dressings

In the first quarter of 2009/10, £58,578 was spent on silver-releasing dressings from the primary care prescribing budget of County PCT. Is this justifiable?

A systematic review of dressings for acute and chronic wounds published in 2007¹, found little or no evidence to support the preferential use of silver-releasing dressings (see PACE Newsletter of November 2007). A systematic review of treatment of pressure ulcers published in 2008², concluded that little evidence supports the use of a specific support surface or dressing over other alternatives. For the 54 trials studying wound dressings (n=2,857), results generally suggested that the dressing being studied was not superior to the alternatives.

A systematic review of silver-releasing dressings in the management of infected chronic wounds was also published in 2008³. The authors concluded that these dressings had an overall positive effect on the

management of chronic infected wounds, however, the quality of evidence was limited and more research was needed. The DARE review⁴ (Database of Abstracts of Reviews of Effects) of this paper concluded “In view of methodological problems and poor reporting in the review, as well as the questionable quality and heterogeneity of the primary studies, the authors’ conclusions may not be reliable.”

A recently published trial, funded by the NHS Health Technology Assessment Programme, has assessed silver-releasing dressings for venous leg ulcers^{5,6}. The VULCAN study found no evidence to support use of silver dressings under compression bandaging for the treatment of venous leg ulcers. Compared with non-silver, low adherent dressings, silver dressings were not more effective in healing ulcers, did not improve quality of life, and were not cost-effective.

The following results were reported:

- There was no difference between the dressings in the primary outcome (59.6% for silver and 56.7% for control dressings). Relative risks of healing for silver versus control dressings at 12 weeks, 6 months, and one year were 1.06, 1.34 and 1.03, respectively (p = NS for all).
- Mean utility scores for the EuroQol 5D and Short Form 6D were similar in both groups at 1, 3, 6 and 12 months.
- Median time to healing was 67 days in the silver dressing group and 58 days with standard dressings. Larger ulcers (>3 cm in diameter) took more time to heal than did smaller ulcers (median 101 days vs 52 days).
- Compared with the control group the silver dressing group had an incremental cost of £97.85 and an incremental quality-adjusted life year gain of 0.0002, giving an incremental cost-effectiveness ratio of £489,250 for the silver dressings.

The authors state ‘our surveys suggested that silver-donating antimicrobial dressings have become widely used. If this reflects national practice then the implication is that the NHS could be spending several million pounds on dressings each year with no evidence of clinical benefit.’ **Is it worth reviewing the use of silver dressings in your practice?**

1. www.npci.org.uk/blog/?p=19
2. JAMA 2008; 300: 2647-62
3. J Clin Nursing 2008; 17:1973-85
4. www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=12008107143
5. www.npci.org.uk/blog/?p=796
6. Health Technology Assessment 2009; Vol. 13: No. 56

More on aspirin for primary prevention

DTB have reviewed the evidence for the use of aspirin for primary prevention of cardiovascular disease¹.

Implications for practice

“Overall, we believe that the currently available evidence does not justify the routine use of low-dose aspirin for the primary prevention of CVD in apparently healthy individuals, including those with elevated blood pressure or diabetes; this is because of the potential risk of serious bleeds and lack of effect on mortality. Recent advice from the Medicines and Healthcare products Regulatory Agency has recommended that, if aspirin is used in primary prevention, ‘the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors for vascular disease ... and the risk of gastrointestinal bleeding’. In practice, this means reviewing individually all those patients currently taking aspirin for primary prevention (either as prescribed or over-the-counter treatment), with the decision to stop or continue treatment being made with the patients after fully informing them of the available evidence. Furthermore, in our view, current evidence makes it hard to recommend starting aspirin for primary prevention.”

Conclusion

“Low-dose aspirin is established in the secondary prevention of cardiovascular disease. Such treatment is also widely used for the primary prevention of cardiovascular disease (an unlicensed indication). However, current evidence for primary prevention suggests the benefits and harms of aspirin in this setting may be more finely balanced than previously thought, even in individuals estimated to be at high risk of experiencing cardiovascular events, including those with diabetes or elevated blood pressure. We believe, therefore, that low-dose aspirin

prophylaxis should not be routinely initiated for primary prevention. With respect to those people already taking low-dose aspirin for primary prevention, the decision about whether to continue with the treatment should be taken by both the patient and a healthcare professional in light of the available evidence. This also includes people who purchase aspirin over the counter for primary prevention”

Shortly after this article was published, the BMJ released an online first meta-analysis of RCTs of aspirin for primary prevention of CV events in people with diabetes². Compared with placebo there was no statistically significant reduction in the risk of major CV events, CV mortality, or all-cause mortality. The authors conclude that a clear benefit of aspirin in the primary prevention of major CV events in people with diabetes remains unproved. The accompanying editorial³ suggests that if possible, clinicians should offer their patients the opportunity to participate in one of the ongoing trials in this area, which will increase the available data and potentially provide a clearer answer.

1. DTB 2009; 47:122-25
2. BMJ 2009; 339:b4531
3. BMJ 2009; 339:b4596

St John's Wort and hormonal contraceptives

A UKMi Q&A asks 'is there an interaction between St John's Wort (SJW) and hormonal contraceptives?' and provides the following answer¹.

Summary

The interaction between oral contraceptives and St John's Wort appears to be established. Its incidence is not known, but the limited poor quality evidence so far, suggests that breakthrough bleeding may be a problem. Pregnancy resulting from this interaction appears to be uncommon. It is not known who is most likely to be at risk of this interaction. There is very little information relating to the effect of SJW on other forms of hormonal contraception.

The recommendation of the CSM/MCA and the Faculty of Family Planning and Reproductive Health Care (FFPRHC) in the UK is that women taking oral contraceptives (both combined and progestogen-only pills) should either avoid St John's Wort or they should use an additional form of contraception.

The FFPRHC clinical effectiveness unit also recommends that, if St John's Wort must be continued, the following general guidelines for the use of liver enzyme inducers with hormonal contraceptives should be followed:

- Women taking combined oral contraceptives should use an ethinylestradiol dose of at least 50 micrograms daily. The dose may be increased further above 50 micrograms if breakthrough bleeding occurs. Omitting or reducing the pill-free interval has not been shown to reduce the risk of ovulation with liver enzyme inducers. Additional non-hormonal methods of contraception, such as condoms, should also be used by patients using combined hormonal contraceptives, both when taking the liver enzyme inducers and for at least 4 weeks after stopping the drug. Alternatives to combined hormonal contraceptives should be considered with long-term use of liver enzyme inducers.
- The progestogen-only oral contraceptive is not recommended for use with liver enzyme inducers. Alternative methods of contraception are advised.

The FFPRHC clinical effectiveness unit gives the following advice about alternative forms of hormonal contraception:

- The depot progestogen-only injection, copper and levonorgestrel-releasing intrauterine devices (IUD) do not appear to be affected by enzyme-inducing drugs, such as St John's Wort, and may be used as alternative contraceptive methods, particularly for women requiring hormonal contraception who are likely to be taking the enzyme inducer in the long-term, as these are unaffected by liver enzyme inducers.
- The combined contraceptive patch may be continued, however additional, non-hormonal methods of contraception, such as condoms, should also be used by patients using the combined contraceptive patch, both when taking the liver enzyme inducers and for at least 4 weeks after stopping the drug. Using more than one patch is not recommended.

- The progestogen-only implant may be continued with short courses of enzyme inducers. Additional non-hormonal methods of contraception, such as condoms, should also be used by patients using the progestogen-only implant, both when taking the liver enzyme inducers and for at least 4 weeks after stopping the drug. Alternatives to the progestogen-only implant should be considered with long-term use of liver enzyme inducers.
- The effectiveness of emergency hormonal contraception will be reduced in women taking liver enzyme inducers. The FFPRHC clinical effectiveness unit states that there appears to be no good evidence on how to manage the interaction between emergency hormonal contraception and enzyme inducers such as St John's wort, but current clinical practice is to increase the contraceptive dose by approximately 50%. The British National Formulary recommends giving a single 3mg dose of levonorgestrel, although this is unlicensed. A copper IUD may also be used as an effective alternative. In the UK, it is possible to buy the progestogen-only emergency hormonal contraception without a prescription; however, it has been advised that patients taking enzyme inducers should be referred to a doctor or family planning service.

Limitations

This document does not consider the effect of SJW on the effectiveness of oral contraceptives when used for non-contraceptive indications, such as acne or hirsutism.

1. [UKMi: Q&A 214.1](#)

Oral contraceptives and venous thromboembolism

All oral contraceptives (OCs) are effective in preventing pregnancy if they are taken correctly, so one of the factors involved in the choice of a preparation is the profile of side effects. Venous thromboembolism (VTE) is one of the most serious side effects, and although it is rare, it can cause death in about 1-2% of cases of VTE in women taking the pill¹. Two recently published studies on the risk of VTE with hormonal contraception have produced remarkably similar results and confirm past studies of the risk of VTE with the pill.

The first study² examined risk in current OC users with a focus on regimen, oestrogen dose, type of progestogen, and route of administration in a cohort of Danish women aged 15 to 49 years, with no history of cardiovascular or malignant disease. The main outcomes were adjusted rate ratios for a first time DVT, portal thrombosis, thrombosis of caval vein, thrombosis of renal vein, unspecified DVT and PE during the study period. A total of 10.4 million woman-years were recorded of which 3.3 million woman-years were in receipt of OCs.

The following results were reported:

- 4,213 venous thrombotic events were observed, 2,045 in current users of OCs.
- The overall absolute risk of venous thrombosis per 10,000 woman years was 6.29 in current users and 3.01 in non-users of OCs.
- Compared with non-users of combined OCs, the rate ratio of VTE in current users decreased with duration of use (less than one year, 4.17 [95% CI 3.73 to 4.66], one to four years, 2.98 [2.73 to 3.26] and more than four years, 2.76 [2.53 to 3.02]; $p < 0.001$) and with decreasing dose of oestrogen.
- Compared with OCs containing levonorgestrel and with the same dose of oestrogen and length of use, the rate ratio for OCs with:
 - norethisterone was 0.98 [0.71 to 1.37],
 - norgestimate was 1.19 [0.96 to 1.47],
 - desogestrel was 1.82 [1.49 to 2.22],
 - gestodene was 1.86 [1.59 to 2.18],
 - drospirenone was 1.64 [1.27 to 2.10],
 - cyproterone was 1.88 [1.47 to 2.42].
- Compared with non-users of OCs, the rate ratio for VTE in users of progestogen only OCs with levonorgestrel or norethisterone was 0.59 [0.33 to 1.03] or with 75 microgram desogestrel it was 1.12 [0.36 to 3.49], and for hormone releasing intrauterine devices it was 0.90 [0.64 to 1.26].

The authors conclude that the risk of venous thrombosis in current users of combined OCs decreases with duration of use and decreasing oestrogen dose. For the same dose of oestrogen and the same length of use, OCs containing desogestrel, gestodene, or drospirenone were associated with a significantly higher risk of venous thrombosis than OCs containing levonorgestrel. Progestogen only pills and hormone releasing intrauterine devices were not associated with any increased risk of venous thrombosis.

They advise that for women of normal weight and without known genetic predispositions, a low dose combined pill should be the first choice for contraception, but for women genetically predisposed to venous thrombosis who want to use hormonal contraception, a progestogen only pill or hormone releasing intrauterine device seems to be the appropriate first choice. They add that before firm general clinical recommendations on type of progestogen can be made, data on the effect of drospirenone on arterial endpoints are needed. However, they suggest that for women with an increased BMI, a low dose combined pill with levonorgestrel should be first choice.

The second study³ examined thrombotic risk associated with OC use, focusing on dose of oestrogen and type of progestogen, amongst 1,524 Dutch premenopausal women aged under 50 years who were not pregnant, not within four weeks postpartum, and not using a hormone excreting intrauterine device or depot contraceptive. The main outcomes were first objectively diagnosed episodes of DVT of the leg or PE. Cases were matched to 1,760 controls.

The following results were reported:

- Currently available OCs increased the risk of venous thrombosis 5-fold vs. non-use (odds ratio 5.0 [4.2 to 5.8]) and this risk differed by type of progestogen and dose of oestrogen.
- Use of OCs containing levonorgestrel was associated with an almost 4-fold increased risk of venous thrombosis (3.6 [2.9 to 4.6]) relative to non-users, whereas the risk compared with non-use was increased:
 - almost 6-fold for gestodene (5.6 [3.7 to 8.4]),
 - 7-fold for desogestrel (7.3 [5.3 to 10.0]),
 - almost 7-fold for cyproterone acetate (6.8 [4.7 to 10]) and
 - 6-fold for drospirenone (6.3 [2.9 to 13.7]).
- The risk of venous thrombosis was positively associated with oestrogen dose.
- There was a high risk of venous thrombosis during the first months of OC use irrespective of the type of OCs.

The authors suggest that the safest option with regard to the risk of venous thrombosis is an OC containing levonorgestrel combined with a low dose of oestrogen. The absolute risk of having a VTE on the pill is low. The baseline risk is 5 per 100,000 person years, and this increases to about 15-25 per 100,000 person years when taking the pill¹. However, because such a large number of women use the pill, even a small increase in adverse events will affect many.

1. BMJ 2009; 339:b3164
2. BMJ 2009; 339:b2890
3. BMJ 2009; 339:b2921

Positive effects of vitamin D

A meta-analysis of RCTs has assessed the effectiveness of oral supplemental vitamin D in preventing fractures in individuals aged 65+ years¹. The effect was dose dependant, with dosages less than 400 IU per day being ineffective. However, dosages of greater than 400IU per day reduced non-vertebral fractures (RR 0.80 [CI 0.72 to 0.89]) and hip fractures (RR 0.82 [CI 0.69 to 0.97]). The NNT for non-vertebral fractures was 93 for 12 to 84 months (mean 37) and for hip fractures was 168 for 12 to 84 months (mean 48). The effect was more pronounced with cholecalciferol (vitamin D3) than with ergocalciferol (vitamin D2).

Another meta-analysis assessed the effect of vitamin D on the risk of falling^{2,3}. High-dose vitamin D supplements (700-1000 IU per day) reduced the relative risk of falling by 19% (RR 0.81 [CI 0.71 to 0.92]). The NNT was 11 over about 21 months (range 2 to 36 months). Doses of less than 700IU daily did not significantly reduce fall risk.

See the [JAPC osteoporosis guideline](#) for the place of vitamin D. The calcium and vitamin D preparations in the PCT Primary Care Formulary are Adcal D3, Calcichew D3 Forte, and Calfovite D3.

1. Arch Intern Med 2009; 169:551-61
2. BMJ 2009; 339: B3692
3. www.npci.org.uk/blog/?p=782

Website of the month

To access the NPC database of patient decision aids (PDAs) go to www.npci.org.uk/iPDAs.php .