

Letters to the Editor

Use of contraception outside the terms of the product licence

That it should take our experts 17 pages to explain the problem of prescribing outside the licences of contraceptives surely exposes a credibility gap between regulation and prescribing. It seems we are now expected to know the detail of every licence of every drug we use and to tell the patient when we are outside the licence.

This is not practical advice. For example, how many of us when prescribing the progestogen-only pill from up to 5 days after Day 1 without an additional method will then explain that this is outside the licence? I suggest the answer is none! To follow the advice of the Clinical Effectiveness Unit (CEU) would be time consuming and may confuse the patient. Furthermore, what about the great majority of prescribers, within and without family planning, who do not read our Journal? How are they expected to follow the advice given? The licence system is clearly discredited, and in my opinion can safely be ignored providing one follows the best expert prescribing advice available. That surely is what we actually do and will continue to do.

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Reply

Thank you for the opportunity to respond to the comments from Dr Michael Cox regarding our CEU Guidance on 'The use of contraception outside the terms of the product licence'.¹ Dr Cox considers that it is unnecessary and impractical to inform patients when drugs are prescribed in circumstances outside the terms of manufacturers' product licences. He suggests that providing this information would cause confusion for patients.

The General Medical Council (GMC) website includes frequently asked questions on prescribing and indicates: "some medicines are routinely used outside the scope of their licence ... where current practice supports the use of a medicine in this way it may not be necessary to draw attention to the licence when seeking consent". Thus, the GMC supports doctors who make a judgment that certain examples of 'off-label' prescribing are so well established that explicitly informing patients is superfluous.

Nevertheless, in the context of contraceptive prescribing, patients will receive their medicine in the manufacturer's packaging along with the manufacturer's patient information leaflet. This leaflet will describe use of the medicine in accordance with the product licence. The CEU considers that a patient should always be informed about any aspects of her regimen that differ from this source of information, in order to minimise confusion and concern.

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Reference

- 1 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (July 2005). The use of contraception outside the terms of the product licence. *J Fam Plann Reprod Health Care* 2005; **31**: 225-242.

Confusion surrounding liver enzyme-inducing drugs

In the CEU Guidance on 'Drug interactions with hormonal contraception' it states in Box 9 that "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)".¹ In contrast, in the CEU Guidance on 'The use of contraception outside the terms of the product licence' it states in Box 23 that "Women may be given advice regarding 'tricycling' combined hormonal contraception ... if using liver enzyme-inducing drugs (Good Practice Point)".² Please clarify.

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References

- 1 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (April 2005). Drug interactions with hormonal contraception. *J Fam Plann Reprod Health Care* 2005; **31**: 144.
- 2 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit FFPRHC Guidance (July 2005). The use of contraception outside the terms of the product licence. *J Fam Plann Reprod Health Care* 2005; **31**: 235.

Reply

Thank you for your letter allowing us to clarify a discrepancy between two of the most recent evidence-based guidance documents from the CEU.^{1,2}

In developing evidence-based guidance documents the CEU undertake a systematic literature review using standard search strategies. In addition to this process our Expert Group may identify publications that we have missed during our systematic review. During the development of guidance on 'Drug interactions with hormonal contraception'¹ we did not identify any published evidence to support improved efficacy of combined oral contraception by avoiding a pill-free interval for women using liver enzyme-inducing drugs. Nevertheless, during a further systematic review for subsequent guidance on 'The use of contraception outside the terms of the product licence'² we identified one publication³ that provided some evidence to support a reduction in the pill-free interval. This evidence was taken into account in the most recent Guidance document.²

The CEU are unable to sustain 'living guidance', which would be actively updated as new information became available. All CEU Guidance documents are developed with the intention of being updated every 3 years. We are grateful to all journal readers and Faculty members who identify errors or inconsistencies, which we will ensure are addressed and rectified where necessary during the process of updating CEU Guidance.

Two CEU Guidance documents – those on 'Emergency contraception'⁴ and 'First prescription of combined oral contraceptive pill'⁵ – are due to be updated in 2006. We have requested feedback from Faculty members on these Guidance documents.

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References

- 1 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (April 2005). Drug interactions with hormonal contraception. *J Fam Plann Reprod Health Care* 2005; **31**: 139-150.
- 2 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (July 2005). The use of contraception outside the terms of the product licence. *J Fam Plann Reprod Health Care* 2005; **31**: 225-242.
- 3 Spona J, Elstein M, Feichtinger W, Sullivan H, Ludicke F, Muller U, et al. Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception* 1996; **54**: 71-77.
- 4 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (April 2003). Emergency contraception. *J Fam Plann Reprod Health Care* 2003; **29**(2): 9-16.
- 5 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (October 2003). First prescription of combined oral contraception. *J Fam Plann Reprod Health Care* 2003; **29**(4): 209-222.

Drug interactions with hormonal contraception

As the authors of the CEU Guidance document on 'Drug interactions with hormonal contraception'¹ make clear, the evidence base in this area remains poor. But when the very-best evidence runs out, as clinicians we still have a woman in front of us who needs help: based on the next-best evidence ...

I argue here that, of three appropriate contraceptive interventions for long-term users of enzyme-inducing drugs (EIDs) using the combined oral contraceptive (COC), available data suggest that eliminating as many pill-free intervals (PFIs) as cycle control allows, plus shortening those that are taken to 4 days, will make a substantial contribution to effectiveness: at least as great as increasing the COC dose or added condom use.

Yet in Box 9 and on page 145 we read: "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)".

First, the obvious: 'absence of evidence' is not the same as 'evidence of absence', that an effect is real. In this case, where is the evidence that such shortening or elimination of PFIs would *not* reduce the risk of ovulation?

Second, there is evidence: the research work reviewed by the World Health Organization (WHO) and the CEU² itself, establishing beyond reasonable doubt that the PFI is when ovarian follicular activity may return, more in some women than others; and that the longer the PFI the greater the ovulation risk. The reverse is also true, as in the very title of one of the reviewed papers, namely 'Shorter pill-free interval in combined oral contraceptives decreases follicular development'.³ The limit of shortening is elimination; and oddly enough the CEU recognises this in Table 3¹ when advising on the lower-risk drug interaction with *non-liver* enzyme-inducing antibiotics: "If fewer than seven pills are left in the packet after antibiotics have stopped the pill-free interval should be omitted...".

Whenever there is reduced ovarian inhibition due to enzyme induction, how could standard 'tricycling' as recommended⁴ and practised for more than 20 years in the UK – by the elimination of usually three PFIs and the shortening of the fourth (since 1999, to the 4 days evaluated by Sullivan *et al.*⁵) – not be advantageous? Pending a definitive randomised controlled trial comparing ovulation rates in EID users on 50 µg COCs with and without tricycling, the biological plausibility that tricycling increases COC efficacy is overwhelming.

As regards long-term users of liver EIDs, the CEU Guidance rightly states that: "Information should be given on the use of alternative methods".

By classifying use of these drugs in Category WHO 3 for the COC,⁶ WHO intends that the COC method "should not usually be recommended". Hence the preferability of an alternative unaffected method, ideally a long-acting method, is not in dispute – and it has been my recommendation for many years.

But what if the woman, after good counselling, comprehensively rejects or has contraindications to the available effective alternatives to the COC? This Guidance makes no distinction between short- and long-term users. It seems that, even in monogamous relationships, a long-term EID user should use an added method such as condoms together with (an increased dose of) the COC, indefinitely. Given how badly condoms are often used, especially I submit by men who perceive that their partner is already protected, the woman's conception risk will remain high.

Worryingly, it is not entirely reassuring that at least she will be using stronger COCs than usual. The problem of breakthrough pregnancies with