Dear Dave

Dear Dave,

can smoking cessation affect the dose of antipsychotics?

Components of cigarette smoke can increase the metabolism of some drugs by inducing cytochrome P450 enzymes (particularly CYP1A2). The classic example is theophylline which is metabolised more rapidly in smokers who consequently, on average, require higher maintenance doses than non-smokers. If a smoker quits, the enzyme activity returns to normal and lower doses of theophylline may be required to avoid toxicity.

There are a number of psychoactive drugs which can have their metabolism increased in smokers including haloperidol, chlorpromazine, fluphenazine, clozapine and olanzapine. Patients on these drugs who quit smoking should be observed as a dose reduction may be necessary. Indications for a possible dose reduction include increased drowsiness and extrapyramidal symptoms.

Most interactions are due to hydrocarbons, and other compounds present in the smoke, rather than nicotine. People who use nicotine replacement therapy when they quit smoking may still require a reduced dose of some antipsychotics.

Cannabis smoking may have a similar effect on the metabolism of some antipsychotic drugs.

Severe mental illness is associated with increased cardiovascular risk. Smoking cessation, although challenging, will be very beneficial.

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Who is Dave?

Pharmaceutical Programme Manager Dave Woods is a graduate of Manchester University (B.Sc. [Hons]) and the University of Otago (MPharm). Dave has extensive experience in hospital pharmacy, drug information, rational use of drugs and quality assurance. He has published on a range of subjects and holds editorial positions for several international journals.

If you have a clinical question email it to **dave@bpac.org.nz**

Dave and other members of the bpac[nz] team answer your clinical questions

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Dear Dave,

do statins cause nightmares?

Various sleep disturbances or abnormal dreams have been reported with statins including atorvastatin and simvastatin. Cases of nightmares associated with simvastatin, atorvastatin and other statins have been reported to ADRAC in Australia.[1]

Gregoor recently reported a case of nightmares in a 72-year-old woman taking atorvastatin.[2] The woman had a long standing history of hypertension, hypothyroidism, heart failure and chronic renal failure and was taking regular amlodipine, atenolol, thyroxine and losartan. Five days after starting atorvastatin she experienced severe nightmares each night for two and a half weeks. When the atorvastatin was stopped for five days the nightmares ceased and they recommenced when the drug was restarted. The nightmares stopped completely when the atorvastsin was discontinued.
A possible association between nightmares and statins has also been reported with the use of simvastatin and metoprolol.[3] In both cases reported in the literature the patients were taking a beta-blocker which have also been linked to nightmares, but they had not experienced any problems prior to starting the statin.

Nightmares or sleep disturbances associated with statins appear to be very rare and no causal link has been established. However, it is possible that the association is often unrecognised and may be more common than reports indicate. All statins have been implicated irrespective of lipid solubility and the time of dosing but it may be worth trying a switch to another statin if symptoms are troublesome.

Please report any suspected adverse events to CARM.

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Dear Dave,
how important is it to give simvastatin at night?

Contributed by Linda Bryant MClinPharm FPSNZ.

Clinical Advisory Pharmacists Association (CAPA)

Simvastatin is recommended to be taken in the evening. Patients are often better at taking medicines in the morning. What is the impact of this on cholesterol reduction?

Several studies indicate a diurnal variation in cholesterol synthesis, with increased synthesis at night.[1-3] The peak effect of simvastatin is approximately two hours after it is taken and the half-life is approximately two hours (complete elimination from the body in approximately 10 hours). Theoretically this means that simvastatin should be taken at night so that there is maximal inhibition of cholesterol production due to maximal simvastatin serum concentrations.

Saito et al undertook a randomised, controlled study in 172 people with dyslipidaemia to determine whether the theoretical principles of night time simvastatin were valid in practice.[3] The simvastatin dosages used were very low at 2.5 mg and 5 mg. Total cholesterol and LDL-cholesterol were measured. The results after three months are summarised in Table 1.

The authors concluded that simvastatin is significantly less effective at reducing total cholesterol and LDL-cholesterol when taken in the morning, compared to being taken in the evening. With a dose of 5 mg, the difference was a 7% less reduction in total cholesterol serum concentrations.

Other studies, using higher doses of simvastatin showed similar reduced effectiveness when taken in the morning.[5,6] These studies measured the lipid profile. There is currently debate about the 'non-lipid' effects and whether the timing of the dosage influences these effects (e.g CRP, endothelial function). Ideally outcome studies would be required to determine this, rather than the use of the lipid profile as a surrogate marker.

Table 1. Reductions in total cholesterol and LDL-cholesterol with morning vs evening doses.

	Reduction in Total cholesterol		Reduction in LDL-cholesterol	
	2.5 mg	5 mg	2.5 mg	5 mg
Morning dose	10.9%	13.7%	15.2%	19.3%
Evening dose	15.4%	20.7%	22.2%	28.5%
	$P < 0.001$	$P < 0.001$	$P < 0.05$	$P < 0.05$

Conclusion

Taking simvastatin in the morning is less effective at reducing total cholesterol and LDL than in the evening. The clinical trials of simvastatin used an evening dosage. This is the recommended dosage regimen and should be standard practice whenever feasible. However, if a person is unable to adhere to an evening dose, then a morning dose with less effectiveness, would be preferable to not taking it at all. The dosage of simvastatin may need to be increased to achieve the target serum cholesterol concentration. The effects on the non-lipid actions of simvastatin are unknown. It also needs to be remembered that the fasting lipid profile, usually done in the morning, would be 24 hours after the last dose, rather than the usual 12 hours when simvastatin is taken at night.

Atorvastatin appears to have an equivalent effect on the lipid profile whether taken in the morning or evening.[7-9]

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