

For any drug to work effectively, the dose has to be high enough. Invariably this will differ from patient to patient. With methadone, argues **Colin Brewer**, the dose could be as high 1100mg a day.

Methadone **the drugs do work** – so long as you prescribe enough

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THE correct dosage of methadone is as vital as the correct dosage of any other medicine. No drug works well – or works at all – if the dose is too low. A change in practice would be demanded if studies show patients suffering from chronic conditions like diabetes, high blood-pressure or epilepsy, were consistently being given inadequate doses.

Yet the fact that the average British methadone maintenance dose of 52mg¹ is roughly half the Department of Health (DoH) recommended dose of between 60-120mg² passes almost without comment.

Last year a very important Slovakian paper in *Heroin Addiction and Related Clinical Problems* cast doubt on even the DoH recommended dosage.³ It states that on average, a user should get more than 120mg per day.

In their study, the Slovaks adjusted doses individually for each patient based on both objective and subjective data. In other words, they increased the dose of methadone until both patient and doctor agreed that it seemed about right.

HIGHER DOSE – BETTER RETENTION

The Slovak researchers quote an important statement by The American Society of Addiction Medicine that, *'Determination of methadone dosage by programme policy is inappropriate. Dosage should be individually determined by well-trained clinicians based on subjective and objective data and be adequate for the individual patient in all cases'*. They add that the benefits of individualised methadone dosing are well documented.

On this point, the Slovaks

seem to know what they are talking about. Their programme has an overall retention rate of 84% at 12 months. Furthermore, only 13% of their patients produce urines positive for heroin on random testing. The average dose of methadone for the patients in this study was 134mg/day.

The retention and positive-urine rates are much better than you will find in almost any British programme.

Like most methadone programmes in former Soviet-block countries, methadone administration is strictly supervised with negligible take-home privileges, except at weekends.

If there is any tendency to be dismissive about this 'far away country of which we know little' as Neville Chamberlain famously said about Czechoslovakia in 1938, we clearly ought to think again.

US AGREE

A recent US paper reached similar conclusions as those in Slovakia. Following a relaxation of methadone regulations in Illinois, Maxwell and Shinderman compared selected 'high-dose' (HD) patients with control group (C) of patients restricted to the previous state maximum of 100mg/day.

The HD group had significantly better retention and fewer 'dirty' urine samples than the C group. Average methadone dose for the HD group was 285mg/day and the highest dose was 1100mg/day.⁴

BLOOD SIMPLE?

The Slovakian team also compared methadone doses with methadone blood-levels in all patients and the results are both fascinating and instructive.

Because there is a general correlation between dose and blood-level, there are numerous exceptions on both sides of the mean. Very few British methadone clinics however do blood methadone levels and virtually none do them routinely. The conventional wisdom is that the desirable range for adequate methadone maintenance treatment lies between 200–600 nanograms (ng) of methadone per ml of blood. (A nanogram is a billionth of a gram).

Despite the use of large doses, by British standards, 17.4% of the Slovak patients had blood methadone levels below the 200ng/ml threshold while slightly fewer, 15.9%, had levels above the 600ng/ml conventional upper limit. However, one patient taking



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275mg daily had a blood-level of only 260ng/ml while two of the highest levels – 800ng/ml and 1200ng/ml – were found in patients taking around 100-125mg daily.

The explanation probably lies in some research by Eap and colleagues from Lausanne.⁵ They showed that methadone metabolism is not as simple as most prescribers seem to think. Drug molecules are three-dimensional arrangements of atoms, mainly carbon, hydrogen, oxygen and nitrogen. But the same molecule often exists in mirror-image, right-handed and left-handed forms called stereo-isomers. Sometimes the two mirror-images of the molecule are equally potent but sometimes, one is much weaker than the other, as with methadone.

In most countries, methadone is supplied as a 'racemic' mixture, containing equal parts of D-(dextro/right-handed) and L-(laevo/left-handed) methadone. While L-methadone has powerful opiate activity, D-methadone has virtually none.

IMPORTANT DISCOVERY

Provided there is an adequate blood level of L-methadone, this doesn't matter very much, but Eap's team have shown that some people metabolise these two stereo-isomers at very different rates. The result is that some people with apparently high total blood-methadone levels have a high level only of inactive D-methadone and a low level of active L-methadone. This probably explains why a patient reported by Leavitt et al⁶ who needed and tolerated a methadone dose that gave him a theoretically lethal blood level of 1800ng/ml without any signs of overdose, also had severe withdrawal symptoms at the lower but still theoretically excessive blood level of 810ng/ml.

Conversely, some people with apparently inadequate blood methadone levels may feel well because their unusual metabolism gives them a relatively high proportion of L-methadone in their blood and only a small proportion of inactive D-methadone. In other words, proper methadone dosing should involve not just the prescriber's objective observations but also the patient's subjective feelings, supported where necessary by stereo-isomer blood-levels.

This discovery by the Lausanne group is one of the most important developments in methadone treatment since it was first used systematically by Dole and Nyswander. However, it only clarifies and explains what was soon apparent to the two pioneers. Dole and Nyswander were above all clinicians. They spent most of their working day treating heroin addicts. They saw their patients frequently and were therefore able to adjust all aspects of their treatment – not just the methadone dose – to their changing needs.

Dole and Nyswander⁷ said that many patients needed doses of methadone around 150-180mg daily for maximum benefit. Sadly, this clinical wisdom has

been ignored, even though it is now increasingly backed up by basic pharmacological research.

Most British methadone programmes are a disgrace and the Slovak model shows how it should be done.

Recently, someone at a BMA conference said that parts of the NHS were of third-world standard. If the speaker had our methadone clinics in mind, he wasn't far from the truth.

BAD POLICIES

Apart from inadequate doses, there is also the matter of inappropriate policy. As well as having cruel and illogical maximum dose limits of 80mg per day or less, many clinics also insist on forced and relentless dose-reductions rather than providing indefinite maintenance, or even maintenance for a minimum period of two years.

The evidence shows very clearly that such forced reductions are counterproductive and merely throw patients back onto the street just as they are starting to get their lives in order. Patients are dying because of these policies and it is time that those responsible for them were threatened with some sanctions unless they very quickly get their houses in order.

Methadone maintenance is by no means the only treatment for heroin abuse but it is a very good one and is extremely well documented.

We must acknowledge that the Slovakian approach works and British doctors and drug workers must learn from their experience. However, nothing is likely to change here until the running of methadone programmes is returned to those – whether doctors, senior nurses or senior psychologists – who not only know the evidence-base but also have regular opportunities for applying that knowledge to the patients they treat. ■

references

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