Improving the use of methadone for drug users with tuberculosis to prevent withdrawal

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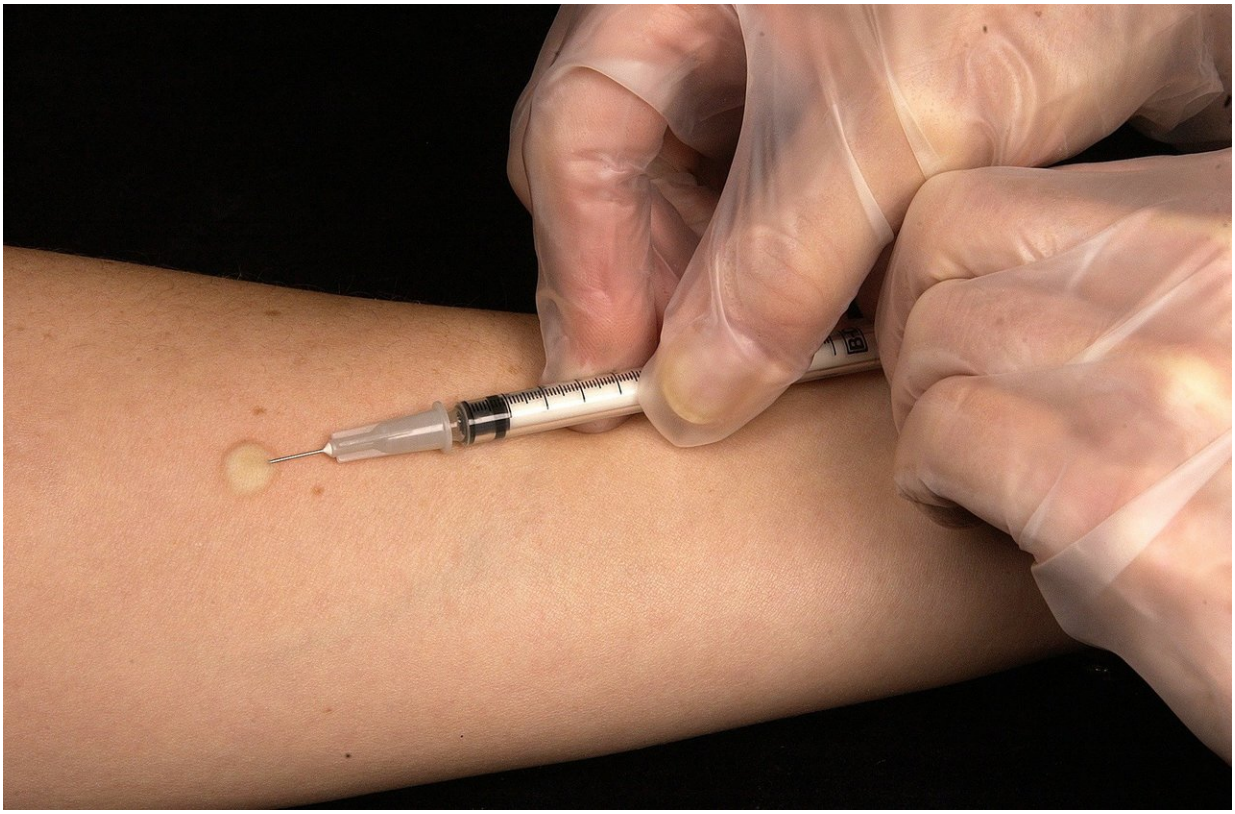

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Drug users on methadone programmes who contract tuberculosis (TB) should receive effective treatment while maintaining the correct level of methadone in their bodies, following a virtual clinical trial by pharmacy researchers at Aston University in partnership with drugs charity

Addaction.

Oral methadone is a widely used medication for opioid substitution treatment globally. To ensure this type of treatment is successful, dose optimisation is critical in ensuring both withdrawal symptoms/cravings and overdose/toxicity effects are limited.

Scientists from the School of Pharmacy at Aston University in Birmingham, have been researching how drugs like methadone interact with other drug treatments such as rifampicin, used to treat tuberculosis. However, a wide range of drugs for epilepsy, HIV and some antibiotics can cause a similar interaction and it is therefore critical to understand what the clinical implications of these types of interactions could be.

By ensuring that the best possible doses are used to treat tuberculosis in patients on methadone, the researchers found their virtual trial to be 94 percent effective in ensuring patients do not get withdrawal symptoms or suffer a relapse into drug addiction while undergoing treatment for TB.

The findings, which are published in *Drug and Alcohol Dependence*, are significant for pharmacists and clinicians who will be able to use the study as a guide for treatment for their patients.

Globally, over 17 million people misuse illicit drugs, with opioids accounting for around 70 percent of drug misuse. Some of the latest data from Public Health England estimates over 257,000 people aged 15 to 64 are using opiates, with 75 percent of those who engage with drug treatment services seeking support for opiates, particularly problems with heroin.

Drug users are often stigmatised and due to lifestyle choices they are at a higher risk of contracting tuberculosis and other infections such as HIV and Hepatitis C.

According to the World Health Organisation, TB remains a major global health problem. It causes ill health for approximately 10 million people each year and is one of the top ten causes of death worldwide. In England in 2017 there were 5,102 TB cases—with 13 percent of those people with TB having at least one social risk factor for the illness, such as a history of substance misuse, homelessness or time spent in prison.

Now Aston University researchers have developed and tested a 'virtual clinical trial' using previous clinical studies that have been published for methadone and used pharmacokinetic modelling (a mathematical computer modelling technique) to simulate the interaction between methadone and the anti-tuberculosis drug, rifampicin, which is known to increase the breakdown of methadone in the body.

While taking rifampicin the level of methadone in the body can significantly drop, so there is a need to increase it gradually and then decrease it at the right level once treatment for TB has ended.

Dr. Raj K. Singh Badhan, Lecturer in Pharmacokinetics, Aston University said: "We found that rifampicin significantly alters the level of methadone in the blood and necessitates dose adjustments, with daily doses of almost double those commonly used in clinical practice required for optimal levels of methadone in the blood.

"This interaction has wider implications, drugs that are routinely used for epilepsy, HIV and some antibiotics may also result in a similar phenomenon occurring and this research hopes to illustrate the clinical implications of this interaction and offer some approaches to mitigating clinical risk."

Using 11 retrospective clinical studies an R-methadone model was developed and the researchers were able to test the impact of differing daily doses of methadone and how it interacted with the TB treatment.

Doses were tested at 60mg, 90mg and 120mg over 365 days. Dose escalation during TB treatment was tested as well as dose reduction following cessation of rifampicin.

A dose increase to 160mg once a day for methadone (from the standard dose range of 60 to 120mg once daily) when starting rifampicin treatment was found to be required to ensure levels of methadone were kept up in the blood.

The virtual trial found that 94 percent of the patients had methadone levels within a range which was associated with a good clinical outcome, meaning the patients were at low risk of suffering withdrawal symptoms or any other toxic effects.

The researchers found when stopping rifampicin treatment a reduction in the methadone dose was required at least one week before rifampicin was stopped. This was key to ensuring 93 percent of subjects would again show a good clinical outcome. This meant a dose reduction of 10 mg every two days commenced just prior to the TB treatment ending to ensure methadone levels were kept stable.

Director of Pharmacy at Addaction, Roz Gittins said: "We know that when people are taking methadone for opioid dependency and rifampicin for tuberculosis at the same time, this can be challenging. We know that there has been a lack of information to advise prescribers on how to change the doses of medication in this situation.

"Using computer modelling, we have looked at how doses of these medicines may be changed to get the best possible patient outcomes. We plan to apply this research in the 'real world' and hope that in the next year we will be able to carry out similar work with other medications that are used in mental health and substance misuse services."

More information: Raj K.S. Badhan et al. The optimization of methadone dosing whilst treating with rifampicin: A pharmacokinetic modeling study, *Drug and Alcohol Dependence* (2019). DOI: 10.1016/j.drugalcdep.2019.03.013