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▶ Critical issues in the treatment of hepatitis C virus infection in methadone maintenance patients.

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European and US studies show that methadone patients stick with therapy for hepatitis C disease and do as well as other patients, bolstering the case for drug services to encourage clients to consider diagnostic testing and therapy.

Abstract This review focuses on the medical care of patients in methadone or buprenorphine maintenance programmes who are infected with the hepatitis C virus, with or without co-infection with HIV. Literature searches identified papers since 1990 on antiviral therapy for hepatitis C infection and on liver transplantation in opioid maintenance patients. Their findings and the review's conclusions are most applicable to developed countries.

Misuse of drugs by injection is the most significant infection risk factor in most developed countries. Sexual transmission is possible but inefficient. From 53–96% of injectors test positive for the hepatitis C antibody (indicative of infection). Infection rates climb rapidly to reach in some studies 65% a year after people start injecting. From 67–96% of patients starting methadone maintenance treatment are already infected and may require treatment.

Currently recommended treatment consists of weekly injections of pegylated interferon supplemented by daily oral ribavirin. This clears the virus ('sustained virological response') in around half of patients, with large variability depending on the variant of the virus and other factors. The recognised criterion for clearance is negative HCV-RNA 24 weeks after the end of treatment. Even if this is not achieved, patients often still benefit from the therapy.

Six studies were found which followed up methadone maintenance patients in treatment for hepatitis C infection. Rates of sustained virological response ranged from 28% to 94%. Studies which contrasted methadone patients with other people also being treated

for hepatitis C infection found no significant differences in success rates or in the frequency of psychiatric side-effects. In five of the six studies from 72% to 100% of methadone patients completed the treatment, excellent completion rates. None of the studies investigated the risk of hepatitis C re-infection (for example, due to relapse to unsafe injecting) in the period after sustained virological response has been established, but other studies of drug users who continue to inject have found this is rare. Co-infection with HIV complicates treatment of both diseases, but in suitable patients antiviral therapy for hepatitis C infection can still be effective.

Liver transplantation may be the only treatment option for patients who have progressed to end-stage cirrhosis. This has been successful in methadone maintenance patients but has not been used widely. In four relevant US studies, post-operative substance use was rarely documented (six out of 52 patients) but, as with non-drug using patients, survival was compromised by recurrent infection and post-operative complications.

Methadone maintenance does not cause or aggravate liver problems, liver disease does not normally affect the required dose of methadone, and the reviewed studies show that high quality hepatitis C infection therapy can successfully be provided to methadone patients. Nevertheless, the current reality for most falls far short of this standard. Barriers to drug injectors receiving antiviral therapy include practical issues such as cost and transport, and lifestyles complicated by substance use, psychiatric problems, and housing and legal difficulties. They may also be unaware of their infection, the nature of the disease, or the treatments available, and distrust health services. Treatment providers may have negative attitudes to substance users and believe they will not comply with treatment. Provision of hepatitis C services through drug treatment programmes is underdeveloped. Research on overcoming these barriers suggests that entry in to methadone maintenance can act as a gateway to hepatitis C treatment. Among methadone patients, compliance with treatment is aided by effective therapy for psychiatric disorders, a multi-disciplinary team, and a treatment site acceptable to the patients (often, but not necessarily, the same site providing methadone treatment).

The authors concluded that the literature strongly supports the feasibility of antiviral therapy in methadone patients. High quality medical care for all aspects of hepatitis C infection can be provided with acceptable rates of compliance with the therapy and of successful outcomes in the form of a sustained virological response. There is no scientific or clinical reason to withhold antiviral therapy from methadone or buprenorphine maintenance patients.

FINDINGS National strategies on hepatitis C published or being prepared across the UK (Northern Ireland; Wales; Scotland; England) aim to raise awareness and improve diagnosis and treatment entry rates. In recent years progress has been made but arrangements remain deeply unsatisfactory.

The Health Protection Agency has summarised the state of play across the UK, where an estimated 184,000 people are chronically infected. Around 90% of new infections occur among drug injectors. All those chronically infected are now considered candidates for treatment, but for most an essential first step is missing because they remain undiagnosed, leaving an estimated 130,000 people in England and Scotland unaware that they may need treatment.

Even among drug service clients, in 2007 nearly half the (in England) 40% or so infected with the virus were unaware of their infection. By that year the proportion of drug service clients who had been tested (not necessarily at the drug service itself) had risen to 75%, but only about 40% recalled being tested within the past two years. Drug services, trusted and regularly visited by their clients, are probably the sites most likely to facilitate testing. Yet in 2004, 22 drug services in England Wales were found on average to have tested just 5% of their caseloads over a six-month period. Introduction of the simpler dried blood spot test more than doubled the testing rate. Oral swab testing has also permitted an expansion of testing at drug services. However, the infrastructure remained poor in 2006/07, when drug action teams had recorded hepatitis C tests for only just over a fifth of injectors attending drug services in their areas. Nearly two thirds of areas had not integrated hepatitis C testing in to their open access services. Responding to hepatitis C was the service strand on which teams scored worst in the review.

Despite England's head start in national planning, lack of funding and of specific targets has undermined implementation; even among those whose chronic infection has been diagnosed, just 3% receive antiviral treatment each year. Local arrangements to identify and transition patients from testing through to treatment have improved, but when last audited by a parliamentary committee, two thirds of responding health commissioning authorities fell short of effectively implementing the national plan. Bottlenecks in treatment capacity reduce the incentive to extend testing and diagnosis. Without treatment slots to go on to, diagnosing more patients would simply extend waiting lists, risking a failure to meet general diagnosis–to-treatment waiting time targets.

In Scotland, the combination of under-testing and poor treatment access has meant that just an estimated 4% of chronically infected individuals have been treated. Among those who have been diagnosed, the proportion is estimated at 14%. A particularly well informed and well funded national plan aims to make significant progress in the near future. At the time of writing Wales had yet to finalise its plan. Northern Ireland's plan was published in 2007.

Guidance from Britain's National Institute for Health and Clinical Excellence (NICE) on antiviral therapy for moderate or severe chronic hepatitis C disease recognises that injectors may not start therapy, or start but quickly leave, but also that beyond this point compliance and disease outcomes match those of other patient groups. Compliance problems were not considered so great as to render treatment no longer cost-effective. Neither was the risk of relapse to injecting considered a bar to treatment, since reinfection was rare. Later NICE extended this verdict to mild forms of the disease.

Around half of drug users in treatment in Britain are in methadone programmes. Regular medical and pharmacy contact offers a ready-made platform for enhancing compliance with the demanding interferon-based therapy for hepatitis C. The featured review shows this has been used to good effect in the USA and Europe. There is also evidence that it cost-effectively contributes to saving lives. A New Zealand study has profiled a hypothetical set of patients being maintained on methadone of whom over 80% are infected with hepatitis C. Its conclusions for non-Maori patients are likely to be broadly applicable to the UK. Because it reduced overdose deaths and suicide, the starting point

was that methadone itself was an effective life-saver. Treating hepatitis C infection once patients had stabilised on methadone further prolonged life but (partly because of the averted costs of later having to treat more advanced disease) at no greater cost per life-year saved. More lives would be saved at lower per-year cost if patients were stabilised and anti-viral therapy started earlier. These calculations did not take in to account the improved quality of life of the patients nor the potential for reduced spread to other people.

Starting anti-viral therapy soon after infection and among younger patients are important factors in its success and should also help reduce transmission of the disease, highlighting the importance of screening high risk groups even if there are no symptoms of disease. The high chance of finding infections means screening programmes among drug injectors meet common European standards of cost-effectiveness in terms of the cost per year of life gained, adjusted for quality of life.

Implications of these and other findings have been encapsulated in recommendations from Westminster's All-Party Parliamentary Hepatology Group. For drug services, integrating the new simpler testing procedures in to their service provision so patients do not have to go elsewhere for testing will be an important first step, enabling advice to be given (such as not drinking) even if treatment is not immediately available. Assuming treatment slots are available, proactively linking patients to these services (such as going with them to their first appointments) and offering continuing support during the therapy will help patients start and complete the therapy. Medically based services such as methadone prescribing units, which in any event require regular attendance, offer an opportunity for hosting hepatitis C clinics to oversee the therapy on the same site.

The medical considerations outlined above are not the only ones to influence the decision on testing and treatment. Issues such as the implications for life insurance or mortgage agreements and psychological and relationship impacts also need to be addressed in pre-test counselling.

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