Which substitution pharmacotherapy is most effective in treating opioid dependence?

Trial: Johnson RE, Chutuape MA, Strain EC, et al. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med 2000; 343: 1290-1297.*

Question

Are levo acetyl methadol (LAAM) and buprenorphine as effective as methadone for substitution treatment of opioid dependence?

Trial details

Design: Randomised controlled trial, double-blind.

Setting: Outpatient clinic in Baltimore, United States.

Participants: 220 people categorised as opioid dependent by DSM-IV;[1] groups similar on demographics and drug use history. Exclusion criteria were medical and psychiatric illness requiring long-term medication, and pregnancy.

Interventions: (i) Levo acetyl methadol (LAAM) at 75–115 mg, (ii) buprenorphine at 16–32 mg, (iii) methadone at 60–100 mg ("high dose"), or (iv) methadone at 20 mg ("low dose"). LAAM and buprenorphine were given three times a week, methadone daily. LAAM and methadone were given orally, buprenorphine sublingually. Participants attended the clinic daily for two weeks of dose induction, then thrice weekly with take-home doses. The scheduled duration of the trial was 17 weeks.

Main outcome measures: Retention in treatment; illicit drug use; participants' global ratings of their drug problem.

Main results: Days retained in the study (mean ± SE) — LAAM (i), 89 ± 6; buprenorphine (ii), 96 ± 4; "high dose" methadone (iii), 105 ± 4; "low dose" methadone (iv) 70 ± 4. Significantly more days retained for groups (i), (ii) and (iii) compared with group (iv) ($P < 0.001$), and group (iii) compared with group (i) ($P = 0.02$). Trial was completed by 53% of group (i), 58% of group (ii), 73% of group (iii), and 20% of group (iv), with 4, 3, 6 and 26 of groups (i), (ii), (iii) and (iv), respectively, transferred to rescue treatment (standard methadone maintenance). Twelve or more consecutive opioid-negative urine specimens were obtained in 36% of group (i), 26% of group (ii), 28% of group (iii) and 8% of group (iv) ($P < 0.005$).

Conclusion: Compared with low-dose methadone, LAAM, buprenorphine and high-dose methadone substantially reduce the use of illicit opioids.

Commentary

Rationale for the trial

Substitution treatment with methadone has proven effective in reducing heroin use and providing an opportunity for improvement in health and social functioning for dependent drug users.[2] However, methadone maintenance does not suit all people. LAAM, a full opioid agonist, and buprenorphine, a partial agonist, are promising alternatives to methadone maintenance. Buprenorphine has a lower risk of overdose than methadone, and both buprenorphine and LAAM can be given less frequently than daily, providing increased flexibility and reduced costs. Previous research supports the feasibility of substitution treatment with LAAM and buprenorphine, and each of these drugs has been compared with methadone in controlled studies.[2] The rationale for this trial by Johnson and colleagues was to compare LAAM and buprenorphine with standard ("high dose") methadone maintenance and a control in a single study. Methadone at 20 mg daily was chosen as the control because it has the capacity to suppress opioid withdrawal, but is only minimally effective as a maintenance treatment. For ethical reasons, a rescue treatment was available for all study participants who responded poorly to experimental treatment.

Trial methods

Participants were stratified, then allocated by random number generation, with participants and clinic staff unaware of group assignments and doses. Each day participants received three solutions (two oral, one sublingual), only one of which contained active medication. Otherwise all groups received equivalent treatment. It seems likely that participants in the "low dose" methadone group might have been able to guess their group allocation, but the adequacy of blinding was not discussed by the authors. There were clear definitions for transfer to rescue treatment, drop-out, and calculation of retention in treatment, and adjustments for missing data. All analyses were based on intention to treat.

New information

LAAM and buprenorphine are significantly more effective than "low dose" methadone in reducing illicit opioid use, and of similar effectiveness to "high dose" methadone. Illicit opioid use was somewhat lower for the LAAM group — the use of larger group sizes might have provided sufficient statistical power for a significant difference to be detected. Participants in the "high dose" methadone group were retained in treatment for more days, although the difference achieved statistical significance only for "high dose" methadone compared with LAAM. Most of the difference between "high dose" methadone and LAAM occurred in the first two weeks of treatment.

Implications for clinical practice

As most doses are supervised by a pharmacist, the possibility of less than daily dosing is a practical benefit of LAAM and buprenorphine. This trial shows that thrice-weekly

dosing with these medications reduces illicit opioid use to a similar extent to that achieved with standard methadone maintenance treatment, and indicates that both buprenorphine and LAAM are more effective than "low dose" methadone. The lower retention rates associated with LAAM make it necessary to have available an alternative therapy for people who do not respond, and to give particular attention to patients during induction. More participants in the LAAM group were withdrawn because of side effects, but the details of these side effects were not reported, and this needs to be explored further. This report did not describe changes in participants' health and social functioning, which are important in considering the overall effectiveness of treatments for opioid dependence.

Buprenorphine is available in Australia, but LAAM is available only under clinical trial arrangements.

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1. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, DC: American Psychiatric Association, 1994.
2. Ward J, Mattick RP, Hall W. Methadone maintenance treatment and other opioid replacement therapies. Amsterdam: Harwood Academic Publishers, 1998.

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