ALCOHOL DRUG FINDINGS *Research analysis*

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Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: a randomized controlled trial.

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From the USA the first study to show that the drug clonidine can not only ease withdrawal from heroin but also help prevent relapse, seemingly by moderating stress-related craving for the drug.

SUMMARY Clonidine is a drug taken orally which though it has no opiate-type effects, helps to subdue some of the unpleasant symptoms of withdrawing from opiate-type ('opioid') drugs such as chills, cramps and diarrhoea. For this reason it has been used to help patients complete detoxification programmes. Based on laboratory studies with animals, researchers suspected that the same drug might also help prevent relapse to illicit opioid use after patients have stopped taking these drugs. The suspected mechanism was that clonidine helps prevent stress leading to craving for drugs which in turn precipitates relapse.

To test this theory, between 2006 and 2013, researchers sited at an outpatient addiction treatment clinic in Baltimore in the USA recruited 208 opioid-dependent patients who agreed to join the study. Those who followed through on their agreement were prescribed buprenorphine on a maintenance basis to substitute for heroin or the other opioid drugs to which they had become dependent. Patients had to attend the clinic every day to be administered buprenorphine.

As indicated by frequent urine tests at the clinic, during the fifth and sixth weeks of their buprenorphine treatment 118 had sustained abstinence from illicit opioids. Abstinence had been incentivised by a 'contingency management' programme which offered shopping or other vouchers for negative tests. Starting the following week, as well as buprenorphine these 118 patients were randomly allocated to be administered clonidine every day for 14 weeks, or an identical but inactive placebo. Typically they were black, male heroin injectors in their late 30s. Interest centred on whether during weeks nine to 20 (after doses had been adjusted) clonidine helped suppress lapse (any opioid-positive or missed urine test) or relapse (two or more consecutive lapses) to illicit opioid use. After this 'intervention' phase, patients were withdrawn from clonidine/placebo, and then after 28 weeks also withdrawn from buprenorphine or helped to transfer to another treatment programme.

Key points
From summary and commentary

Clonidine is a medication commonly used to ease heroin withdrawal, but it may also help prevent resumption of heroin use by avoiding stress-related craving for the drug.

The first study to test this theory found that buprenorphine-maintained patients allocated at random to clonidine were on some measures less likely to use illicit opiate-type drugs and less likely to experience craving for heroin associated with stress or poor mood.

This single study has not yet established that in routine practice clonidine will prove useful in this new role; in other circumstances patients may simply not take the pills.

Main findings

During the intervention phase patients allocated to clonidine lasted longer without lapsing to illicit opioid use. After nine weeks on clonidine/placebo, nearly all the placebo patients had used illicit opioids or missed a test compared to only just over a quarter of clonidine patients. Adjusted for cocaine use at the start of the trial, the extra delay to lapse was statistically significant. Clonidine patients also sustained continuous abstinence for a significantly longer time – on average 35 versus 26 days. However, clonidine did not significantly delay relapse to consecutive days of illicit opioid use, nor were clonidine patients more likely to provide opioid-negative urine samples. Though cocaine use was unaffected, clonidine patients were more likely to test negative for cannabis use.

Patients had been offered rewards to respond to signals from an electronic diary emitted four times a day by recording their degree of stress, intensity of craving for heroin, mood (the dimensions were happiness, irritation, tiredness, and boredom), and whether in the past hour they had encountered 'cues' (such as seeing the drug) which might prompt heroin use. Craving for heroin was more likely when cues had been experienced and when patients felt stressed or in a poor mood. However, poor mood and stress were significantly less likely to prompt craving among clonidine than among placebo patients, an effect most marked at intermediate levels of stress or poor mood. When stress or poor mood were absent or rated at the highest level, there were generally little or no differences in the degree to which craving was also present. It was as if clonidine partially 'decoupled' craving from stress and poor mood, weakening the relationships between them. This was not the case with environmental cues to heroin use. Neither stress, mood, nor cue-exposure was associated with the likelihood that the next urine test would reveal illicit use of heroin or other opioids.

The authors' conclusions

The featured study was the first to show that clonidine could be used to prevent lapse to illicit use of opiate-type drugs as well as to help ease withdrawal. Though demonstrated among patients maintained on buprenorphine, there is no reason to believe that the effect would be limited to such patients. In addition, clonidine was modestly effective in decoupling stress from craving for heroin.

The clinical benefit of delaying initial lapses seems clear in the context of findings that 'abstinence begets abstinence'. Though clonidine did not delay multiple consecutive lapses ('relapses'), it did extend the average length of time patients sustained non-use of opioid drugs. Patients most likely to experience this benefit are those susceptible to stress-induced lapses and those who experience persistent though moderate stress.

That clonidine delayed lapse but not relapse seems in line with laboratory studies which have found that such

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That clonidine delayed lapse but not relapse seems in line with laboratory studies which have found that such medications can block drug-seeking and craving induced by stress, but not by having been given the drug. Similarly, in this study initial lapse was delayed by clonidine, but the medication did not prevent this experience of taking an opiate-type drug leading to further use.

FINDINGS COMMENTARY A relatively safe, non-abusable drug which does not itself induce dependence would be a valuable addition to the range of medications available to help moderate opiate use among patients dependent on heroin or other opioid drugs. Clonidine also avoids the absolutist nature of the opiate-blocker naltrexone, which patients generally stop taking because it renders opiate use ineffective. For reasons discussed below, while the potential is clear, as the authors acknowledge this single study has not yet established that in routine practice clonidine will prove useful in this new role.

It took seven years to find the 208 patients who agreed to join the study and only 118 of these both followed through on their agreement and were able to become abstinent from illicit opioids, perhaps indicative of their being an atypical set of patients. Those most in need of moderating their opioid use – the ones who could not become abstinent – were excluded from the study. The rest became abstinent with the help of monetary incentives not normally available at British clinics.

The authors argue that the presumed ways clonidine prevents lapse – by avoiding craving being stimulated by stress or poor mood – should make it suitable for patients other than those being prescribed buprenorphine. There is, however, a practical reason why clonidine might have less of a role beyond buprenorphine or methadone maintenance programmes. In the study, to get their buprenorphine patients had to attend the clinic daily, and at these visits they were also administered clonidine along with buprenorphine. Without the incentive of an opiate-type medication to induce attendance, many more may have simply dropped out and not taken the clonidine, as may patients prescribed clonidine to take at home. Even if in theory clonidine would help prevent lapse in a range of opiate-dependent patients, it cannot do so unless they take it. To make the most of this medication, arrangements may need to be made (as for oral naltrexone) for family or other associates to ensure the patient takes the pills.

Clonidine is thought to prevent lapse by avoiding craving being stimulated by stress or poor mood. Plausible as this is, the study provided no direct confirmation. Clonidine helped avoid stress or poor mood being accompanied by craving for heroin, but stress and poor mood were not related to subsequent lapse to illicit opiate use. Stress- or mood-related craving may have been moderated by clonidine, but whether this is what helped prevent lapse is unclear. It also seems possible that rather than stress and poor mood leading to craving, the reverse was the case – that patients who were trying to sustain abstinence but found themselves tempted to use became stressed, unhappy and irritable. Then clonidine's role might have been to prevent craving leading to stress and poor mood, not the reverse. Arguing against this is that craving due to any cause was less likely to be experienced by the clonidine patients.

Depending on the phrasing of the questions and how many patients chose each response option, the levels of poor mood and stress at which clonidine helped prevent craving may be interpreted as simply 'normal'. If this was the case, the implication would be that clonidine prevented craving when patients were feeling average on these dimensions. When stress and poor mood became unusually high, clonidine no longer protected against craving. This interpretation would be contrary to the study authors' presumptions about how clonidine worked.

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