Clonidine: new use of an old medication to reduce stress-related substance use

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ABSTRACT FROM: Kowalczyk WJ, Phillips KA, Jobes ML, *et al.* Lonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: a randomized controlled trial with ecological momentary assessment. *Am J Psychiatry* 2015;172:760–7.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Alcohol, marijuana and opioids can reduce anxiety, elevate one's mood and people sometimes turn to them for relief from stress.[1] This self-medication can lead to a substance use disorder in someone that has never had one; precipitate a relapse; compromise treatment response; or result in a fatal overdose. Relief is typically short-lived and continued use can result in a new disorder. For example, heavy alcohol use can increase anxiety and depression; and stimulants increase anxiety, precipitate psychotic symptoms or cause depression (crashing). These issues are described in the substance use section of the Diagnostic and Statistical Manual (DSM).[2]

METHODS OF THE STUDY

The study was a randomised trial to see if clonidine decouples stress-related cocaine and heroin administration in patients maintained on buprenorphine. The investigators consented 208 at the start of a maintenance programme where they had three drug screens a week and could earn a voucher exchangeable for goods and services for each opioid negative urine test. The 118 that were abstinent from drugs in weeks 5–6 were randomised to clonidine (N=61) or placebo (N=57) while continuing buprenorphine. Clonidine or placebo was started at week 7 and the clonidine dose increased from 0.1 mg/day at week 7 to 0.3 mg/day by week 9 and continued through week 20. All participants were given an electronic diary with an audible prompt at four randomly chosen times during waking hours. At each prompt they were asked to report on stress, craving, mood and drug-related environmental cues and to answer stress, craving and mood prompts with 'NO!!', 'no??', 'yes??' or 'YES!!'. Clonidine was tapered to zero in weeks 21 and 22 and a buprenorphine taper was started in week 28 and ended in 8 weeks if the participant was not transferred to methadone.

Outcomes were lapse and relapse during weeks 9–20. Lapse was defined as any opioid-positive or missed urine test; relapse as two or more consecutive lapses. Dropouts were counted as having lapsed and relapsed. Randomised participants were older (38.7 vs 36.3 years) and used opioids on fewer days in the month before enrolment (24.7 vs 26.8) but otherwise similar to those not randomised. Approximately two-thirds of participants in each group completed the first 20 weeks. The clonidine group had the longest duration of consecutive day's abstinent (34.8 day's vs 25.2 days) but there was no difference in time to relapse though clonidine patients took longer to lapse. Reports of stress were associated with increased heroin craving but clonidine partly blunted this relationship when stress was highest. Further analyses showed that clonidine reduced the likelihood of heroin craving (6.3% vs 11.8%) and decoupled stress from craving ($p<0.001$). This buffering was not seen for drug-related cues. No significant adverse effects were observed and additional analyses showed some clonidine effect in reducing marijuana positive drug tests.

WHAT DOES THIS PAPER ADD

- It provides experimental data that are consistent with the observations about negative affects precipitating drug use in an attempt to 'self-medicate.'[1]
- It demonstrates how electronic technology can be used to assess clinically relevant but fleeting events that are difficult to identify by patient interviews.
- Addiction has often been thought of as a moral failure or lack of will power. These data provide 'food for thought' about its biological components and point to a potential new use for an old medication.

LIMITATIONS

- The effects were mild or moderate; they extended the time to lapse but did not stop it and did not reduce relapse.
- The prompts asking to report on stress, craving, mood and drug-related environmental cues could have missed events that occurred at other times and might have changed the results.

WHAT NEXT IN RESEARCH

Study findings need to be replicated in one or more research or practice settings. This work might best be started with patients on agonist treatment and then extended to patients with stimulant or other non-opioid addictions that are not being treated with agonist maintenance. Second, clonidine may be useful for exploring biological mechanisms of craving that are relevant in view of craving being part of the DSM-5 criteria for diagnosing substance use disorders.[2]

DO THESE RESULTS CHANGE PRACTICE AND WHY?

Probably not. These findings need replication if they are to change practice, however they seem worth trying with a few patients that are self-medicating to reduce anxiety, depression or other negative effects. Making sure the patient understands the potential side effects of clonidine, that using it is 'off-label', and monitoring for clinically significant hypotension would need to be part of the treatment plan. Such clinical experiences could be helpful in formulating the design of clinical trials to see if these findings can be replicated.

Competing interests None declared.

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