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Reduction in arterial stiffness and vascular age by naltrexone-induced interruption of opiate agonism: a cohort study

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ABSTRACT

Objective: To prospectively assess if opiate antagonist treatment or the opiate-free status could reverse opiate-related vasculopathy.

Design: Longitudinal Open Observational, Serial 'N of One', over 6.5 years under various treatment conditions: opiate dependence, naltrexone and opiate-free.

Setting: Primary care, Australia.

Participants: 20 opiate-dependent patients (16 males: 16 cases of buprenorphine 4.11±1.17 mg, two of methadone 57.5±12.5 mg and two of heroin 0.75 ±0.25 g).

Intervention: Studies of central arterial stiffness and vascular reference age (RA) were performed longitudinally by SphygmoCor Pulse Wave Analysis (AtCor, Sydney).

Primary outcomes: Primary outcome was vascular age and arterial stiffness accrual under different treatment conditions.

Results: The mean chronological age (CA) was 33.62 ±2.03 years. The opiate-free condition was associated with a lower apparent vascular age both in itself (males: p=0.0402 and females: p=0.0360) and in interaction with time (males: p=0.0001 and females: p=0.0004), and confirmed with other measures of arterial stiffness. The mean modelled RA was 38.82, 37.73 and 35.05 years in the opiate, naltrexone and opiate-free conditions, respectively. The opiate-free condition was superior to opiate agonism after full multivariate adjustment (p=0.0131), with modelled RA/CA of 1.0173, 0.9563 and 0.8985 (reductions of 6.1% and 11.9%, respectively).

Conclusions: Data demonstrate that opiate-free status improves vascular age and arterial stiffness in previous chronic opiate users. The role of opiate antagonist treatment in achieving these outcomes requires future clarification and offers hope of novel therapeutic remediation.

ARTICLE SUMMARY

Article focus

- Opiate-related vasculopathy identified consistently in several large studies but reversibility has not been studied.
- Vascular age is a proxy for organismal age.
- Reversal of atherosclerosis and slowing of the ageing process are both important subjects of current research in their own right.

Key messages

- Opiate agonist-related vasculopathy associated with even low doses of opiates, can be reversed by antagonist-induced drug-free state with large effect sizes of 6% and 12% in naltrexone and opiate-free conditions, respectively.
- Naltrexone implants are a useful bridge to produce this opiate-free condition in many patients.
- Improvement in major measures of surrogate biological age implies that wider evaluation and deployment of naltrexone implants for their apparent health benefits should be considered in opiate-dependent populations.

Strengths and limitations of this study

- Serial 'N if One' Study design, where each patient serves as their own control.
- Large effect sizes and statistically highly significant results achieved even in a small study.
- Replication in larger samples, including study of other biomarkers of ageing, is indicated.

INTRODUCTION

Opiate dependence is an increasingly common disorder with significant public health impacts for many reasons, including the increasing use of opiate analgesics for chronic pain management in an aging population, and increased risk of overdose deaths among illicit injecting opiate users.

A small but increasing literature has consistently identified an association between chronic use of opiates and increased rates of cardiovascular risk factors (inclusive hypertension, hypercholesterolaemia,[1 2] diabetes[3 4] and raised hs-CRP[5]) and of clinically significant atherosclerotic disease. For example an

Iranian group has found that opiate-dependent males have an increased rate of coronary disease requiring surgical revascularisation, with revascularisation at an average of 2 years before non-dependent controls.[6] Moreover in men, opiate dependence was the major risk factor for coronary disease over-riding conventional risk factors.[7 8] A large 21-year review of an opiate substitution programme in Australia found that patients had a 2.2-fold risk of cardiovascular death.[9] Similarly, a large prospective Iranian population-wide programme found a rate of coronary death to be elevated 1.90-fold, worse in females (HR=2.90, 95% CI 2.10 to 3.99; males HR=1.58, 95% CI 1.26 to 1.98).[10] Another Australian study found that 17% of patients over the age of 44 years dying from heroin overdose had a coronary stenosis of 75% or greater.[11] It was further reported that methadone treatment of heroin dependency appeared to exacerbate many forms of heart disease[12] consistent with a more complete pattern of opiate agonism by the longer acting agent. This is consistent with data from the USA where a 33-year follow-up of opiate-dependent persons maintained on methadone reported a highly significant threefold to sixfold elevation of years of life lost to fatal heart disease across all racial subgroups.[2]

While the mechanisms via which opiates act are likely to be multifaceted some likely candidate mechanisms exist. For example opiates are known to impact stem cell activity[13] and be immunostimulatory,[14] processes which are relevant to atherogenesis. Contrariwise, naltrexone, a broad-spectrum opiate antagonist active at both classical (μ, δ and κ) and non-classical (perinuclear receptors and toll-like) receptors (TLRs), stimulates stem cell activity and suppresses immunostimulation,[13 14] raising the possibility that naltrexone maintenance treatment may be associated with reduced cardiovascular disease compared with conventional opiate agonist treatments such as methadone.

Vascular ageing has been described as being one of the most important features of the ageing syndrome.[15 16] For this reason cardiovascular age has been nominated as a surrogate for organismal age.[15 16] The significance of the above findings therefore is amplified by the presence of elevated rates of various features of the ageing syndrome such as hair greying,[17] chronic periodontitis,[18] osteopaenia,[19] neuropsychiatric disorders,[20] a senescence-mimetic polyclonal immunopathy,[21 22] reduced circulating stem cell counts[23] and elevated rates of many malignancies in opiate-dependent patients.[10 24]

None of the above comments are intended to gainsay the well-established benefits of opiate maintenance with methadone or buprenorphine versus no treatment at all.[25]

While great interest has surrounded the phenomenon of the prolongation of the cardiac QTc interval by opiates with many authors finding the problem to be relatively benign,[26] notwithstanding the above cited tantalising findings there is little cardiological research in opiate dependency beyond their QTc effects. The availability of the rapid and portable SphygmoCor system from AtCor (Sydney) implies that measures of central arterial stiffness, and its correlate vascular age, are measurable in ambulatory patients as an important endophenotype of vascular ageing. The present study was prospectively designed to examine whether treatment with naltrexone and associated opiate abstinence in persons chronically exposed to several years of opiate use affected measures of their arterial stiffness and vascular age.

METHODS

Patient recruitment and drug usage

A total of 20 opiate-dependent patients (N=16 buprenorphine; 2 methadone and 2 heroin) were recruited opportunistically prior to naltrexone implant insertion. Data relating to tobacco, alcohol and drug use histories were also documented. The current form of opiate administration (heroin, methadone or buprenorphine) was recorded. Radial arterial tonometry (RAT) was performed on all patients prior to naltrexone implant treatment, at least once postimplant treatment (mean ± days), and where possible following a period of opiate abstinence. Time was measured from the time of the first naltrexone implant insertion (baseline RAT reading). Implants have an active clinical life of 135 days.[27] After that time patients were designated as being opiate-free postnaltrexone implant treatment. The study was performed during May 2006–December 2012 in primary care.

Arterial tonometry

Patients were laid supine for 5 min to rest. No restrictions on smoking or food or beverage intake were imposed prior to the study. Patients were not allowed to talk or fall asleep during the study. The brachial blood pressure was recorded at the left upper arm using an oscillatory device Omron HEM 907 Intellisense professional blood pressure monitor. RAT was performed using the SphygmoCor 8.0 hardware (Atcor, Sydney). The right radial artery was used unless it was unavailable or unsuitable. Studies were conducted in quintuplicate. Acceptable studies had an Operator Index greater than 70 and were not inconclusive. Each day's readings were averaged. The main parameters of interest were the chronological age (CA), the vascular reference age (RA), the difference between the two (RA–CA), the ratio of the RA and CA (RA/CA), the central aortic augmentation pressure (C_AP) corrected to a heart rate of 75 bpm (C_AP_HR75), the central aortic compliance defined as the central augmented pulse pressure divided by the central pulse height (C_AGPH) corrected to a pulse rate of 75 bpm (C_AGPH_HR75, also referred to as the 'augmentation index'). Other indices of interest were the central pulse height (C_PH), the central augmentation load (C_AL), the peripheral–central pulse pressure amplification ratio (PPAmpRatio), the maximum peripheral dP/dT (P_MAX_DPDT), the

peripheral systolic and diastolic pressures (SP and DP), the central systolic and diastolic pressures (C_SP and C_DP), the central mean pressure (C_MEANP) and central end systolic pressure (C_ESP), the heart or pulse rate (HR), the ejection duration in milliseconds (ED), the central stroke volume index (C_SVI) or Buckberg index, the central tension-time index (C_TTI) and the central diastolic-time index (C_DTI).

Naltrexone implants

Naltrexone implants used in this clinic were obtained from 'Go Medical' Industries Australia. Patients had a single naltrexone implant inserted under local anaesthetic most often beneath the skin of the left iliac fossa, by standard surgical techniques which have been previously described.[28] The legal framework within which this work was undertaken was the Special Access Scheme which allows Australian patients with serious illnesses access to new and investigational drugs, pursuant to formal notification of the Federal Health Department Therapeutic Goods Administration (TGA). Patients were detoxified prior to implant insertion.

Statistics

Data is listed as mean±SEM (standard error of mean). Continuous data were transformed as appropriate informed by the Shapiro-Wilks test and boxcox analysis in 'R' (2.15.2, Central 'R' Archive Network at University of Melbourne). For RA and CA, RA/CA, weight and SP, this was the reciprocal transformation. Repeated measures multiple regression was performed using the nonlinear mixed effects package. The comparator condition was the opiate-treated condition. In each case the random effects were unity and the case number. The 'log-likelihood value' was abbreviated to 'LogLik'. Model estimates for the various treatment conditions were calculated by inserting the appropriate mean values into the final models using untransformed parameters. Graphs were drawn in 'R' with ggplot2. Missing data were deleted case wise. Value $p<0.05$ was considered significant.

Ethics

After appropriate consultation and advice patients gave informed consent to the study Pulse Wave Analysis (PWA) procedures. Patient confidentiality was respected and maintained throughout. All patients were carefully and fully advised of the risks and benefits of the naltrexone implant insertion and gave formal written consent prior to this procedure. The study was approved by the Human Research Ethics Committee of the Southcity Medical Centre, and conformed with both the Declaration of Helsinki as well as the code of ethical practice of the National Health and Medical Research Council of Australia.

RESULTS

A total of 20 individuals (16 males) were studied on 124 occasions. 721 individual PWA studies were performed on 124 occasions (5.81±0.12, mean±SEM). The mean age at enrolment was 33.62±2.03 years. The mean study duration per patient was 460±82.22 days (range 11–2414 days). A total of 14 patients were followed for 360 days or more. The mean age on the study was 34.88 ±1.96 years. Baseline patient data are given in table 1. The time base from the first naltrexone implant varied from −915 to 2393 days (−2.50 to 6.55 years). There were 74 PWA studies performed during opiate treatment, 38 on naltrexone and 12 while opiate-free. In 16 cases the opiate used was buprenorphine (4.11 ±1.17 mg), in 2 cases it was methadone (57.5±12.5 mg) and in 2 cases heroin (0.75±0.25 g).

Figure 1 shows the vascular age and various measures of arterial stiffness over time by treatment type. As the PPAmpRatio normally declines with age its projection has been inverted. At repeated measures regression, opiate-free status was a significant determinant of RA both as a factor (est.=0.0122, dF=99, p=0.0008) and in interaction with time (est.=−0.0000156, dF=99, p=0.0043, model AIC=−714.79 and LogLik=356.39). The mean modelled RAs in each condition were 38.82, 37.73 and 35.05 years, respectively..

There was no missing data for key dependent variables of interest such as RA, CA, SP, DP, BMI, C_AP_HR75 and C_AGPH_HR75.

Of the stiffness measures, significant differences were also seen for the augmentation index with the opiate-free status being significant both as a factor (est.= −7.4071, dF=99, p=0.0050) and in interaction with time (est.=−0.0127, dF=99, p=0.0016, model AIC=857.93 and LogLik=−420.96). When the C_AP_HR75 was considered, the time: opiate-free interaction was superior to opiate agonism (est.=0.0036, dF=99 and p=0.0283), and there was a trend for opiate-free status as a factor (est.= −1.9642, dF=99 and p=0.0687; model AIC=649.49, LogLik=−316.74). When the C_PH was considered, the time: naltrexone interaction was better than the opiate treatment (est.=−0.0032, dF=101, p=0.0068, model AIC=797.06 and LogLik=−392.53).

Figure 2 shows the RA/CA ratio, and the changes which occur with adjustment for various other parameters. The CA, height and SP were shown in preliminary analyses to be the major significant determinants of RA. Biochemical parameters were not significant in any preliminary analyses. When the RA/CA ratio was regressed against interactions between time, height, SP and treatment type with an additive term for weight in a mixed effects model, the opiate-free status was again found to be significant both as a factor alone, and in interaction with time and with time and SP as shown in table 2. These results model a mean RA/CA ratio of 1.0173, 0.9563 and 0.8985 under opiate, naltrexone and opiate-free postnaltrexone treatment conditions.

When RA/CA was regressed interactively against cumulative time in treatment on opiates, naltrexone and opiate-free, the interaction between cumulative opiate and opiate-free time trended towards significance (est.=−0.0000003, p=0.0548, model AIC=56.47 and LogLik=−24.23).

With respect to RA/CA the opiate-free condition was superior in both males and females both as a factor (males: est.=0.3186, p=0.0402; females: est.=0.3285 and p=0.0360) and in interaction with time (males: est.=−0.0001, p=0.0320 and model AIC=90.72, LogLik=−37.36; females: est.=−0.00044, p=0.0460, model AIC=48.35 and LogLik=−16.18).

No patient suffered a significant major adverse effect as a result of the treatment or their PWA studies during the observation period on the study.

DISCUSSION

Study data indicate that the opiate-free state was associated with a reduction of arterial stiffness indices and vascular age, and by extension, in apparent biological age. The high statistical significance in this numerically small study suggests a robust effect. The effect was consistent across several indices of arterial stiffness,

Table 1 Baseline patient characteristics

	Mean (+SE)	Range
Biometric		
CA	33.62±(2.03)	24.4–54.1
Height (cm)	176.00 (1.62)	160–190
Weight (kg)	84.10 (4.03)	63–122
Body mass index (kg/m^2)	27.26 (1.35)	18.84–40.3
Substance use		
Heroin dose (g)	0.37 (0.05)	0.1–1
Heroin duration (year)	11.375 (1.59)	3–31
Heroin dose-duration (g-year)	4.85 (1.47)	0.75–31
Cigarettes/day	10.85 (2.07)	0–25
Selected laboratory values		
Alanine transaminase (IU/l)	67.21 (20.27)	14–360
Glucose(mmol/l)	5.62 (0.28)	4–8.6
High sensitivity-C reactive protein (g/l)	4.18 (0.97)	0.1–13.9
Cholesterol (mmol/l)	4.84 (0.32)	2.3–7.3
Low-density lipoprotein (mmol/l)	2.99 (0.27)	1.13–4.33
High-density lipoprotein (mmol/l)	1.36 (0.11)	0.64–2.25
Cardiovascular parameters		
CVS ageing		
Operator quality index	88.80 (1.21)	79–99
RA	35.00 (4.68)	20–86
RA/CA	1.00 (0.07)	0.65–1.58
RA–CA	2.01 (2.77)	−10.83–31.58
Augmentation		
C_AP_HR75	2.60 (1.46)	−7–16
C_AGPH_HR75	6.25 (3.55)	−19–40
C_PH	36.45 (1.92)	21–62
PPAmpRatio	158.80 (3.69)	119–187
P_MAX_DPDT	921.90 (46.05)	382–1182
Pressures		
SP	128.60 (2.9)	103–161
DP	71.00 (1.99)	58–89
C_MEANP	89.05 (2.22)	73–105
C_ESP	95.80 (2.42)	78–114
Timing		
HR	70.90 (3.25)	52–95
ED	316.45 (4.85)	274–352
C_SVI	147.20 (8.5)	86–216

Abbreviations as per Methods Section.
C_AGPH_HR75, corrected to a pulse rate of 75 bpm; C_AP_HR75, corrected to a heart rate of 75 bpm; CA, chronological age; C_ESP, central end systolic pressure; C_MEANP, central mean pressure; C_SVI, central stroke volume index; CVS cardiovascular ; ED, ejection duration; HR, heart rate; SP, systolic pressure; DP, diastolic pressure; P_MAX_DPDT, maximum peripheral dP/dT; C_PH, central pulse height; PPAmpRatio, peripheral–central pulse pressure amplification ratio; RA, vascular reference age.

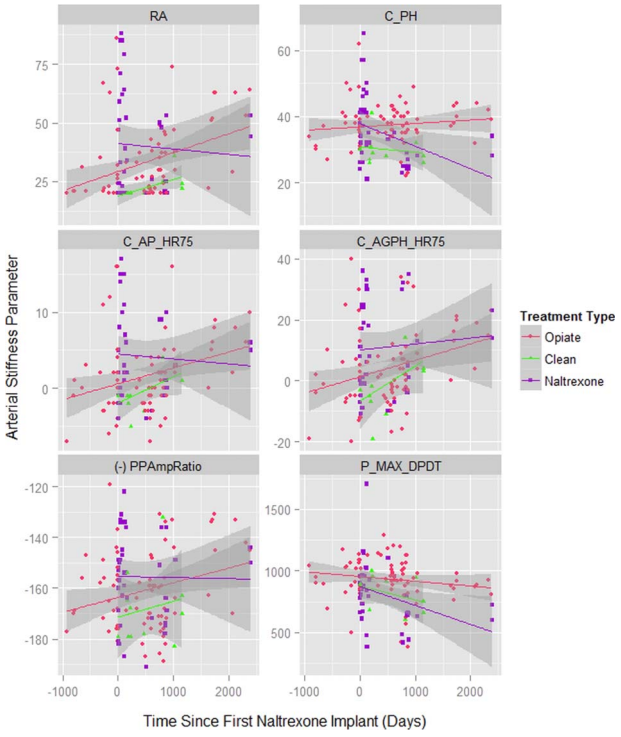

Figure 1 Arterial stiffness indices by time since first naltrexone implant. See Methods Section for abbreviations. C_AGPH_HR75, corrected to a pulse rate of 75 bpm; C_AP_HR75, corrected to a heart rate of 75 bpm; P_MAX_DPDT, maximum peripheral dP/dT; C_PH, central pulse height; PPAmpRatio, peripheral–central pulse pressure amplification ratio; RA, reference age.

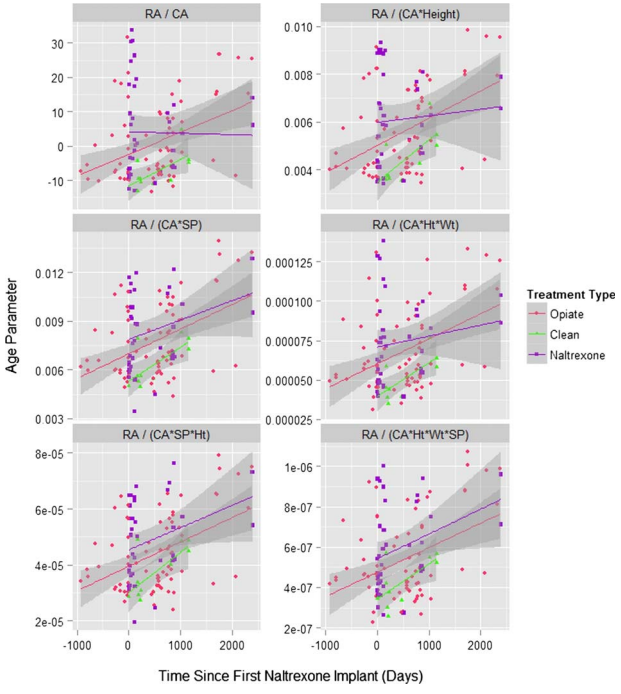

Figure 2 Adjusted ageing indices by time since first naltrexone implant. See Methods Section for abbreviations. CA, chronological age; Ht, height; RA, reference age; SP, systolic pressure; Wt, weight.

remained after full statistical adjustment for other confounding factors, and was seen in each sex separately.

The importance of arterial stiffness as a cardiovascular risk factor has been noted by a large body of literature. It was particularly encouraging therefore that a reduction in arterial stiffness was associated with opiate-free state following treatment with the opiate antagonist, naltrexone. The magnitude of the effect observed was noted to be relatively small. Compared to a mean age on the study of 34.88 years, the modelled RAs were 38.82, 37.73 and 35.05 in the opiate, naltrexone and opiate-free conditions respectively, representing 111.30, 108.17 and 100.49%. These are equivalent to differential effects on vascular age of 3.13% (opiate–naltrexone) and 10.84% (opiate–opiate-free). These data are in good agreement with the modelled RA/CA ratios after full multivariate mixed effects adjustment which found 1.0173, 0.9563 and 0.8985 in the three conditions, suggesting differentials of 6.10 and 11.88%, respectively.

These findings need to be interpreted in the light of at least two major considerations. First, opiate agonist treatment is frequently initiated for many years and often decades. Hence a 6.1% effect as found here continued over 30 years is equivalent to a +590.82% effect in amplification, and −84.86% in diminution if continued at a similar rate for the whole period because of the compounding interest effect over protracted periods of time. For an 11.88% effect the similar 30-year results are +2847.21% in amplification and −97.75% in reduction. Hence while the quanta observed here are not large, over extended time periods they can become very considerable. This begins to address the uniformity of the deleterious nature of the pathologies identified by various authors in the field.[9–12 29]

Second, the level of opiate exposure was relatively low level, with most patients on low-dose buprenorphine. As a partial opiate agonist, buprenorphine is likely to have more moderate opiate agonist effects than full agonists such as physeptone. Moreover, the mean dose employed in these patients was much lower than that commonly reported.[30] Accordingly, findings reported here represent a lower bound on the magnitude of the observed opiate agonist effects.

A gender difference in opiate-related cardiovascular pathology has been reported previously by an Iranian group,[10] with 17/26 pathologies reported worse in females (Wilcoxson matched pairs test Z=2.28 and p=0.022).

While it is possible that changes in diet, exercise, smoking, alcohol consumption or other drug use may account in part for the changes noted herein, the present dataset does not allow such alternative hypotheses to be formally tested. However, the authors are aware of no apparent trend which would be indicative of such changes in this group.

Some of the most fascinating questions to emerge from this study relate to the possible mechanisms which are likely to account for these changes apparently over a relatively short period. While this is not a mechanistically focused

Table 2 Final mixed effects multiple regression

	Value	SE	dF	t-Value	p-Value
Time:clean status	−0.0048	0.0018	93	−2.7675	0.0068
Clean status	2.9680	1.1733	93	2.5296	0.0131
Time:clean status:SP	0.5064	0.2029	93	2.4956	0.0143
SP:naltrexone status	120.6398	55.6741	93	2.1669	0.0328

Model AIC=56.19, BIC=94.25 and LogLik=−14.09.
SP, systolic pressure.

study some concise remarks may be of interest. As stated above, opiates are known to have effects both on stem cells[13] and on immune modulation.[14] It seems likely that the immunostimulatory effects also induce well-described immunosuppressive effects.[31] Opiate ligation of toll-like receptor 4 (TLR4) is particularly potent and is coupled downstream to numerous immune-effector pathways including interleukin 1 (IL-1), IL-6, tumor necrosis factor-α (TNFα), monocyte chemotactic protein-1/chemokine (C–C motif) ligand 2 (MCP-1/CCL2), transforming growth factors β (TGFβ), mitogen-activated protein kinases (MAP kinase), several interferon response factors, nuclear factor κB (NF-κB) and sphingosine-1-phosphate signalling.[14] Importantly, it now appears that there are many biological interactions between stem cell behaviour and immune response. Cytokines are known to inhibit most stem cells.[32] Two key stem cell master genes, Oct4 and Nanog, have cytokine response sequences in their promoters particularly for the gp130 cytokine series and STAT (Signal Transducer and Activator of Transcription)-1 and STAT-3.[33 34] Indeed it was recently shown that generalised DNA unwrapping occurs from nucleosomes loosening the epigenetic control of the histones, and facilitating widespread gene transcription as in nuclear reprogramming in induced pluripotent stem cells, under the control of TLR3.[35] At least two key cytokines, high molecular group box 1[36] and vascular endothelial growth factor[37] undergo regulated trafficking across the nuclear pore so as to control widespread gene transcription cassettes. Furthermore, there are three-way interactions between stem cells, immunity and metabolic regulation, further confusing the roles of cardiovascular disease mechanism induction and risk factor potentiation alluded to the above.[37 38]

Naltrexone[39] and the opiate-free state may also benefit patients by reducing their use of stimulants including tobacco.

The longitudinal open cohort design of this study did not allow for the estimation of the relative importance of opiate antagonist treatment and associated opiate abstinence (naltrexone) versus opiate-free status in the absence of postnaltrexone treatment. Future studies that compare PWA outcomes following periods of opiate-free status not associated with opiate antagonist treatment (eg, following entry into a therapeutic communities) versus opiate free associated with opiate antagonist treatment will enable such assessments to be made. Among these patients naltrexone was crucial to achieving opiate freedom.

The present work has various strengths and limitations. Major design strengths include the application of modern cardiovascular investigative technologies to the problem of clinical opiate dependence which in itself is distinctly novel; the long period of follow-up achieved for many patients; the ability to follow-up patients with these clinical characteristics, who are notoriously transient and itinerant; and the serial 'N of one' design where each patient served as their own control. Limitations of the study included its small size, the absence of mechanistic studies and the lack of a formal instrument to quantitate lifetime drug and treatment exposure. When the study is replicated it is recommended that spot testing for drugs and alcohol be undertaken at every encounter, particularly since these importantly confound the interpretation of arterial stiffness testing. It is also hoped that other tests of cardiovascular health will be applied to this problem and the monitoring of its various treatments.

The numbers in this study, with a sample size of 20, are clearly small. Thus this data should be considered as preliminary hopefully to further larger and more comprehensive studies which will examine the issue either with this, or perhaps complementary technologies. Patient enrolment was constrained by the rarity of performing naltrexone implants in our service, and the difficulty of patient follow-up, problems in which latter problem in particular is notorious in such patient groups. The study design was open, in that no prearranged cohort size was determined before hand, and no follow-up period was set prior to the starting of the study. During the course of the study other data indicated that a period of 5–7 years would be preferable to facilitate the longitudinal analysis of trends. In the upshot, it is indeed noteworthy that statistically significant findings have been made with such a small patient group. The numbers of female participants in this group is too small to make definite conclusions about gender differences, but nevertheless the trends observed are very consistent with other analyses prepared from this site (manuscript in preparation).

In conclusion we have shown that the elevated vascular age and arterial stiffness associated with opiate dependence can be reduced by the opiate-free condition. The effect is estimated at being 6–11%, is robust to multivariate adjustment, is seen in both sexes, and is likely to become significant over several decades. It is believed to underlie the pattern of accelerated ageing

occurring in opiate-dependent patients in many tissue beds. Further research is indicated.

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Contributors ASR reviewed the literatures, designed the study, acquired and analysed the data, composed the graphs and wrote the initial draft of the paper. GKH advised on data interpretation, revised the manuscript for intellectual content. All authors read and approved the final version prior to publication.

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