

*Our of the Shadows, Into the Limelight –
Sobering Saliency of Meta-Analysis of Chronic Periodontitis in Drug Addiction*

Short Title:

Meta-Analysis of Dental Health in Addiction

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Summary Comment

Baghaie's excellent meta-analysis concisely summarizes studies showing worse dental health including chronic periodontitis, one of the major hallmarks of human aging, in drug dependent patients. This highlights the need for dental care in this group and the negative effect of addiction on human oral and systemic health and aging processes.

Like a still point in a turning universe the superb meta-analysis by Baghaie and colleagues in this month's *Addiction* journal is a splendid piece of scientific writing which examines the unequivocal but often unspoken and overlooked fact of appalling dental health typically experienced by most long-term drug dependent patients (1). In a modern global environment in which drug policy is often confusing and is skewed by a global media increasingly controlled by the virtually unlimited funding streams of global financial elites who boldly declare their anarchistic and chaotic drug use paradigms (2) sponsoring deteriorating global addiction epidemics (3-5), such touchstones of common sense and concise pithy summaries in a meta-analysis of an important subject are an arresting and objective "in your face" reminder of real world reality.

It is said that the first thing you do when you buy a horse is inspect its teeth as that is a fair indicator of the overall condition of the mammal. Statements from the NIH Institute devoted to dental health (6) and elsewhere (7) draw similar inferences in humans. "Growing long in the tooth" is one of the cardinal signs of human aging and is due to the loss of the alveolar bone around the base of the tooth socket exposing the dentine below the enamel, giving rise to an apparent lengthening of the tooth (8). Such chronic periodontitis is caused by a failure of osteoblastic processes and the increased bone resorption accompanying chronic infection-inflammation and is demonstrated at dental examination by probing the strength of attachment of the gingiva to the base of the tooth with a probe to explore potential pocket depth.

Coming from an expert academic dental group this paper has it all: review of 28 studies comparing 4,086 patients with 28,031 controls, careful consideration of interstudy heterogeneity, discussion of probe pocket depth, the place of radiology in the assessment of dental disease, consideration of one drug and multi-drug affected groups, detailed statistical analyses, lengthy Forrest plots, usually narrow confidence intervals, consideration of papers emanating from both medical and dental groups, and detailed lists of implications for different professional groups, this whole impressive corpus is delivered in a understated tone which further underscores their important findings (1).

Meta-analysis revealed an elevated rate of dental decay in users of opioids (mean score difference 5.64, 95% C.I. 1.07-10.21), amphetamines (4.41, C.I. 2.53-7.69) and mixed drugs (3.46, C.I. 1.77-5.15), with, in mixed drug users, an elevated rate of decayed, missing and

filled (DMF) teeth (score difference 5.15, C.I. 2.61-7.69) and surfaces of 17.83 (C.I. 6.85-28.80). Yet these patients uniformly had less access to dental care including fewer dental restorations (fillings).

Importantly the odds ratios of total periodontitis was 3.35 (C.I. 2.23-5.03) and of severe periodontitis defined by deep pockets O.R.=2.78 (1.23-6.27). A significant relationship with the duration of exposure was shown in some studies (1, 9, 10) and dose-response relationships of heroin and methadone exposure were clearly demonstrated in supplementary analyses (10) including associations with stem cell failure in other beds (hair greying, another *sine qua non* of human aging) (11) and mental disorders (12). Indeed principal component analysis of combined indices of dental, mental and hair aging show significant differences from controls (22% older, $P < 0.0005$) (11). The association of addiction with accelerated aging has been demonstrated elsewhere (13-17).

Importantly the authors were able to warn that advanced dental decay beyond what might be expected for patient age should flag to dental clinicians that patients may be involved in substance use directly implicating the clinical utility of the association of clinical biomarkers with accelerated aging in addiction (1). Dental health impacts systemic health through bacteraemia, immune complex, pathogenic stimulation and toll-like receptor – Nuclear Factor- κ B signalling (1, 7, 9, 11, 18) which directly suppresses stem cells (19).

These results are important for many reasons: they are robust evidence for clinical non-benignity of opioid, amphetamine and mixed drug use; they suggest that the long term effects of methadone on oral and systemic health are non-trivial and significant and thereby indicate the development of new and non-toxic treatments; and they directly document and exacerbate pro-aging processes both locally and systemically. Moreover these data indicate that just as it is rational health care to make efficacious hepatitis C treatments generally available to vulnerable populations to avoid the long term health effects and associated budgetary costs of poor systemic health, so it is important to facilitate and improve access for drug dependent patients to formal dental care by direct pathways from the clinics which care for them.

References

1. Baghaie H, Kisely S, Siskind D, Forbes M., Sawyer E. A systematic review and meta-analysis of the association between poor oral health and substance abuse. *Addiction*. 2017 2017:This issue.
2. Open Society Foundation. Open Society Foundation on Medical Cannabis New York: Open Society; 2016 [cited 2016 12th September 2016]. Available from: <https://www.opensocietyfoundations.org/search?key=medical%20cannabis>.
3. Karithanom M. CDC Drug Related Death Rates Bethesda Maryland, NIDA, NIH: NIDA, NIH; 2016 [Available from: <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>].
4. United Nations Office of Drugs and Crime. World Drug Report 2016. Geneva: United Nations Office of Drugs and Crime; 2017. 1-174 p.
5. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013 Nov 09;382(9904):1575-86. PubMed PMID: 23993280.
6. Diseases NIODaC. Oral Complications of Systemic Diseases Bethesda, Maryland: National Institutes of Health; 2017 [cited 2017 26th January 2017]. Available from: https://www.nidcr.nih.gov/OralHealth/OralHealthInformation/SystemicDiseases/?_ga=1.111385415.2111965632.1469710922.
7. Scannapieco FA. Systemic effects of periodontal diseases. *Dent Clin North Am*. 2005 Jul;49(3):533-50, vi. PubMed PMID: 15978240.
8. Chien KR, Karsenty G. Longevity and lineages: toward the integrative biology of degenerative diseases in heart, muscle, and bone. *Cell*. 2005 Feb 25;120(4):533-44. PubMed PMID: 15734685. Epub 2005/03/01. eng.
9. Reece AS. Dentition of addiction in Queensland: poor dental status and major contributing drugs. *Australian dental journal*. 2007 Jun;52(2):144-9. PubMed PMID: 17687962. eng.
10. Reece A.S. Dental Health in Addiction. *Australian dental journal*. 2009;54(2):185-6. Epub 2009.
11. Reece AS. Differing age related trajectories of dysfunction in several organ systems in opiate dependence. *Aging Clin Exp Res*. 2012 Feb;24(1):85-96. PubMed PMID: 21339699. Epub 2011/02/23. eng.
12. Reece AS. An intriguing association between dental and mental pathology in addicted and control subjects: a cross-sectional survey. *Br Dent J*. 2008 Dec 13;205(11):E22-E9. PubMed PMID: 18953330. Epub 2008/10/28. eng.

13. Bachi K, Sierra S, Volkow ND, Goldstein RZ, Alia-Klein N. Is biological aging accelerated in drug addiction? *Curr Opin Behav Sci.* 2017 Feb;13:34-9. PubMed PMID: 27774503. PMCID: PMC5068223.
14. Reece A.S., G.K. H. Impact of Lifetime Opioid Exposure on Arterial Stiffness and Vascular Age: Cross-sectional and Longitudinal Studies in Men and Women. *BMJ Open.* 2014 2014;4(6):1-19. PMCID: 24889849 Epub 3rd June 2014.
15. Reece AS. Evidence of Accelerated Ageing in Clinical Drug Addiction from Immune, Hepatic and Metabolic Biomarkers. *Immun Ageing.* 2007 Sep 24;4(1):6-15. PubMed PMID: 17892544. Eng.
16. Reece AS, Davidson P. Deficit of circulating stem--progenitor cells in opiate addiction: a pilot study. *Substance abuse treatment, prevention, and policy.* 2007;2:19-28. PubMed PMID: 17615060. eng.
17. Tatia M.C. Lee, Gordon L.F. Cheng, Hung Zeng, Meikei Leung, Hui-Jun Zhang, Benson W.M. Lau, et al. Heroin abuse accelerates biological aging: A novel insight from telomerase and brain imaging interaction. *Translational Psychiatry.* 2013;3:e260.
18. Reece AS. High-sensitivity CRP in opiate addiction: relative and age-dependent elevations. *Cardiovasc Toxicol.* 2012 Jun;12(2):149-57. PubMed PMID: 22297435. Epub 2012/02/03. eng.
19. Deverman BE, Patterson PH. Cytokines and CNS development. *Neuron.* 2009 Oct 15;64(1):61-78. PubMed PMID: 19840550. Epub 2009/10/21. eng.