Reviewer’s report

Title: Chronodentistry: The role & potential of molecular clocks in oral medicine

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Reviewer: Francis Lévi

Reviewer's report:

Chronodentistry is an interesting and innovative review topics, that is well focussed. Although it is rather well documented, I feel its structure deserves some reappraisal while additional references and work should be discussed and cited. Reports regarding rodents and humans should be clearly separated.

As this is a review rather than an original report, the questions regarding Methods, Controls and Statistics are not relevant. I can assess all three but not in this manuscript.

A comprehensive view of the circadian timing system (CTS) would help the reader understand the links between the brain pacemaker (SCN) that both measures light and darkness and coordinates an array of physiological rhythms, including sleep, and the peripheral clocks, including those in the oral cavity, which you are addressing more specifically. Such systems approach will help you highlight the relevance of a functional CTS for chronodentistry over the 24 h, so that interventions can be timed to maximize efficacy and tolerability according to local molecular clocks. In contrast, CTS dysfunction, irrespective of its cause - genetic, lifestyle or other - can result in poor coordination of the oral cavity clocks, possibly resulting in abnormal development or local diseases, and requiring clock-targeted systemic or local treatments. In this respect the relevance of atypical lifestyles or poor circadian synchronisation during development for dentition could be discussed.

Several statements such as "this tissue is able to produce the core components of the circadian clock" is not very sound and is repeated throughout in almost each subsection. You might want to say that "the core clock genes are expressed in all the tissues that are relevant for chronodentistry, including……" or something alike.

There are several old works that deserve to be cited and updated regarding the circadian changes in tooth pain thresholds in humans (Reinberg, Pollmann), and more recent ones regarding the cell cycle and clock genes circadian expression in human oral mucosa (Bjarnason), and their implications for chronoradiotherapy (Bjarnason and others), as well as for chronochemotherapy of head and neck cancers (several Chinese papers).

There is a need for comprehensive figures that summarize the main implications of circadian clocks for oral Health.

Are the methods appropriate and well described? 
If not, please specify what is required in your comments to the authors.
Unable to assess

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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