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NaQuinate: a drug that selectively synergizes with mechanical loading stimuli in vivo to generate greater cortical bone mass and architectural modifications

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Background: Response to applied mechanical loading is pivotal in the generation of bone mass and architecture sufficient to withstand habitual use and resist fracture. We have previously found that NaQuinate, a naphthoquinone carboxylic acid, contributes to maintaining bone quality and quantity in rat and mouse ovariectomy models of rapid bone loss. Herein, NaQuinate's ability to alter mechanoadaptive response in cortical and trabecular tibial bone following mechanical loading has been investigated.

Methods: Female 12wk-old C57/Bl6 mice (n=8/group) were randomly allocated to two groups, receiving either NaQuinate (750 µg/Kg/day) or vehicle 5d/wk over 3 wks. On three alternate days in the last 2wks, the right tibia of all mice was subjected to non-invasive, dynamic axial loading (12N, 40cycles/day, 2Hz, with 10s rest periods between cycles), with the left serving as non-loaded contralateral control. Three days after the last load episode, tibiae were removed and scanned by high-resolution micro-CT (5um) for measurement of traditional indices of bone mass and architecture in defined trabecular regions and along the whole of the cortex. A linear mixed effects model followed by Fisher's least significant difference post-test was used for statistical analysis

Results: Comparison of non-loaded tibiae in the two groups showed small, significant NaQuinate-related increases in cross-sectional area (CSA) at restricted midshaft and tibio-fibular junction locations (Fig 1A/C). NaQuinate markedly enhanced mechanoadaptive cortical responses, generating significantly greater load-related increases in CSA, thickness and J score across extensive proximal tibia regions (Fig. 1B/D); revealing clear synergy, with increases in CSA and J significantly greater than their distinct additive effects (Fig 1E). NaQuinate treatment also amplifies load-related increases in trabecular thickness and generates more vertically-orientated trabeculae when compared to load alone; which was not evident in contralateral tibiae

Conclusions: These data reveal that NaQuinate significantly interacts with mechanical loading in the trabecular compartment and targeted cortical bone regions. This constructive interaction between NaQuinate and mechanical loading indicates functional utilisation of *bones' mechanostat* in the regulation of bone mass and architecture and supports the notion that NaQuinate treatment can provide a novel therapeutic approach to skeletal disorders such as osteoporosis.