

# Phenytoin Therapy is Associated with Increased Risk of Osteoporosis, Osteopenia, and Spinal Fractures in Adult Epileptic Patients: A Propensity-Matched Comparison

Authors: Sterling DeShazo<sup>1</sup>, Garrett Ozmer<sup>1</sup>, Kyle Horton<sup>1</sup>, William M. Weiss<sup>2</sup>, MD, MSc, FRCSC, FAANA, FAAOS

University of Texas Medical Branch<sup>1</sup>, Department of Orthopaedic Surgery and Rehabilitation<sup>2</sup>

**Introduction:** Osteoporotic fractures lead to significant decreases in quality of life with increases in morbidity, mortality, and disability. Treatment with a variety of anti-epileptic drugs, such as Phenytoin, has been understood to cause a decrease in bone mineral density. This subsequently predisposes patients on these therapies to an increased risk of fractures. In this study, we evaluate the effect of Phenytoin on bone health through the incidence of osteoporosis and osteoporotic-fragility fractures in adult epileptic patients.

## Methods:

**Design:** In this retrospective cohort study, the global health research network database, TriNetx, was used to evaluate de-identified patient information from 57 healthcare organizations (HCOs) and over 90 million patients on the network in the United States.

**Participants:** Two cohorts were evaluated for this study. Cohort A was identified as patients that were 18 to 55 years old that had epilepsy and recurrent seizures (ICD10:G40) that were also prescribed Phenytoin (RxNorm:8183). Cohort B was identified as patients that were 18 to 55 years old that had epilepsy and recurrent seizures but were not prescribed Phenytoin or other anti-epileptic medications. Cohorts were propensity matched for alcohol use disorders, nicotine dependence, type 2 diabetes mellitus, and demographic factors such as age at index, race, ethnicity, and sex.

**Setting:** Data was gathered from HCOs from June 1st, 2003, to June 1st, 2023. The outcomes evaluated were: osteoporosis without pathological fracture, fracture of metatarsal bone, fracture of shoulder and upper arm, fracture of distal radius, fracture of thoracic vertebra, fracture of cervical vertebra, fracture of lumbar vertebra, fracture of femoral head or neck, peritrochanteric fracture, femoral shaft fracture, and distal tibia fracture. Outcomes were evaluated from 1 day to 5 years after the indexed event.

**Results:** A total of 35,028 patients with epilepsy that were prescribed Phenytoin were matched with 114,619 patients with epilepsy that were not prescribed Phenytoin. After cohort propensity matching, epileptic patients on Phenytoin therapy had an increased associated risk for all outcomes evaluated. Patients on Phenytoin therapy were at significantly higher risk for osteoporosis without pathological fracture (1.17% vs 0.34%,  $p < 0.0001$ ), fracture of metatarsal bone (0.49% vs 0.20%,  $p < 0.0001$ ), fracture of shoulder and upper arm (1.33% vs 0.61%,  $p < 0.0001$ ), fracture of distal radius (0.42% vs 0.24%,  $p < 0.0001$ ), fracture of thoracic vertebra (0.47% vs 0.16%,  $p < 0.0001$ ), fracture of cervical vertebra (0.95% vs 0.32%,  $p < 0.0001$ ), fracture of lumbar vertebra (0.41% vs 0.16%,  $p < 0.0001$ ), fracture of femoral head or neck (0.31% vs 0.09%,  $p < 0.0001$ ), peritrochanteric fracture (0.17% vs 0.06%,  $p < 0.0001$ ), femoral shaft fracture (0.14% vs 0.04%,  $p < 0.0001$ ), and distal tibia fracture (0.28% vs 0.09%,  $p < 0.0001$ ).

**Conclusion:** In the last 20 years (2003 to 2023), epileptic patients on Phenytoin therapy that were 18 to 55 years old exhibited higher associated risk of osteoporosis and osteoporotic-fragility fractures of various regions. Patients that undergo Phenytoin therapy for epilepsy treatment should be educated on the increased risk of bone fractures as well as put on treatments and or lifestyle changes to best mitigate bone mineral density loss.

**Significance/Clinical Relevance:** Patients that undergo Phenytoin therapy for epilepsy should receive education on bone health focused lifestyle optimization, guidance on supplementation, avoidance of poly-AED therapy, and regular bone health checkups.

