Case Reports in Women's Health 25 (2020) e00160

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh

# Antipsychotic therapies and bone health

Stavroula A. Paschou [a,b,*], Paraskevi Mentzelopoulos [b], Irene Lambrinoudaki [b]

[a] Division of Endocrinology and Diabetes, "Aghia Sophia" Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[b] Second Department of Obstetrics and Gynecology, Aretaeion Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Mental disorders affect more than 15% of adults in the Western World and psychotropic medications are among the most highly prescribed agents [1]. Antipsychotic medications specifically, originally designed and approved by drug regulatory authorities for the treatment of psychosis associated with schizophrenia and bipolar disorder, are increasingly prescribed even off label for diverse indications. Moreover, they are often used in children and older people. Antipsychotic therapies have been associated with increased risk of obesity, dyslipidemia and type 2 diabetes mellitus, while there is emerging clinical evidence that these medications can increase the risk of osteoporosis and fractures [1,2].

Many patients receiving antipsychotics have risk factors for osteoporosis, such as smoking, very low or very high body mass index (BMI), poor nutrition, low levels of physical activity, high levels of alcohol consumption, or vitamin D deficiency [3]. Furthermore, genetic predisposition, low-grade inflammation and elevated cytokines concentrations in patients with schizophrenia may additionally affect bone strength and quality [2].

However, it seems that the use of antipsychotic medications *per se* is predominantly associated with osteoporosis. A large longitudinal cohort drawn from a population-based registry in Canada, including 68,730 individuals, with 485,322 person-years (68,730 persons; median 6.7 years) of observation, provided evidence that schizophrenia was significantly associated with a major osteoporotic fracture (MOF) (hip, vertebral, humerus or forearm): adjusted hazard ratio, aHR 1.82, 95% CI 1.16–2.85 [1]. Antipsychotics were associated with both MOF (aHR 1.48, 95% CI 1.21–1.81) and hip fracture (aHR 2.18, 95% CI 1.58–3.02). In simultaneous analyses of mental illness and medication use, only medication use was independently associated with fracture. Interestingly, FRAX score underestimated the 10-year risk of hip fracture by 171% in patients who used antipsychotics [1].

A number of other recent cross-sectional and longitudinal studies and meta-analyses have also shown that antipsychotic use leads to reduced BMD and increased fracture risk [4–8]. Most studies indicate that the risk is increased in both men and women [4–7], while others indicate possible gender differences [8]. When 120 patients with a first episode of schizophrenia were treated with clozapine, quetiapine or aripiprazole and were compared with healthy controls 12 months after drug initiation, BMD was found to be significantly lower for all drug categories [6]. Interestingly, in pediatric populations antipsychotics increased the fracture risk by 2 to 3 times and this was associated with a reduction in bone mass [9,10]. Very recently, Swedish registers were used to identify adults with two consecutive dispensations of risperidone ($n = 38{,}211$), other atypical antipsychotics ($n = 60{,}691$), or typical antipsychotics ($n = 17{,}445$) within three months, in order to estimate HR for osteoporosis-related fractures [11]. Differences between various categories were noted in this large study, as risperidone use was not associated with such an increased risk compared with other atypical antipsychotics. Results were similar for both hip and non-hip fractures. For typical antipsychotics, a moderately elevated risk of hip fractures was noted compared with other atypical antipsychotics [11].

Possible pathophysiological mechanisms of bone health problems after antipsychotic use include alterations in dopaminergic and/or serotonergic signaling pathways. As these medications are distributed to the bone marrow as well as to the brain, it is possible that drug-induced fractures are due to both centrally mediated effects and direct effects on bone turnover [2]. A popular hypothesis is that antipsychotics affect BMD and increase fracture risk due to hyperprolactinemia. Indeed, antipsychotic medications have caused hyperprolactinemia in women, men and children [2,9]. It is well known that the subsequent hypogonadism leads to bone loss. On top of hypogonadism, hyperprolactinemia may have a direct impact on bone tissue and the rate of bone metabolism. Indeed, elevated prolactin concentrations have been associated with increased bone resorption (predominantly) and bone formation [12]. Bone turnover is regulated by the sympathetic nervous system too, and therefore possible dysregulation of the sympathetic output to bone could also be involved in the bone loss that is induced by antipsychotics. Furthermore, dopamine is present in bone marrow, inhibiting osteoclastogenesis and osteoblastogenesis. The effects of dopamine antagonists in such molecular procedures may be responsible for the increased risk of osteoporosis in patients receiving these medications [2,13].

In conclusion, chronic use of antipsychotics represents in general a risk factor of osteoporosis and fractures. The fracture risk in these patients is rather independent of FRAX estimates. Antipsychotic-induced fractures seem to be the result of both centrally mediated effects and direct effects on bone turnover. Given the growing patient population that is prescribed these medications for both on- and off-label indications, understanding the risk and the underlying mechanisms is crucial. Physicians dealing with such patients should account for these bone health

* Corresponding authors at: Division of Endocrinology and Diabetes, "Aghia Sophia" Hospital, Medical School, National and Kapodistrian University of Athens, Thivon and Papadiamantopoulou, 11527 Athens, Greece.
*E-mail address:* s.a.paschou@gmail.com (S.A. Paschou).

https://doi.org/10.1016/j.crwh.2019.e00160

effects in their prescription, patient monitoring and prevention practices.

## Contributors

Stavroula A. Paschou designed the article, searched the literature and wrote the initial draft.

Paraskevi Mentzelopoulos searched the literature and wrote the initial draft.

Irene Lambrinoudaki designed the article and revised the manuscript for important intellectual content.

All authors approved the final version of the article.

## Conflict of interest

The authors have no conflict of interest regarding the publication of this editorial.

## Funding

No funding was sought or secured in relation to this editorial.

## Provenance and Peer Review

This editorial was commissioned and not externally peer reviewed.

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