Opšti pregledi /
General reviews

ADHERENCE TO PHARMACOTHERAPY IN PATIENTS WITH OSTEOPOROSIS – *A brief review*

ADHERENCA FARMAKOTERAPIJI KOD PACIJENATA SA OSTEOPOROZOM – *Kratak pregled*

Ivana Minaković[1,2], Jelena Zvekić-Svorcan[1,3], Sandro Kopilović[4,5]

Correspondence to:

Ivana Minaković,
University of Novi Sad,
Faculty of Medicine,
Hajduk Veljkova 3,
21000 Novi Sad, Serbia,
E-mail: ivana.minakovic@uns.ac.rs

[1] University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

[2] Health Center Novi Sad, Novi Sad, Serbia

[3] Special Hospital for Rheumatic Diseases, Novi Sad, Serbia

[4] Institute for Emergency Medicine, Novi Sad, Serbia

[5] Department of Scientific Research Education and International Cooperation, Novi Sad, Serbia

Abstract

Osteoporotic fractures are a significant cause of morbidity and mortality, and their annual prevalence is expected to increase due to population ageing and increased lifespan. Although the incidence of osteoporotic fractures can be reduced by 30-70% with regular use of pharmacotherapy, more than half of patients do not start therapy or do not use it appropriately. Medication non-adherence may be associated with worsening of disease symptoms, complications, increase in the frequency of hospitalizations and mortality. The results of various studies suggest an association between non-adherence in patients with osteoporosis and more complicated medication regimes, the severity of symptoms, personal perception of risk and benefits, patient knowledge and education, age, polypharmacy, side effects. It is important to identify risk factors associated with non-adherence and to achieve efficient communication between the patient and the healthcare providers to improve adherence and thus the outcome of the disease.

Key words

Anti-osteoporotic therapy; Adherence; Osteoporosis; Predictors of non-adherence

Ključne reči

Antiosteoporotska terapija; Adherenca; Osteoporoza; Prediktori neadherence;

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone density and bone structure deterioration which leads to an increase in bone fragility and susceptibility to fracture.[1-4] It is described as a silent disease,[5] since it is usually asymptomatic until a fracture occurs.[6] Osteoporosis affects about 200 million people worldwide, and 27.6 million people in Europe with more than 3.5 fractures each year.[5] Osteoporotic fracture presents a substantial economic burden since they are a significant cause of morbidity and mortality, especially in developed countries. [7] The annual prevalence of osteoporotic fractures is expected to increase due to population ageing and increased lifespan.[8]

Pharmacological treatment of osteoporosis effectively reduces the incidence of fractures, sustaining bone strength and decreasing symptoms of structural fracture deformations.[5] The use of pharmacotherapy in the treatment of osteoporosis can reduce the incidence of fragile fractures by 30-70% in high-risk patients. Despite the proven benefit, more than half of patients who were recommended to use pharmacotherapy either do not initiate therapy or do not use therapy appropriately.[9]

Adherence to pharmacotherapy is defined as a measure of matching a patient's behaviour with medical instruction of their physician [10] and consists of the three phases: initiation, implementation and discontinuation.[11] Primary medication non-adherence (PMN) means non-initiation of therapy after a doctor's recommendation, while secondary non-adherence means the discontinuation of therapy in a person who has previously used it.[12]

This work aimed to overview the risk factors associated with non-adherence to antiosteoporotic medication.

PHARMACOLOGICAL INTERVENTIONS

In the absence of contraindications, pharmacological therapy is indicated for high-risk patients, and after clinical assessment and exclusion of secondary causes of osteoporosis. [2] The drugs used in the treatment of osteoporosis are

either antiresorptive or anabolic.[5] The most commonly used agents in the treatment of osteoporosis are raloxifene, the bisphos phonates alendronate, ibandronate, risedronate and zoledronic acid, agents derived from parathyroid hormone and denosumab.[13] The ways and frequency of using different antiosteoporotic agents are given in **Table 1**. All of these drugs have been shown to reduce the risk of vertebral fractures, some of them reduce the risk of non-vertebral fractures, or specifically reduce the risk of hip fractures. [13] The choice of therapy should be individualized with careful benefit-harm assessment and patients should be educated on how to reduce the adverse effect of medication.[6]

Table 1: The way of using antiosteoporotic agents

Antiresorptive Agents	Way of using
Bisphosphonates	
Alendronate	Oral once daily or weekly
Risedronate	Oral once daily, weekly, or monthly
Ibandronate	Oral once monthly or intravenous every 3 months
Zoledronic acid	Intravenous once yearly
RANK ligand inhibitor	
Denosumab	Subcutaneous injection every 6 months
Oestrogen	
Estradiol, estropipate, conjugated oestrogen	Oral, transdermal, implant
Selective oestrogen receptor modulators	
Raloxifene	Oral once daily
Bazedoxifene	Oral once daily
Bazedoxifene and conjugated oestrogen	Oral once daily
Anabolic Agents	**Way of using**
Parathyroid hormone receptor agonist	
Teriparatide	Subcutaneous injection daily
Abaloparatide S	Subcutaneous injection daily

*This table is adapted from [2]

RISK FACTORS FOR NON-ADHERENCE TO PHARMACOTHERAPY

Non-adherence is one of the reasons for treatment failure, worsening of disease symptoms, complications, increase in the frequency of hospitalizations, and even mortality. [14,15,16] Patients with chronic diseases who have mild symptoms or those without symptoms have poorer adherence to medications. [17] Two recent meta-analyses found that 15% (17%) of patients, or one in six patients, show no adherence when introducing a new drug to treat a chronic illness. [12,18] The percentage of PMN was higher in patients with osteoporosis and patients with hyperlipidemia, and it was 25%. This difference can be explained by the nature of the two mentioned diseases, ie the fact that the patients may not have significant clinical symptoms, which led to a lower tendency to start chronic treatment. [18]

The use of pharmacotherapy in the treatment of osteoporosis can reduce the incidence of fragile fractures by 30-70% in high-risk patients.It is important to emphasize that, in most cases, the use of first-line drugs with adherence with at least 75%, for at least one year, is necessary to achieve a clinically significant reduction in fracture risk. [9] However, patients with osteoporosis often choose not to initiate therapy. [19] More than half of the patients do not start using the recommended therapy or do not use it properly.[9] Their decision is influenced by the personal perception of risk concerning the perception of benefits, [19] and the individual decision to start treatment depends on the knowledge, values, and preferences of the patient. [9] The decision to take medication is also influenced by cultural factors, feedback from peer groups, previous experience with medication and gender. Gender differences in the perception of the disease relate to the fact that osteoporosis has long been considered a female disease, and men may not believe that they have risk. [19]

The comorbidities associated with poorer adherence in patients with osteoporosis are depression, diabetes mellitus, ischemic heart disease and rheumatoid arthritis.[8] Additionally, adherence is affected by patient age, polypharmacy, side effects, and patient education [11] as well as high treatment costs. [8]

According to many guidelines, bisphosphonates are first-line drugs in the treatment of osteoporosis, whether used orally or parenterally. [20] One Italian study conducted at the level of primary health care, have reported that the most frequent reasons for drug discontinuation are: another doctor's recommendation to discontinue therapy (40%), lack of motivation (20%), lack of improvement in BMD (14%), uncomfortable way of administering the drug (11%), side effects (6%), fear of side effects (1.6%), polypharmacy (0.8%), other reasons (6.6%). [21] A recent system report has shown that adherence and persistence for oral bisphosphonates are better in elderly patients, as well as in patients prescribed therapy on a weekly rather than daily basis.[1] Paskins et al. [22] reported that side effects and special instructions for the use of oral bisphosphonates can be a burden for treatment because they cause concern in the patient. Concerns and associated fears are prevailing in patients, and the need for therapy may be underestimated if the consequences of osteoporosis and fragility fractures are not explained.

When it comes to parenteral administration of bisphosphonates, Spangeus et al. [20] showed that the oldest patients have the lowest persistence for zoledronic acid. The acute phase reaction is manifested by influenza-like symptoms and occurs in about 40% of patients after the first dose of zoledronic acid. Symptoms such as fatigue, arthralgia, nausea, headache, and fever are usually mild and usually pass a few days after the infusion. The reactions of the acute phase may be more serious and more difficult to tolerate in older, weaker patients, where they can have a more serious impact on the activities of everyday life.

In a recent systematic review was reported that one-third to one-half of patients do not take medication as directed, and that dosing frequency is likely to affect persistence in parenteral therapy. Persistence was better for lower dosing drugs such as denosumab and zoledronic acid, compared to higher dosing drugs such as teriparatide and ibandronate.[7]

Gamboaet al. [23] found that that 65% of patients who had previous fracture stop using oral bisphosphonates after

12 monthswhich is significantly contributed by poorer health and functional status before fractures.

CONCLUSION:

The findings of this review suggest that non – adherence is common among patients with osteoporosis and decreases over time. Improving adherence to anti-osteoporosis therapy requires efficient communication between the patient and the healthcare providers, as well as careful monitoring of patients.

Abbreviations:

PMN –Primary medication non-adherence

Sažetak

Osteoporotski prelomi su značajan uzrok morbiditeta i mortaliteta, a očekuje se da će godišnja prevalenca ovakvih preloma rasti zbog starenja stanovništva i produženog životnog veka. Iako se redovnim korišćenjem farmakoterapije učestalost osteoporotskih preloma može smanjti za 30-70%, više od polovine pacijenata ne započinje da koristi terapiju, ili je ne koristi na odgovarajući način. Neadherenca terapiji može biti povezana sa simptomatskim pogoršanjem bolesti, komplikacijama, povećanjem učestalosti hospitalizacije i mortaliteta. Rezultati različitih studija ističu povezanost između neadherence terapiji i složenijih režima korišćenja lekova, težine simptoma, lične percepcije rizika i koristi, znanja i obrazovanja pacijenta, starosti, polifarmacije, neželjenih efekata. Važno je identifikovati faktore rizika povezane sa neadherencom i postići efikasnu komunikaciju između pacijenata i zdravstvenih radnika kako bi se poboljšala adherenca, a tako i ishod bolesti.

REFERENCES

1. Fatoye F, Smith P, Gebrye T, Yeowell G. Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review. BMJ Open. 2019;9(4):e027049.

2. Compston JE, McClung MR, Leslie WD. Osteoporosis. Lancet. 2019;393:364–76.

3. Vučić Z, Bondžić N,Zvekić-Svorcan J. Quality of life in postmenopausal women with reduced bone mineral density. MD-Medical Data. 2018;10(3):143–7.

4. Štrangar E, Zvekić-Svorcan J.Risk evaluation in fragilefracture formation.MD-Medical Data. 2016;8(2):087–094.

5. Awasthi H, Mani D, Singh D, Gupta A. The underlying pathophysiology and therapeutic approaches for osteoporosis. Med Res Rev. 2018;38(6):2024–57.

6. Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Screening for Osteoporosis to Prevent Fractures. JAMA. 2018;319(24):2521–31.

7. Koller G, Goetz V, Vandermeer B, Homik J, McAlister FA, Kendler D. Persistence and adherence to parenteral osteoporosis therapies: a systematic review. Osteoporos Int. 2020;31(11):2093–102.

8. Yeam CT, Chia S, Tan HCC, Kwan YH, Fong W, Seng JJB. A systematic review of factors affecting medication adherence among patients with osteoporosis. Osteoporos Int. 2018;29(12):2623–37.

9. Wilton-Clark MS, Feasel AL, Kline GA, Billington EO. Autonomy begets adherence: decisions to start and persist with osteoporosis treatment after group medical consultation. Arch Osteoporos. 2020;15(1):138.

10. Straka I, Minár M, Škorvánek M, Grofik M, Danterová K, Benetin J, et al. Adherence to Pharmacotherapy in Patients With Parkinson's Disease Taking Three and More Daily Doses of Medication. Front Neurol. 2019;10:799.

11. Cornelissen D, de Kunder S, Si L, Reginster JY, Evers S, Boonen A. Et al. Interventions to improve adherence to anti-osteoporosis medications: an updated systematic review. Osteoporos Int. 2020;31(9):1645–69.

12. Lemstra M, Nwankwo C, Bird Y, Moraros J. Primary nonadherence to chronic disease medications: a meta-analysis. Patient Prefer Adherence. 2018;12:721–31.

13. Kanis JA, Cooper C, Rizzoli R, Reginster, JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30(1):3–44.

14. Walsh CA, Cahir C, Tecklenborg S, Byrne C, Culbertson MA, Bennett KE, et al. The association between medication non-adherence and adverse health outcomes in ageing populations: A systematic review and meta-analysis. Br J Clin Pharmacol Title. 2019;85(11):2464–78.

15. Gruszczyńska M, Wyszomirska J, Daniel-Sielańczyk A, Bąk-Sosnowska M. Selected psychological predictors of medication adherence in the older adults with chronic diseases. Nurs Open. 2020;8(1):317–26.

16. Qiao X, Tian X, Liu N, Dong L, Jin Y, et al. The association between frailty and medication adherence among community-dwelling older adults with chronic diseases: medication beliefs acting as mediators. Patient Educ Couns. 2020;130(12):2548–54.

17. Moon S J, Lee WY, Hwang JS, Hong YP, Morisky DE. Accuracy of a screening tool for medication adherence: A systematic review and meta-analysis of the Morisky Medication Adherence Scale-8. PLOS ONE. 2017;12(11):e0187139.

18. Cheen MHH, Tan YZ, Oh LF, Wee HL, Thumboo J. Prevalence of and factors associated with primary medication non-adherence in chronic disease: A systematic review and meta-analysis. Int J Clin Pract. 2019;73(6):e13350.

19. Silverman S, Gold DT. Medication Decision-making in Osteoporosis: Can We Explain Why Patients Do Not Take Their Osteoporosis Medications? Curr Osteoporos Rep. 2018;16(6):772–4.

20. Spångeus A, Johansson S, Woisetschläger M. Adherence to and persistence with zoledronic acid treatment for osteoporosis—reasons for early discontinuation. Arch Osteoporos. 2020;15(1).

21. Donato P, Pepe J, Colangelo L, Danese V, Cecchetti V, Minisola S, Cipriani C. Adherence to bisphosphonates in the general population: a study in patients referred to a primary care service. Arch Osteoporos. 2019;14(1):42.

22. Paskins Z, Crawford-Manning F, Cottrell E, Corp N, Wright, J, Jinks C. Acceptability of bisphosphonates among patients, clinicians and managers: a systematic review and frameworksynthesis. BMJ Open. 2020;10(11):e0400634.

23. Gamboa A, Duaso E, Marimón P, Sandiumenge M, Escalante E, Lumbreras C, et al. Oral bisphosphonate prescription and non-adherence at 12 months in patients with hip fractures treated in an acute geriatric unit. Osteoporos Int. 2018;29(10):2309–14.