

FOR YOUR INFORMATION

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Osteoporosis: Risk Factors in Schizophrenia and a Review of Treatment

INTRODUCTION

If osteoporosis is a major concern in the general population, it should be an even larger concern in the schizophrenic patient population.

Osteoporosis is a prevalent condition that afflicts 1 in 4 women and 1 in 8 men in the general population in Canada.¹ It is characterized by decreased bone mass caused by an imbalance between the function of osteoblasts (bone forming cells) and osteoclasts (bone removal cells). There are few associated symptoms and often, the first manifestation of osteoporosis is a fragility fracture, clinically defined as a fracture from a fall of standing height or less.¹ The 2002 Canadian clinical practice guidelines for the diagnosis and management of osteoporosis recommends that patients with at least one major risk factor or two minor risk factors should be assessed for osteoporosis. These risk factors are as follows:¹

Bone strength is dependent on bone mineral density (BMD) and bone quality. BMD is the most readily accessible and quantifiable marker of bone strength and is often used as a predictor of fracture risk.¹

Fragility fractures can occur in any bone but hip, vertebrae, and wrist fractures are especially common in osteoporosis.¹ Hip fractures are associated with significant morbidity and these patients have a higher than average mortality rate of up to 20%.¹ Approximately 40% of hip fracture patients have ambulatory problems even up to one year after their hip fracture and 27% of patients require nursing home care.² Vertebrae fractures often go undiagnosed due to subtle symptoms but they can be associated with shortened stature, kyphosis, back pain, and are considered predictors for future hip fractures.³ Wrist fracture patients also have a higher than average risk for future fragility fractures.⁴

Major Risk Factors	Minor Risk Factors
Age > 65 years	Rheumatoid arthritis
Vertebral compression fracture	Past history of clinical hyperthyroidism
Fragility fracture after age 40	Chronic anticonvulsant therapy
Family history of osteoporotic fracture, especially maternal hip fracture	Low dietary calcium intake
Systemic glucocorticoid therapy >3 months duration	Smoker
Malabsorption syndrome	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Weight <57kg
Osteopenia apparent on x-ray film	Weight loss >10% of weight at age 25
Hypogonadism	Chronic heparin therapy
Early menopause (before age 45)	

OSTEOPOROSIS IN SCHIZOPHRENIA

Although the frequency of osteoporosis in the schizophrenic population has not been determined, a large proportion of these patients have risk factors that predispose them to osteoporosis and fractures from falls. These patients are often substance abusers and a large percentage smoke or abuse alcohol. They also tend to have poor nutrition and are at risk for low dietary calcium intake. The majority of these patients are managed on antipsychotics, which by way of dopamine blockade can lead to hyperprolactinemia, hormone imbalances, and amenorrhea. Antipsychotics may also increase a patient's propensity to fall by causing daytime sedation, orthostatic hypotension, and movement disorders.

Yarden et al reported that schizophrenic patients who suffered hip fractures had worse ambulatory outcomes compared to nonpsychiatric patients with hip fractures. Eighty-one percent of schizophrenic patients were

rated as having a poor outcome at one-year post hip fracture compared to 8% in the non-psychiatric group. This difference was statistically significant. This study also reported that 25% in the schizophrenic group suffered a subsequent fracture in the opposite femur within a year whereas no patients in the control group suffered another fracture. This too was statistically significant.⁵

Risk factors in the Schizophrenic Patient Population

Polydipsia

Polydipsia is a symptom that is reported in about 25% of schizophrenic patients.⁶ A study performed by Delva et al showed a correlation between polydipsia and osteopenia. Ten chronic schizophrenic male patients with polydipsia were compared with ten nonpolydipsic controls matched for age, gender, diagnosis, and duration of illness and race. The investigators found that bone mineral density in the lumbar spine was significantly lower in the polydipsic group compared to the control group. The polydipsic patients also had a significant increase in the number of fractures detected in the axial and appendicular skeletons compared to the controls. The authors theorize that chronic polyuria may lead to increased urinary calcium loss possibly caused by extracellular space volume expansion. Negative calcium balance may potentially lead to decreased bone mass in some patients.⁷

Hyperprolactinemia

Conventional antipsychotics and risperidone are associated with high prolactin levels. There is currently a study underway by Zhang-Wong et al to test the relationship between menstrual irregularities and prolactin levels and between prolactin levels and bone mineral density.⁸ Currently, it is believed that antipsychotic-induced hyperprolactinemia may lead to low estrogen levels and secondary amenorrhea. Low estrogen levels correlate with an increased risk for osteoporosis. This is evidenced by the rise in the risk for osteoporosis in post-menopausal women and the lower incidence of hip fractures in women who take hormone replacement therapy.⁹

A study performed by Halbreich et al demonstrated that bone mineral density (BMD) in the lumbar spine

was negatively correlated with prolactin levels in men but not in women.¹⁰

Hormone Levels

Decreased estrogen and amenorrhea are side effects often associated with antipsychotics and believed to be secondary to hyperprolactinemia. Surprisingly, the investigators did not find a significant correlation between estradiol levels and BMD at any site in women.¹⁰ Zhang-Wong et al are currently investigating if there is a correlation between menstrual irregularities and BMD.⁸

Other risk factors

Risk factors for osteoporosis are considered to be additive. Alcohol and drug abuse in schizophrenic patients is not uncommon. Smoking rates in the schizophrenic population is reportedly almost three times more (88%) than the general population.¹¹ Even though there are currently no studies showing that smoking, alcohol use, exercise, or low calcium intake alone are independent risk factors for osteoporosis, we must still take them into consideration when determining a patient's overall risk.

Age is considered a major risk factor for osteoporosis and fractures in the general population because BMD decreases with age. The 10 year probability of sustaining a forearm, humerus, spine or hip fracture increases by approximately 8-fold in women and 5-fold in men between ages 45 and 85.¹² The elderly schizophrenic patient may be at even greater risks for fragility fractures due to the additional risk factors conferred by antipsychotic medications such as sedation and movement disorders.

PREVENTION AND TREATMENT

For primary prevention of osteoporosis, health care professionals should encourage smoking cessation and promote regular weight bearing activity. A patient's nutritional intake should be assessed for adequate calcium (1000 – 1500mg elemental calcium/day) and Vitamin D (400 – 800IU/day).¹ Salt, caffeine, and alcohol intake in moderation should also be promoted as these factors have been implicated in raising the risk for osteoporosis.¹

Pharmacological interventions include bisphosphonates (alendronate, etidronate, risedronate), calcitonin,

hormone replacement therapy, and selective estrogen-receptor modulators (raloxifene). Regardless of intervention, calcium and vitamin D should be supplemented if the daily dietary intake is inadequate.¹

BISPHOSPHONATES

Bisphosphonates form a chemically stable bond with bone and inhibit bone resorption by interfering with osteoclast recruitment, differentiation, and action. Bisphosphonates also induce osteoclast apoptosis.¹

Alendronate (Fosamax®)

For prevention of osteoporosis, the usual dose is 5mg once daily or 35mg once weekly. For treatment of osteoporosis, the usual dose is 10mg once daily or 70mg once weekly. Alendronate should be taken in the morning, at least 30 minutes before the first food or beverage of the day to facilitate absorption. Patients should be encouraged to take it with a full glass of plain water and to avoid lying down minimize the risk of mucosal/esophageal irritation or reflux. Mineral supplements or antacids can interfere with the absorption of alendronate and should only be taken 30 minutes after the administration of alendronate.¹³

Risedronate (Actonel®)

The dose for the treatment or prevention of osteoporosis is 5mg once daily or 35mg once weekly. The same administration directions apply to risedronate as they do with alendronate.¹⁴

Etidronate (Didronel®)

Is available as 200mg and 400mg tablets or as a 90 day pre-packed kit containing fourteen 400mg tablets and seventy-six 1250mg calcium carbonate tablets (Didrocal®). Etidronate is administered intermittently in a cyclical regimen as 400mg daily for 14 days and drug free for 76 days where the patient only receives supplemental calcium. Continuous daily administration of etidronate without a drug free period is associated with impaired bone mineralization and increased fractures. Etidronate may be administered with juice or water but should not be taken within 2 hours of food to facilitate absorption. Mineral supplements and antacids should not be taken within 2 hours of etidronate.¹⁵

NASAL CALCITONIN

Calcitonin (Miacalcin®) is a human peptide hormone that is physiologically secreted in response to high serum calcium levels to inhibit bone resorption by affecting osteoclast activity. The pharmacological form of calcitonin is derived from salmon and is more potent with a longer duration of action than human calcitonin. Calcitonin cannot be taken orally because it is a polypeptide and will be digested by the gastrointestinal system before it is absorbed. It is available in two forms: injectable and intranasal. The intranasal form is most commonly used due to convenience and lower side effect profile compared to parenteral. The usual dose for the treatment of osteoporosis is 200IU (one metered dose spray) in one nostril a day, alternating nostrils daily.¹⁶

SELECTIVE ESTROGEN RECEPTOR MODULATOR

Raloxifene (Evista®) has mixed estrogen receptor agonist and antagonist activity depending on tissue site. Raloxifene acts as an agonist to inhibit bone resorption at the bone while acting as an estrogen antagonist at the breast and uterine tissue. The usual dose for prevention or treatment of osteoporosis is 60mg once daily without regard to food or time of day.¹⁷

HORMONE REPLACEMENT THERAPY

Hormone replacement therapy (HRT) is an acronym for estrogen and progesterone/progestin therapy. Despite limited evidence from randomized controlled trials, HRT was historically used as a first line agent to slow the process of bone loss after menopause. This was, in part, due to the perceived safety and potential cardiac benefits with prolonged use. With the results of the WHI trial, we have significant evidence that HRT can prevent fractures at all sites, including the hip and vertebrae.⁹ Unfortunately, we now also have evidence that HRT may confer a slight increase in risks for coronary heart disease, stroke, and invasive breast cancer.⁹ Thus, Canadian guidelines suggest that the risks may outweigh the benefits when using HRT in postmenopausal women solely for the prevention of osteoporosis.¹

Canadian 2002 clinical practice guidelines for the treatment and prevention of osteoporosis¹

	First line agent	Second line agent
Preventive therapy in postmenopausal women with low bone density	Alendronate Etidronate Risedronate Raloxifene	Hormone replacement therapy
Treatment for post-menopausal women with osteoporosis, especially those with pre-existing vertebral fractures	Alendronate Risedronate Etidronate Raloxifene	Nasal calcitonin Hormone replacement therapy
Prevention or treatment of glucocorticoid-induced osteoporosis	Alendronate Risedronate Etidronate	
Treatment for men with low bone mass or osteoporosis	Alendronate Etidronate	Nasal calcitonin
Non-pregnant, premenopausal women with osteopenia or osteoporosis	Therapy has not been examined adequately in premenopausal women. It is suggested that nasal calcitonin may be used due to its safety profile and bisphosphonates may be considered on a case-by-case basis. Contraception is recommended.	
Women who experience menopause before age 45	Hormone replacement therapy	

SUMMARY

Schizophrenic patients should be routinely assessed for osteoporosis risk factors. Evidence shows that certain subgroups of schizophrenic patients have low bone density. Schizophrenia is also associated with poor outcome after a hip fracture. Non-pharmacological osteoporosis preventative measures such as adequate calcium and vitamin D, weight bearing exercises, smoking cessation, and limiting alcohol intake should be emphasized. Pharmacological therapy should be considered where appropriate.

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