1.1. Bisphosphonates and depressive reactions

Introduction

Bisphosphonates are the most commonly prescribed medications for the treatment of osteoporosis [1].
Alendronate (Fosamax®) is indicated for the *treatment and prevention of osteoporosis in postmenopausal women, treatment to increase bone mass in men with osteoporosis, treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density, and treatment of Paget's disease of bone in men and women* [2]. Alendronate with colecalciferol (vitamin D3) (Fosavance®) is indicated for *the treatment of postmenopausal osteoporosis in patients at risk of vitamin D insufficiency* [3].
Risedronate (Actonel®) is used for the same indications as alendronate [4]. Risedronate with calcium (Actokit®) is indicated for the *treatment and prevention of osteoporosis in postmenopausal women* [5].
Etidronate with calciumcarbonate (Didrokit®) is indicated for *the prevention and treatment of osteoporosis in post-menopausal women and the prevention of corticosteroid induced osteoporosis* [6].
Ibandronate (Bonviva®) is indicated for *the treatment of osteoporosis in postmenopausal women at increased risk of fracture* [7].
Pamidronate (Pamipro®) is used intravenously for a different indication than most other bisphosphonates, namely *tumour-induced hypercalcaemia, osteolytic lesions in patients with breast cancer related bone metastasis and multiple myeloma stage III* [8]. Intravenous pamidronate is also used as APD infusion for the indication *osteoporosis*.
Zoledronate (Zometa®) is indicated for *prevention of skeletal related events in patients with advanced malignancies involving bone or treatment of tumour-induced hypercalcaemia* [9].
The most commonly used bisphosphonate in the Netherlands [10], alendronate (Fosamax®), was granted marketing authorization in 1996 [2].

Lareb received several reports of depression, depressed state or mood with the use of the bisphosphonates alendronate, etidronate and pamidronate. Although no reports of depressive reactions were received for other bisphosphonates, we included these in the overview of the literature.

According to the DSM-IV criteria [11] depressive disorders can be divided in major depressive disorder, dysthymic disorder and depressive disorder not otherwise specified. The essential feature of a major depressive episode is a period of at least two weeks during which there is either depressed mood or the lost of interest or pleasure in nearly all activities. The individual must also experience four symptoms drawn from a list which includes changes in appetite or weight, sleep, psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty thinking, concentrating or making decisions, or recurrent thoughts of death or suicidal ideation or plans or attempts [11].

Depression or depressed mood is not described in the SmPC of alendronate (Fosamax®) [2], alendronate with colecalciferol (Fosavance®) [3], risedronate (Actonel®) [4], risedronate with calcium carbonate (Actokit®) [5], etidronate with calcium carbonate (Didrokit®) [6], ibandronate (Bonviva®) [7], pamidronate (Pamipro®) [8] or zoledronate (Zometa®) [9].

Reports

On July 22, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained 14 reports concerning depression with the use of alendronate, etidronate or pamidronate.

Table 1. Reports of depression associated with the use of bisphosphonates

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 16425 F, 61 – 70 years	alendronate 10 mg daily, osteoporosis	spironolactone, furosemide, ipratropium, budesonide	depressed state, hoarseness, drowsiness, abdominal discomfort	6 weeks discontinued not reported
B 17110 F, 70 years and older	alendronate 10 mg daily, unspecified	hydrophilic cream ('lanette'), calcium carbonate	depressed state	6 weeks no change not reported
C 19211 M, 41 – 50 years	etidronate cyclical use of 400 mg daily during 14 days followed by 72 days of calcium carbonate, osteoporosis	beclomethasone	depressed state	3 weeks discontinued recovered after one month
D* 19212 F, 51 – 60 years	etidronate cyclical use of 400 mg daily during 14 days followed by 72 days of calcium carbonate, osteoporosis	ranitidine, isradipine, triamterene/ epitizide	depressed state	4 years discontinued recovered
D* 19212 F, 51 – 60 years	pamidronate 90 mg per IV, osteoporosis		depressed state, agitation	quickly after start discontinued recovered
E 22487 F, 31 – 40 years	alendronate 10 mg daily, osteoporosis fluvoxamine 50 mg 3 times daily		drug level decreased, depression aggravated	not reported discontinued not reported
F 28069 F, 70 years and older	alendronate 10 mg daily, osteoporosis	ibuprofen, temazepam	depressed state	not reported discontinued recovered
G 45315 F, 61 – 70 years	alendronate 70 mg weekly, osteoporosis		depression, gastro-intestinal disorder, bone pain, peripheral oedema, fatigue	not reported exactly, gradual onset discontinued recovering
H 47307 F, 51 – 60 years	alendronate 70 mg weekly, osteoporosis	diazepam	depression, restlessness, emotional lability	couple of days discontinued, recovered, positive rechallenge
I 48815 M, 51 – 60 years	alendronate 70 mg weekly, unspecified		depressed state, bone pain, oedema legs, fatigue, allergic reaction	not reported discontinued not reported

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
J 65558 F, 70 years and older	alendronate with colecalciferol 70 mg/2800 ie weekly, osteopenia	diazepam, maprotiline, nitrazepam, vitamin C + garlic	depressed state	5 hours discontinued recovered
K, 104474 F, 61 – 70 years	alendronate 70 mg weekly, osteoporosis		depressed mood, anxiety	not reported discontinued recovered
L 88028 F, 61 – 70 years	alendronate 70 mg weekly, osteoporosis	pantoprazole, salbutamol	depressed mood	month discontinued recovered
M 101865 M, 41 – 50 years	etidronate cyclical use of 400 mg daily during 14 days followed by 72 days of calcium carbonate, osteoporosis		depressed mood	within a day discontinued and replaced by risedronate recovered
N 70459 F, 31 – 40 years	anastrozole 1 mg, breast cancer, goserelin 3.6 mg in injection, breast cancer, alendronate 70 mg weekly, prevention	ibandronate calcium carbonate/ colecalciferol, zolpidem	depressed mood, arthralgia, cough, insomnia, nausea	2 weeks discontinued, recovered, rechallenge only for the anastrozole and goserelin

* Patient D appears twice in table 1. See the description of this case below.

Patient A uses budesonide as concomitant medication. For this drug depression is listed in the SmPC as a rare adverse drug reaction (incidence 0.1 - 0.01%) [12].

The cases of patient C en D were previously published by *Wolffenbuttel &.van der Klauw* [13] and also reported to Lareb.

Patiënt C is male aged 41 – 50 years who was treated with etidonate for osteoporosis. He had a medical history of chronic obstructive pulmonary disease and had been treated with corticosteroids for a prolonged period. The patient suffered from fatigue, concentration impairment, irritation, spontaneous crying and depressed feelings. The reaction occurred after each cycle of etidronate use and recovered within weeks. Each following time etidronate was used again, the reaction reoccurred. The blood calcium level was within the normal range in this patient. Etidronate was withdrawn and the reaction did not occur again for the following five years.

Patient D appears twice in table 1, this case had not been divided into two separate case reports with their own ID-numbers at the time of reporting (1997).
Patient D had been treated for osteoporosis with etidronate since she was 50. At the age of 54 changes in her mood, memory impairment and difficulties with concentration occurred. She felt depressed and emotionally drained. The blood calcium level was within the normal range in this patient. After withdrawal of etidronate the patient recovered within two months. Her other medication had not been changed during this period.
When the patient was 56 pamidronate 90 mg per IV was started to treat her osteoporosis. Quickly after start of pamidronate the same reactions occurred again and the patient became depressed and agitated. Pamidronate was withdrawn and she recovered. Treatment with bisphosphonates was not started again; the patient was treated with colecaliferol, vitamin D and calcium.

Patient E had a history of depression. Fluvoxamine had been used for years and every time this drug was discontinued a relapse of the depression occurred. The last six years the patient had been using fluvoxamine constantly and had not suffered from a relapse of the depression. After alendronate was started, the depression worsened again. In hospital the blood level of fluvoxamine was determined; this had decreased without a known cause. A possible interaction between alendronate and fluvoxamine was reported to the pharmacovigilance centre. At the time of reporting (12-10-1998), alendronate was discontinued but the patient had not recovered.

Patient J (consumer report) reported that the first couple of weeks after alendronate with colecaliferol she only suffered from complaints a few hours after intake. Gradually the depressed state prolonged and she also suffered from fatigue. In her report the patient asked if there was a possibility for an interaction between maprotiline and alendronate with colecalciferol. After withdrawal of the suspect drug she recovered. The indication for the use of maprotiline, a tricyclic antidepressant, is not given in this report.

Patient M only suffered from a depressed mood during the 14 days of etidronate use during a cycle. During the following 72 days of calcium carbonate use the reaction recovered.

Patient N (consumer report) reported that she thinks the combination between anastrozole and goserelin was the main cause for her depressed mood. There was a positive dechallenge for all suspected drugs (anastrozole, goserelin and alendronate) but a positive rechallenge was only reported for anastrozole and goserelin. The patients' serious illness could also be a factor in the occurrence of the depressed state.

Other sources of information

SmPC

Depressive reactions including depression or depressed state or mood are not described in the Dutch SmPC's of the various bisphosphonates [2-9]. The Dutch SmPC of pamidronate [8] describes some psychiatric adverse drug reactions like agitation and visual hallucinations. The Dutch SmPC of zoledronate mentions anxiety, sleep disturbance and confusion as possible psychiatric reactions [9].
Depression is not described in the US SmPC of alendronate (Fosamax®) [14]. The US SmPC of etidronate (Didronel®) mentions neuropsychiatric events including amnesia, confusion, depression and hallucination as events based on worldwide postmarketing experience [15].
The US SmPC of risedronate (Actonel®) mentions that depression occurred with an incidence of 6.8% compared to 6.1% with placebo in combined phase 3 postmenopausal osteoporosis treatment trials [16]. Four randomized, double-blind, placebo-controlled multinational trials of 3232 women aged 38 to 85 years with postmenopausal osteoporosis were combined. The duration of the trials was up to three years, with 1619 patients exposed to placebo and 1613 patients exposed to risedronate 5 mg. Based on the numbers on the SmPC, this difference is not statistically significant (2-sided X^2-test p-value = 0.43)
During a study which compared risedronate 5 mg daily and 35 mg weekly for the treatment of osteoporosis in postmenopausal women (n=965), the incidence of depression was 2.3% for both groups [17].
The US SmPC of zoledronate (Zometa®) describes that in 3 randomized, double-blind, active, and placebo-controlled clinical trials in patients with multiple myeloma and bone metastases, the incidence of depression in patients receiving zoledronic acid 4 mg (n=1,031) compared to pamidronate 90 mg (n=556) and to placebo (n=455) was 14% versus 17% versus 11%, respectively [18].
Based on the numbers in the SmPC, the difference between zoledronate and placebo is not statistically significant (2-sided X^2-test p-value = 0.13). The difference between pamidronate and placebo is statistically significant (2-sided X^2-test p-value = 0.007)

Literature

In the article by *Wolffenbuttel &.van der Klauw* [13] a third patient is presented, whose case was not reported to Lareb. This patient was a female, aged 67 who also suffered from a depressed mood, agitation and impaired concentration with cyclical use of etidronate. The blood calcium level was within the normal range in this patient. Shortly after withdrawal of etidronate, she recovered. There were no other emotional or psychosocial problems. Alendronate was started and the depressed mood reoccurred together with insomnia, palpitations and rash. Alendronate was withdrawn and the patient recovered. Three monthly intravenous pamidronate was started without reoccurrence of the reactions.
To the best of our knowledge no other case reports about bisphosphonate-induced depressive reactions have been published.

Databases

Table 2. Reports of depressive reactions associated with bisphosphonates in the Lareb database

Drug	Number of reports	ROR (95% CI)
Alendronate	11	1.3 (0.7 - 2.5)
Etidronate	3	2.5 (0.8 – 7.9)
Bisphosphonates in total	14	1.5 (0.9 - 2.6)

For the Lareb database the MedDRA Preferred terms depression and depressed mood in association with bisphosphonates, with and without calcium or colecalciferol were taken into account. One patient also suffered from depressed feelings during the use of pamidronate, a reporting odds ratio was not calculated for pamidronate.

Table 3. Reports of depressive reactions associated with bisphosphonates in the WHO database

Drug	Number of reports	ROR (95% CI)
Alendronate	638	2.3 (2.1 - 2.5)
Etidronate	18	0.7 (0.5 - 1.1)
Pamidronate	89	1.9 (1.5 – 2.3)
Bisphosphonates in total	986	1.5 (1.4 - 1.6)

For the WHO database the terms WHO-ART terms depression, depression aggravated and depression psychotic in association with bisphosphonates, with and without calcium or colecalciferol were taken into account.

On August 3rd the Eudravigilance database contained 753 reports of depression associated with use of one of the bisphosphonates. Specified for individual bisfosfonates results in the following number of reports of depression: alendronate 636, risedronate 42, zoledronate 214, etidronate 1, clodronate, ibandronate 46, pamidronate 116. Because in some reports, more than one bisphosphonate was reported as a suspect drug the total number exceeds 777.

Prescription data

The number of patients using bisphosphonates in the Netherlands is shown in table 4.

Table 4. Number of patients using bisphosponates in the Netherlands between 2006 and 2009* [10]

Drug	2006	2007	2008	2009
Etidronate	2	.	.	.
Etidronate with calcium	12,735	9,295	7,133	5,742
Alendronate	144,080	139,770	141,250	149,300
Aledronate with colecalciferol	12,567	17,883	21,309	25,610
Ibandronate	4,855	8,481	10,756	12,083
Risedronate	59,033	61,755	66,077	72,343
Risedronate with calcium	10,973	12,400	12,798	12,763
Zoledronate	275	452	603	1,367

* There are no data for pamidronate available

Mechanism

The mechanism through which bisphosphonates might induce depressive symptoms is unknown. Bisphosphonates, including alendronate, can cause hypocalcaemia. Acute hypocalcaemia is commonly associated with symptoms of breathlessness, palpitations, tingling, and spasm. In comparison, chronic hypocalcaemia is more commonly associated with fatigue, irritability, memory loss, depression, confusion, delusions, and hallucinations. However, the decrease in serum calcium is generally mild and occurs with the start of therapy and then plateaus over time [19].
In the patients that were described by *Wolffenbuttel &.van der Klauw* [13], the blood calcium levels were within the normal range.
The authors of a case report of hallucinations associated with alendronate described the hypothesis that changing from the once-daily to the once-weekly formulation of alendronate, although resulting in similar values for the area under the concentration-time curve, yields a greater maximum serum concentration of the drug, ultimately precipitating the adverse reaction their patient experienced. However, this could not be confirmed in their patient since the poor bioavailability with oral administration of alendronate results in serum concentrations below the lower limit of quantification (5 ng/ml) [19].

There were two cases reported to Lareb where a possible drug interaction between alendronate (with colecalciferol) and fluvoxamine (patient E) or maprotiline (Patient J) was mentioned. An interaction between bisphosphonates and antidepressant drugs such as SSRI's or TCA's is not described in *Stockley's Drug interactions* [20].

Discussion

Lareb received 14 reports concerning depressive reactions with the use of alendronate or etidronate. In nine cases there was a positive dechallenge and in one patient also a positive rechallenge. In the other four cases the outcome was not reported. A close temporal relationship with the start of each cycle of use of etidronate was reported in patient D and M.
In the literature information about this association is scarce, although the US SmPCs of certain bisphosphonates mention the occurrence of depression as an adverse drug event [15,17,18]. However, for risedronate and zoledronate the occurrence of depression was similar in the placebo and the treated group [16].
Lareb has received only reports about three of the bisphosphonates available on the Dutch market namely etidronate, pamidronate and alendronate. In the WHO database there are also reports of depression with other bisphosphonates. This association could possibly be a class-

effect for all the bisphosphonates. However, a possible class-effect is not fully supported by the cases Lareb received.
Depression is mentioned in the literature as one of the possible risk factors for osteoporosis [21].

Conclusion

These cases illustrate a possible signal of depressive reactions occurring with alendronate, pamidronate and etidronate. This association could possibly be a class-effect for all the bisphosphonates.

- Possible new signal of alendronate, pamidronate and etidronate associated with depressive reactions

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This signal has been raised on November 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).