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**Observational Study**

- 1 Physicians' knowledge and attitude regarding bisphosphonates-related adverse events: An observational study

*El Osta L, El Osta N, Tannous R, Aoun A, Ghosn M, El Osta H*

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Observational Study

## Physicians' knowledge and attitude regarding bisphosphonates-related adverse events: An observational study

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### Abstract

#### AIM

To assess the knowledge and attitude of Lebanese physicians regarding bisphosphonates (BPs)-related complications.

#### METHODS

An observational cross-sectional study was conducted at a major tertiary teaching hospital in Beirut city, and its affiliated primary health care center. Data were collected through a new self-administered questionnaire distributed *via* a delegated secretary to physicians expected to regularly prescribe BPs ( $n = 215$ ). It assessed participants' knowledge, fear and experience regarding BPs-reported complications.

#### RESULTS

One hundred and fifty-seven physicians fulfilled the

questionnaire (response rate: 73.0%): 77.7% and 75.2% considered that gastrointestinal intolerance and osteonecrosis of the jaw are linked to BPs, respectively. Conversely, the least recognised complications are ocular inflammation (7.6%) and severe musculoskeletal pain (37.6%). The association of BPs with oesophageal cancer, atrial fibrillation and hepatotoxicity was reported by 11.5%, 13.4% and 24.8% of respondents, respectively. The multivariate analysis showed a significant association between level of knowledge and physicians' department affiliation ( $P$ -value = 0.043), their gender ( $P$ -value = 0.044), whether or not they prescribe a BP ( $P$ -value = 0.012), and the number of BP prescriptions delivered monthly ( $P$ -value = 0.012). Physicians are mainly concerned about osteonecrosis of the jaw and nephrotoxicity when prescribing a BP. Yet, the complications commonly met in their practice are gastrointestinal intolerance (44.6%) and acute phase reactions (26.7%).

### CONCLUSION

This study revealed the presence of a deficient knowledge regarding BPs-related adverse events among our physicians. Professional training proposals are needed to increase their knowledge and improve their practices. Pharmaceutical industries should reconsider the instructions they provide to physicians regarding the complications of medications they promote. Moreover, they must actively collaborate with education providers and institutions in educational interventions.

**Key words:** Knowledge; Bisphosphonates; Malignant bone diseases; Osteoporosis; Drug complications

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**Core tip:** Bisphosphonates (BPs) have been proven to be effective, tolerated and relatively safe to a large number of patients. However, they were associated with reports of multiple adverse events. Given the widespread use of these medications, detailed knowledge on occurrence of even rare side effects is imperative. In this study, we assess the knowledge and approach of our physicians regarding BPs-related complications. Eventually, this evaluation will facilitate the elaboration of appropriate training programs to increase their awareness and improve their practice. It will incite pharmaceutical companies to reconsider the instructions they provide to physicians about the complications of treatments they promote.

El Osta L, El Osta N, Tannous R, Aoun A, Ghosn M, El Osta H. Physicians' knowledge and attitude regarding bisphosphonates-related adverse events: An observational study. *World J Rheumatol* 2017; 7(1): 1-7 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v7/i1/1.htm> DOI: <http://dx.doi.org/10.5499/wjr.v7.i1.1>

## INTRODUCTION

Bisphosphonates (BPs) are powerful inhibitors of osteo-

clast-mediated bone resorption and thus, are mainly used in the prevention and treatment of osteoporosis. They are also recommended in the treatment of bone lesions in multiple myeloma, bone metastases, hypercalcaemia of malignancy, treatment-related bone loss in breast and prostate cancer, and less common conditions that feature bone fragility such as Paget's disease<sup>[1,2]</sup>. Currently their therapeutic use has been increased with several millions of prescriptions written every year, because of their safety profile, good tolerability and efficacy. However, these benefits were linked to many undesirable events, which could be serious. Given the limitations of clinical trials to detect rare adverse effects, these complications continue to emerge with post-marketing surveillance and increasing clinical experience<sup>[1,3,4]</sup>.

Given the widespread use of BPs, detailed knowledge on occurrence of even rare side effects is imperative. We believe that practitioners' awareness of BPs-reported adverse events can potentially avoid the onset of more serious complications due to a fast detection and management. We conducted this survey to assess our physicians' knowledge and attitude with regard to BPs-related complications. Eventually, this appraisal will allow the development of appropriate educational programs to raise their awareness and improve their practice.

## MATERIALS AND METHODS

### Participants and data collection

An observational cross-sectional study was conducted at a major tertiary teaching hospital in Beirut city, and its affiliated primary health care center between May and July 2014. The study population included clinical physicians (professors, attending physicians and fellowship residents) practicing in the departments expected to regularly prescribe a BP: Endocrinology, family medicine, gynecology, internal medicine, nephrology, oncology, orthopedics, and rheumatology departments. The fellowship residents who participated in the study are the residents who graduated from medical school, and thereafter successfully completed their first year of core curriculum in medicine or surgery residency. The total number of eligible physicians was 215. The surveys were anonymously distributed to the selected departments via a delegated secretary to be filled by the physicians themselves: 157 valid questionnaires were retrieved, generating an effective response rate of 73.0%.

### Survey questionnaire

A questionnaire was developed from an exhaustive and up-to-date literature review on the BPs-reported side effects<sup>[1-20]</sup>. A pre-test was conducted in the same study context. This enabled us to develop the final version of the questionnaire and to guarantee its reliability.

The final version consisted of three parts: (1) demographic and professional characteristics; (2) practices associated to the use of BPs; and (3) knowledge and attitude regarding the BP-related undesirable events, which contained three sections of 11 items each one. The items represented the BPs-related undesirable events



**Table 1 Bisphosphonates-reported side effects, characteristics, and rating**

Side effects	BPs incriminated	Causality link	Rating of correct answers	Rating of false answers
Upper GI intolerance	Oral amino-BPs	Established	2	0
Acute phase reaction	IV amino-BPs	Established	2	0
Hypocalcaemia	IV > oral BPs	Established	2	0
Renal toxicity	Zoledronate and pamidronate	Established	2	0
Severe musculoskeletal pain	Oral BPs	Probable	1	0
Ocular inflammation	All BPs	Probable	1	0
Atypical femoral fractures	BPs treatment for osteoporosis	Probable	1	0
Osteonecrosis of the jaw	IV BPs treatment in oncology	Probable	1	0
Atrial fibrillation	---	Unproven	1	-1
Esophageal cancer	---	Unproven	1	-1
Hepatotoxicity	---	Unproven	1	-1

BPs: Bisphosphonates; GI: Gastrointestinal; IV: Intravenous.

largely reported in the literature (Table 1). The first section tested the level of knowledge regarding these complications. The answers to the items were categorized into Yes, No, and I don't know. Thereafter, they were judged correct (1 or 2) or incorrect (0 or -1), according to the complication's causality link to the BPs. Thus, the undesirable events with an established causality link to the BPs were counted "0" or "2" if considered unrelated or related, respectively. Those whose causality link is probable were rated "0" or "1" if considered unrelated or related, respectively. Those whose correlation is not proven yet were scored "1" if considered unrelated to BPs and were penalized "-1" otherwise (Table 1). The non-response and "I don't know" were scored "0". Summing the answers provided the total knowledge score of each participant. The maximum score that might be achieved was 15. Moreover, the percentage of correct answers was assigned to each item. The second section assessed the physicians' fear regarding the BPs-related complications, and the third section exposed the complications encountered in their medical practice. The replies were dichotomized as Yes or No. The participants were also requested to exhibit their interest to learn more about these undesirable events, and to keep their knowledge updated.

### Ethical considerations

The Institutional Review Board of the Hôtel-Dieu de France university hospital of Beirut approved the study protocol (CEHDF 721). Written informed consent was obtained from the participants.

### Statistical analysis

Statistical analyses were performed using the software program SPSS for Windows version 18.0 (SPSS, Chicago). The alpha error was set at 0.05. A descriptive study was done for each variable.

In the initial stages, univariate analyses of categorical variables were carried out using the Fisher exact tests and the  $\chi^2$  independence tests. The student's *t*-test and ANOVA were also used to compare scores between groups.

A multiple regression analysis was successively conducted with the level of knowledge as the dependent

variable. The variables related to the demographic and professional characteristics, and to the BPs prescriptions, which showed associations with *P*-value < 0.2 in the univariate analyses, were subsequently entered in the multivariate model. Collinearity among independent variables was also verified. Independent variables highly correlated were excluded. It has already been suggested not to include two independent variables where there is a correlation of 0.7 or more<sup>[21,22]</sup>. The variable "number of patients on BP attended per month" was not included in the model, since it was highly correlated to the "number of BP prescriptions delivered per month", indicated by the Pearson correlation coefficient.

## RESULTS

### Survey participants

One hundred and fifty seven physicians participated in the survey: 86 (54.8%) respondents were fellowship residents, 54 (34.4%) were attending physicians, and 17 (10.8%) were professors or department chiefs; 99 (63.1%) attended more than 10 patients per day, and 48 (30.6%) received more than 10 medical sales representatives per week. The participants represented 8 clinical departments, and 114 (72.6%) belonged to medical departments.

### Practices associated to the use of BPs

Almost two-third of the physicians (68.8%) were treating patients with BPs: High professional positions more than fellowship residents (*P*-value < 0.0001), and medical specialists more than surgeons (*P*-value = 0.031). Weekly oral BPs (Alendronate and Risedronate) were prescribed by 69 (63.9%) participants and zoledronate several times yearly by 19 (17.6%), followed by monthly oral formulations (Risedronate and Ibandronate) by 18 (16.7%) participants. The indications for BPs are osteoporosis for 90 (83.3%) prescriber physicians, and malignant bone lesions for 29 (26.9%).

### Level of knowledge regarding BPs-reported complications and associated factors

One hundred and twenty-two (77.7%) and 118 (75.2%) physicians considered that gastrointestinal intolerance and

**Table 2** Our 157 physicians' knowledge, fear and experience regarding bisphosphonates-reported side effects

Side effects	Reported by physicians <i>n</i> (%)	Feared by physicians <i>n</i> (%)	Encountered by physicians <i>n</i> (%)
Acute phase reaction	86 (54.8)	12 (7.6)	42 (26.8)
Atrial fibrillation	21 (13.4)	12 (7.6)	0 (0.0)
Atypical femoral fractures	67 (42.7)	48 (30.6)	13 (8.3)
Esophageal cancer	18 (11.5)	11 (7.0)	0 (0.0)
Hepatotoxicity	39 (24.8)	18 (11.5)	2 (1.3)
Hypocalcaemia	72 (45.9)	33 (21.0)	27 (17.2)
Ocular inflammation	12 (7.6)	3 (1.9)	2 (1.3)
Osteonecrosis of the jaw	118 (75.2)	93 (59.2)	38 (24.2)
Renal toxicity	84 (53.5)	67 (42.7)	33 (21.0)
Severe musculoskeletal pain	59 (37.6)	10 (6.4)	24 (15.3)
Upper GI intolerance	122 (77.7)	45 (28.7)	70 (44.6)
No side effect	2 (1.3)	7 (4.5)	32 (20.4)

GI: Gastrointestinal.

osteonecrosis of the jaw are linked to BPs, respectively. Conversely, the least recognised complications are ocular inflammation (7.6%) and severe musculoskeletal pain (37.6%). The association of BPs with esophageal cancer, atrial fibrillation and hepatotoxicity was reported by 18 (11.5%), 21 (13.4%) and 39 (24.8%) participants, respectively (Table 2). For the whole sample the mean knowledge score was  $8.27 \pm 2.79$ , while 33.8% had a global score more than 10 over 15.

**Univariate analyses:** As shown in Table 3, there were statistically significant associations between the level of knowledge and physicians' department affiliation ( $P$ -value < 0.0001), their gender ( $P$ -value = 0.016), whether or not they prescribe a BP ( $P$ -value = 0.001), the number of BP prescriptions delivered monthly ( $P$ -value = 0.006), the most frequently form prescribed ( $P$ -value = 0.033), and the number of patients already on BP attended per month ( $P$ -value < 0.0001).

**Multivariate analysis:** Table 4 summarizes the predictive factors affecting the level of knowledge of Lebanese physicians regarding the BPs-reported undesirable events. The multiple regression analysis showed that the physicians' department affiliation was significantly associated with the level of knowledge. Physicians affiliated to medical departments are more knowledgeable in BPs' complications than surgeons ( $P$ -value = 0.043). Gender was also associated with the level of knowledge; males were less informed than females. Moreover, physicians who prescribed a BP were more familiar with BPs' side effects than non-prescribers ( $P$ -value = 0.012). Finally, increasing number of BP prescriptions delivered per month was associated with higher level of awareness ( $P$ -value = 0.012).

Most of participants (86.6%) were interested to learn more about these drug-related undesirable events, and to keep their knowledge updated.

### Physicians' fear and experience regarding BPs-reported complications

Our physicians are mainly concerned about osteonecrosis

of the jaw (59.2%) and nephrotoxicity (42.7%) when prescribing a BP, especially oncologists and nephrologists ( $P$ -value < 0.0001). Moreover, 48 (30.6%) respondents are worried about atypical femoral fracture, oncologists less than other specialties ( $P$ -value < 0.0001).

The BPs-related toxicities commonly met in their practice are gastrointestinal intolerance (44.6%), oncologists fewer than others ( $P$ -value = 0.003). Flu-like symptoms and osteonecrosis of the jaw were also encountered by 42 (26.7%) and 38 (24.2%) physicians, respectively. Most of them were oncologists ( $P$ -value < 0.0001) (Table 2).

## DISCUSSION

With the aging of the population, the incidence of osteoporosis and malignant diseases is rising more and more. Accordingly, the treatments of these diseases, particularly the BPs, are expected to increase in the coming years. Thus, physicians must be vigilant to BP-related side effects and recognize the level of evidence supporting them to better communicate the balance between benefits and potential risks to patients<sup>[3,4]</sup>. The purpose of our survey was to evaluate the knowledge and attitude of Lebanese physicians regarding BPs-reported undesirable events.

Despite the fact that various safety issues related to BPs have triggered lately widespread debate, the mean knowledge of our physicians on BPs-reported side effects was deficient. These misunderstandings among our doctors can jeopardize the safety of their patients and expose them to serious problems. However, the level of awareness among our doctors was discordant since 33.8% had a global score more than 10 over 15. The scores were superior among BPs prescribers, and increased with the increasing number of BP prescriptions delivered monthly. This reflects the effect of practice and interest as a stimulus to seek information. The higher scores among medical specialties could be explained by their concern to prescribe medications more than surgeons who are interested in technical surgeries. However, the higher scores among female need some explanations. We were surprised to find that higher professional qualifications were not associated

**Table 3** Univariate analyses of factors associated with the level of knowledge

Independent variables	Knowledge score (mean $\pm$ SD)	n	P-value
Professional position			0.232
Professor	8.82 $\pm$ 2.83	17	
Attending physician	8.65 $\pm$ 2.57	54	
Fellowship resident	7.93 $\pm$ 2.90	86	
Department affiliation			< 0.0001 <sup>a</sup>
Medical	8.92 $\pm$ 2.55	114	
Surgical	6.56 $\pm$ 2.69	43	
Department affiliation			< 0.0001 <sup>a</sup>
Rheumatology	10.62 $\pm$ 2.83	8	
Oncology	10.10 $\pm$ 1.77	20	
Nephrology	9.70 $\pm$ 2.63	10	
Endocrinology	9.45 $\pm$ 2.51	11	
Internal medicine	8.21 $\pm$ 2.48	29	
Family medicine	8.08 $\pm$ 2.52	36	
Orthopedics	7.38 $\pm$ 3.09	21	
Gynecology	5.77 $\pm$ 2.02	22	
Age			0.213
< 30 yr	7.91 $\pm$ 2.87	80	
30-50 yr	8.53 $\pm$ 2.77	55	
> 50 yr	8.95 $\pm$ 2.46	22	
Gender			0.016 <sup>a</sup>
Male	7.84 $\pm$ 2.63	95	
Female	8.94 $\pm$ 2.91	62	
No. of patients attended per day			0.874
< 10 patients	8.29 $\pm$ 2.84	52	
10-20 patients	8.32 $\pm$ 2.89	65	
> 20 patients	8.03 $\pm$ 2.42	34	
No. of medical sales representatives received per week			0.149
0	7.55 $\pm$ 2.60	20	
< 10	7.98 $\pm$ 2.76	86	
10-20	8.91 $\pm$ 2.62	34	
> 20	9.07 $\pm$ 2.99	14	
Time consumed for patients care			0.906
< 25%	8.25 $\pm$ 2.06	4	
25%-50%	8.00 $\pm$ 2.77	37	
51%-75%	8.43 $\pm$ 2.88	68	
> 75%	8.25 $\pm$ 2.75	44	
Time consumed for academic work			0.171
< 25%	8.23 $\pm$ 2.78	57	
25%-50%	8.42 $\pm$ 2.80	76	
51%-75%	7.25 $\pm$ 2.54	16	
> 75%	10.50 $\pm$ 1.91	4	
BP prescription			0.001 <sup>a</sup>
Yes	8.78 $\pm$ 2.69	108	
No	7.16 $\pm$ 2.70	49	
No. of BP prescriptions delivered per month			0.006 <sup>a</sup>
$\leq$ 5 prescriptions	8.27 $\pm$ 2.64	73	
6-10 prescriptions	9.70 $\pm$ 2.46	27	
> 10 prescriptions	10.86 $\pm$ 2.48	7	
Most frequent form of BP prescribed			0.033 <sup>a</sup>
Oral form	8.48 $\pm$ 2.73	87	
Intravenous form	9.90 $\pm$ 2.22	20	
No. of patients on BP attended per month			< 0.0001 <sup>a</sup>
0 patient	6.64 $\pm$ 2.06	11	
1-5 patients	7.85 $\pm$ 2.52	81	
6-10 patients	8.26 $\pm$ 2.81	34	
> 10 patients	9.97 $\pm$ 2.99	31	

<sup>a</sup>P-value < 0.05 (level of significance). BP: Bisphosphonate.

with better knowledge. Also the number of medical sales representatives received per week was not correlated with superior knowledge. This alarming result emphasized the lack of pharmaceutical companies in appropriately disseminating the complications of

medications they promote.

Our questionnaire assessed participants' knowledge and attitudes regarding the BPs-related undesirable events largely reported in the literature. The most prevalent adverse events are upper gastrointestinal

**Table 4 Multiple regression analysis of factors associated with the level of knowledge**

	Unstandardized coefficients		Standardized coefficients	Student	P-value	Partial correlations
	$\beta$	Standard error	$\beta$			
Department affiliation	1.253	0.610	0.201	2.054	0.043 <sup>a</sup>	0.204
Gender	1.103	0.539	0.194	2.045	0.044 <sup>a</sup>	0.203
No. of medical sales representatives received per week	0.167	0.330	0.048	0.506	0.614	0.051
Time consumed for academic work	0.144	0.331	0.038	0.434	0.665	0.044
BP prescription	-1.455	0.566	-0.242	-2.569	0.012 <sup>a</sup>	-0.252
No. of BP prescriptions delivered per month	1.106	0.431	0.241	2.567	0.012 <sup>a</sup>	0.252
Most frequent form of BP prescribed	0.870	0.671	0.122	1.296	0.198	0.130

<sup>a</sup>P-value < 0.05 (level of significance). BP: Bisphosphonate.

discomfort for oral amino-BPs and acute phase reactions for intravenous forms<sup>[5,6]</sup>, which are recognized by more than half of the physicians. However, rare are physicians who feared these complications, mainly because of their nonthreatening feature. Hypocalcaemia, renal toxicity and osteonecrosis of the jaw are rare, but could be potentially dangerous<sup>[7-10]</sup>. This explains why our physicians feared these complications. Moreover, they occur more frequently in cancer patients who receive high doses of intravenous BPs with a frequent dosing schedule, than those with osteoporosis<sup>[9-11]</sup>. This justifies why oncologists are mainly concerned about these complications when prescribing BPs. By using these drugs with care and according to the prescription information, physicians can prevent the occurrence of these undesirable events. Atypical femoral fractures remain a probable complication of chronic oral BP treatment in osteoporotic women<sup>[12]</sup>. However, their risk among cancer patients receiving intravenous BPs at higher cumulative doses remains unclear. This is why oncologists are the least to worry about atypical femoral fractures. Few cases have been reported in patients with malignant skeletal lesions treated with intravenous zoledronate<sup>[13,14]</sup>. Oncologists should consider the possibility of atypical fractures in patients with malignant bone disease who are treated with high doses of intravenous BPs. However, the major therapeutic benefits resulting from the appropriate targeted use of BPs should not be lost as a result of the anxiety concerning rare adverse events such as atypical femoral fracture and osteonecrosis of the jaw. Severe musculoskeletal pain and ocular inflammatory reactions are rare complications, and thereafter may be under recognized by physicians<sup>[15,16]</sup>, which was exposed in our study. Based on current data, the association of BPs with esophageal cancer, hepatotoxicity and atrial fibrillation remains doubtful<sup>[1,3,17-20]</sup>. Fortunately, this was identified by the majority of our participants.

This study was subject to several limitations. First, it was limited to the population of Lebanese physicians affiliated with a major tertiary hospital in Beirut city, with a relatively high level of medical expertise. Any generalization to other populations especially to physicians participating in non-university centers, may be inappropriate. Second, the study was based on a self-reported questionnaire, inducing an inconsistency

between physicians' self-reported and actual attitude and knowledge. Since the use of data sources was not permitted, and since the physicians were assured that their response would be kept confidential, our data represent a picture of "real world" knowledge in this setting.

Despite these limitations, the results of the present study are sufficient to affirm the presence of a deficient knowledge regarding BPs-reported side effects among our physicians. However, the majority of respondents demonstrated interest in learning more about these drug-related undesirable events, and in keeping their knowledge updated. Professional training proposals are needed to increase the knowledge of our physicians and improve their practices. Throughout a range of educational strategies, practitioners who are experienced and very confident in this area may be ready to play a greater role. Moreover, pharmaceutical industries should reconsider the instructions they provide to physicians regarding the complications of medications they promote. They must actively collaborate with education providers and institutions in educational interventions. Subsequently, an evaluation of these interventions should be performed to guarantee a better approach and management of patients treated by a BP.

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## COMMENTS

### Background

Physicians' awareness of bisphosphonates (BPs)-related side effects can potentially lead to prevent the occurrence of more serious complications due to an earlier detection and management. It can also increase the safety of a therapy proven to be effective to numerous patients. At the same time, the major therapeutic benefits resulting from the appropriate targeted use of BPs are not lost as a result of the anxiety concerning rare adverse events such as atypical fracture and osteonecrosis of the jaw.

### Research frontiers

BPs-related complications have generated lately a great interest in the medical and research societies. They have triggered widespread debate and received extensive media coverage. The research hotspot is to evaluate the awareness and attitude of Lebanese physicians regarding these adverse events.



### Innovations and breakthroughs

Studies evaluating physicians' awareness concerning BPs-related undesirable events are limited. The present study revealed the presence of a deficient knowledge regarding these complications among the physicians, which can compromise the safety of their patients. Moreover, the number of medical sales representatives received by the physicians did not correlate with higher knowledge, which highlighted the lack of pharmaceutical companies in appropriately disseminating the complications of treatments they support.

### Applications

The data in this study underlined the need for professional training initiatives to enhance the physicians' knowledge and improve their practice. Moreover, pharmaceutical industries should reconsider the instructions they provide to physicians regarding the complications of medications they promote. They must actively collaborate with education providers and institutions in educational interventions. Subsequently, an evaluation of these interventions should be performed to guarantee a better approach and management of patients treated by a BP.

### Terminology

BPs are the best known of the antiresorptive therapies, which inhibit the bone resorption part of the continual cycle of bone turnover. Hence, they are a useful group of drugs for the treatment of metabolic and oncologic bone disorders including osteoporosis, malignancy-associated bone disease, and Paget's disease. BPs have a relatively good safety profile and are generally well tolerated. However, the benefits related to the use of these medications were associated with reports of multiple undesirable events, some of which may be serious.

### Peer-review

The data is interesting and the study is clear and well written.

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