http://dx.doi.org/10.2106/JBJS.K.01181

TABLE E-1 Causality Assessment (Naranjo Criteria) of Published Case Reports of Atypical Femoral Fractures Associated with Bisphosphonate Use[24]*

Study	No.	Sex, Age Range	Fracture Type	Agent	Duration of BP Use *(yr)*	Biopsy Results	Comorbidities	Concomitant Medicines	Fracture-Healing	Naranjo ADR Probability Score[22]
Odvina (2005)[7]	5	Female, 49-76 yr	Femoral diaphysis, subtrochanteric bilateral fractures	ALN	3-8	Decreased bone formation rate, decreased osteoblasts, low bone resorption	Unclear	Prednisone 11 yr (n = 1), estrogen (n = 1)	3 mo-2 yr	4 (possible ADR)
Husada (2005)[119]	1	Female	Femoral diaphysis	ALN		None				4 (possible ADR)
Armamento-Villareal (2006)[95]	1	Male	Subtrochanteric fracture	ALN	5	SSBT	None	None	Delayed	7 (probable ADR)
Schneider (2006)[120]	1	Female	Femur diaphysis	ALN		None				
Lee (2007)[121]	1	Female	Femoral diaphysis	ALN		None				3 (possible ADR)
Cheung (2007)[25]	1	Female, 82 yr	Femoral diaphysis	ALN	10	SSBT	None	None		5 (probable ADR)
Goh (2007)[24]	9	Female, 44-71 yr	Femoral diaphysis	ALN	2.5-5	None				4 (possible ADR)
Demiralp (2007)[122]	1	Female, 65 yr	Femoral diaphysis bilateral	ALN	7	None	Empty sella syndrome	Hydrocortisone, thyroxine		4 (possible ADR)
Lee (2008)[123]	1	Female, 73 yr	Femoral diaphysis	ALN	1.5	None				3 (possible ADR)
Visekruna (2008)[96]	3	Female, 51-72 yr	Femoral metaphysis	ALN	5-10	Increased osteoclastic activity, decreased connectivity, decreased activation frequency	RA, Crohn disease	Prednisone, raloxifene, estrogen	Delayed to 12 months	5 (probable ADR)
Kwek (2008)[124]	17†	Female, 53-82 yr	Femoral diaphysis	ALN	2-7	None		Prednisone (n = 2)		5 (probable ADR)

Wernecke (2008)[125]	1	Female, 72 yr	Femoral diaphysis	ZOL-PAM	11	Hypocellular bone marrow, no evidence of MM, thin sclerotic trabeculae, absence of osteoclasts and osteoblasts	Multiple myeloma			5 (probable ADR)
Neviaser (2008)[26]	25‡	Mean, 74 ± 10 yr	Femoral diaphysis	ALN	Mean 6.2	None	Osteoporosis			5 (probable ADR)
Sayed-Noor (2008)[126]	1	Female, 72 yr	Subtrochanteric	ALN	7	None				2 (possible ADR)
Bush (2008)[127]	1	Male, 61 yr	Femoral diaphysis	ZOL	1.5	None	Prostate cancer	Chemotherapy, dexamethasone		3 (possible ADR)
Lenart (2008)[128]	15	Female	Femoral diaphysis	ALN	5.4 ± 2.7	None				3 (possible ADR)
Schilcher (2009)[29]	5	Female, >75 yrs	Femoral diaphysis		5.8 (range 3.5-8.5)	None				3 (possible ADR)
Grasko (2009)[129]	2	Median, 59 yr	Subtrochanteric (bilateral n = 1)	PAM, ZOL			Myeloma, ONJ	Chemotherapy, dexamethasone		3 (possible ADR)
Glennon (2009)[130]	6	Female, 60-87 yr	Subtrochanteric, diaphysis		1.5-15 for ALN, 3 for RIS	None				4 (probable ADR)
Sayed-Noor (2009)[131]	2	Female, 48 and 75 yr	Femoral diaphysis	ALN	10	None	Alcoholic liver disease			3 (possible ADR)
Goddard (2009)[132]	1	67 yr	Femoral diaphysis (bilateral)	ALN RIS	10	None				3 (possible ADR)
Capeci (2009)[133]	7	Female, 53-75 yr	Subtrochanteric and diaphysis (bilateral)	ALN	8.4	None				3 (possible ADR)
Lee (2009)[134]	1	Female, 82 yr	Femoral diaphysis	ALN	8	None				3 (possible ADR)
Leung (2009)[135]	6	Female, 63-78 yr	Femoral diaphysis	ALN	0.5-6	None				3 (possible ADR)

Schneider (2009)[136]	1	Male, 53 yr	Subtrochanteric	ALN	7	None				3 (possible ADR)
Somford (2009)[53]	1	Female	Bilateral femoral diaphysis	ALN	8	Decreased bone formation (iliac crest) and increased bone resorption (femur)	RA	Prednisone, infliximab, MTX, omeprazole	Delayed healing at 6 months	5 (probable ADR)
Ing-Lorenzini (2009)[94]	8	7 female	Femoral diaphysis	ALN (5), ALN/IBN (2), PAM (1)		Partial bone bridging in periosteum, chronic absence of fracture remodeling or healing within cortex	RA, COPD	Prednisone (4) PPI (4)	Delayed healing	5 (probable ADR)
Armamento-Villareal (2009)[137]	8	Female, mean 54 yr	Femoral diaphysis	ALN	4-10	SSBT (n = 5)	RA, alcohol abuse, DM II, asthma			7 (probable ADR)
Cermak (2010)[138]	4	Female	Subtrochanteric and femoral diaphysis	ALN	5.5-12	None	MM (1), breast cancer (1)			4 (possible ADR)
Bunning (2010)[139]	4	Female, 49-59 yr	Femoral diaphysis	ALN (2), PAM (1)	5-6	None	Myeloma, CAD, hypogonadism	Chemotherapy, dexamethasone (n = 1)	Delayed healing (n = 1)	4 (possible ADR)
Edwards (2010)[140]	1	Female, 60 yr	Femoral diaphysis (bilateral)	ALN	6, 8	None	Asthma	Prednisolone		
Isaacs (2010)[141]	41	Mean 57 ± 7 yr	Femoral insufficiency fractures		72.5-73.4	None				3 (possible ADR)
Girgis (2010)[142]	20	Mean 78 yr	Subtrochanteric, diaphysis	ALN (15), RIS (2)	5 for ALN, 3 for RIS	None				4 (probable ADR)
Odvina (2010)[143]	13		Subtrochanteric and femoral shaft	ALN (10), RIS (2)	2-11	SSBT (n = 5), low bone turnover (n = 1)	RA, PMR, MG	Prednisone (4), estrogen or TMX (n = 5)		4 (possible ADR)

Napoli (2010)[144]	1	Female, 56 yr	Femoral diaphysis	ZOL	10	None	MM, SCT, CKD	Prednisone 60 mg		3 (possible ADR)
Wang (2010)[145]	63	10 male and 53 female	Femoral			None				3 (possible ADR)
Girgis (2010)[146]	17		Femoral diaphysis	ALN		None				3 (possible ADR)
Dell (2010)[39]	10	Male and female, mean 72 ± 10 yr	Subtrochanteric and femoral	ALN	5.5	None				5 (probable ADR)
Koh (2010)[27]	33§	Female, mean 33 yr	Femoral diaphysis and metaphysis	ALN 32, ZOL 1	4.5	None			Delayed healing	5 (probable ADR)
Kim (2011)[31]	10	85% female, mean 79.9 ± 8 yr	Subtrochanteric and diaphyseal	ALN, RIS	HR > 2.0 if BP use > 5 yr	None		PPI, GCs, benzodiazepine		4 (possible ADR)
Giusti (2011)[147]	10		Subtrochanteric			None		GC		3 (possible ADR)
Puah (2011)[148]	1	Female	Subtrochanteric and shaft	ALN, IBN	2	None	Breast cancer, asthma, DM	Letrozole, prednisone	Developed 2 AFFs healed with BP discontinuation (5 yrs), resumed IBN for 7 months sustained 2 new AFFs	5 (probable ADR)
Gunawardena (2011)[149]	1	Female, 67 yr	Subtrochanteric bilateral	ALN	2	Normal	Pemphigus vulgaris (no secondary factors for bone loss), DXA T-score −2.0 (osteopenia)	Prednisone	After first fracture, ALN was not discontinued, 2 yrs later another subtrochanteric fracture was identified	5 (probable ADR)

http://dx.doi.org/10.2106/JBJS.K.01181

Gomberg (2011)[150]	1	Female	Bilateral diaphyseal	ALN	13	None	Low bone turnover markers		Vitamin-D deficiency treated with PTH(1-34) with fracture-healing	4 (possible ADR)
Koh (2011)[151]	48#	Female, mean 67 ± 10 yr	Lesions (fractures) were lateral and 10 cm from greater trochanter. Area of maximal stress	ALN, ZOL, RIS	4	None			Fractures occur in areas of maximal tensile stress	4 (possible ADR)
Falkenberg (2011)[152]	3	Female		ALN	5	None			Hip fractures have declined by 35%	4 (possible ADR)
Curtin (2011)[153]	3	Female		ALN	3	None	RA	Prednisone	Presented as peri-prosthetic pain	4 (possible ADR)
Mulgund (2011)[154]	10	Female		ALN	8	None	RA	Prednisone	2 bilateral fractures, remaining 8 had stress reaction in contralateral femur	4 (possible ADR)
Ishizuna (2011)[155]	1	Female	Subtrochanteric	ZOL	2	None	Breast cancer	Letrozole, exemestane	Vertebral metastases	4 (possible ADR)
Ahlman (2012)[156]	1	Female	Subtrochanteric	ALN	6	None				4 (possible ADR)

*BP = bisphosphonate, ADR = adverse drug reaction, ALN = alendronate, SSBT = severely suppressed bone turnover, DM = diabetes mellitus, CKD = chronic kidney disease, RA = rheumatoid arthritis, ZOL = zolendronate, PAM = pamidronate, MM = multiple myeloma, ONJ = osteonecrosis of the jaw, RIS = risedronate, CAD = coronary artery disease, MTX = methotrexate, IBN = ibandronate, COPD = chronic obstructive pulmonary disease, PPI = proton pump inhibitor, PMR = polymyalgia rheumatica, MG = myasthenia gravis, TMX = tamoxifen, SCT = stem cell transplant, HR = hazard ratio, GCs = glucocorticoids, AFF = atypical femoral fracture, DXA = dual x-ray absorptiometry, and PTH = parathyroid hormone. †Includes eight from Goh et al. ‡Includes ten from Lenart et al. §Includes the seventeen cases from Kwek et al. #Includes the thirty-three cases from Koh et al. (2010), which includes the seventeen cases from Kwek et al.

http://dx.doi.org/10.2106/JBJS.K.01181

TABLE E-2 Adverse Drug Event (ADE) Probability Scale*

To assess the adverse drug event, please answer the following questionnaire and give the pertinent score.

	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?				
2. Did the adverse event appear after the suspected drug was administered?				
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?				
4. Did the adverse reaction reappear when the drug was re-administered?				
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?				
6. Did the reaction reappear when the placebo was administered?				
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?				
8. Was the reaction more severe when the dose was increased?				
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?				
10. Was the adverse event confirmed by objective evidence?				
			Total score	

*Reprinted by permission from Macmillan Publishers Ltd: Clin Pharmacol Ther. 1981 Aug;30(2):239-45. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Copyright 1981. http://www.nature.com/clpt/index.html.

References

119.
Husada G, Libberecht K, Peeters T, Populaire J. Bilateral mid-diaphyseal femoral stress fractures in the elderly. Eur J Trauma. 2005;31:68-71.

120.
Schneider JP. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics. 2006 Jan;61(1):31-3.

121.
Lee P, van der Wall H, Seibel MJ. Looking beyond low bone mineral density: multiple insufficiency fractures in a woman with post-menopausal osteoporosis on alendronate therapy. J Endocrinol Invest. 2007 Jul-Aug;30(7):590-7.

122.
Demiralp B, Ilgan S, Ozgur Karacalioglu A, Cicek EI, Yildrim D, Erler K. Bilateral femoral insuffiency fractures treated with inflatable intramedullary nails: a case report. Arch Orthop Trauma Surg. 2007 Sep;127(7):597-601. Epub 2007 Jun 16.

123.
Lee P, Seibel MJ. More on atypical fractures of the femoral diaphysis. N Engl J Med. 2008 Jul 17;359(3):317; author reply 317-8.

124.
Kwek EB, Goh SK, Koh JS, Png MA, Howe TS. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury. 2008 Feb;39(2):224-31. Epub 2008 Jan 28.

125.
Wernecke G, Namdari S, DiCarlo EF, Schneider R, Lane J. Case report of spontaneous, nonspinal fractures in a multiple myeloma patient on long-term pamidronate and zoledronic acid. HSS J. 2008;4(2):123-7. Epub 2008 Jul 16. Erratum in: HSS J. 2009 Sep;5(2):204. Namduri, Surena [corrected to Namdari, Surena].

126.
Sayed-Noor AS, Sjödén GO. Subtrochanteric displaced insufficiency fracture after long-term alendronate therapy—a case report. Acta Orthop. 2008 Aug;79(4):565-7.

127.
Bush L, Chew F. Subtrochanteric femoral insufficiency fracture following bisphosphonate therapy for osseous metastases. Radiol Case Rep. 2008;2:232.

128.
Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. N Engl J Med. 2008 Mar 20;358(12):1304-6.

129.
Grasko JM, Herrmann RP, Vasikaran SD. Recurrent low-energy femoral shaft fractures and osteonecrosis of the jaw in a case of multiple myeloma treated with bisphosphonates. J Oral Maxillofac Surg. 2009 Mar;67(3):645-9.

130.
Glennon DA. Subtrochanteric stress fractures in six patients on long term bisphosphonate therapy: a case series. Bone. 2009;44 (Suppl 1):S77-8.

131.
Sayed-Noor AS, Sjödén GO. Case reports: two femoral insufficiency fractures after long-term alendronate therapy. Clin Orthop Relat Res. 2009 Jul;467(7):1921-6. Epub 2009 Feb 6.

132.
Goddard MS, Reid KR, Johnston JC, Khanuja HS. Atraumatic bilateral femur fracture in long-term bisphosphonate use. Orthopedics. 2009 Aug;32(8). pii: orthosupersite.com/view.asp?rID=41933. doi: 10.3928/01477447-20090624-27.

133.
Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. J Bone Joint Surg Am. 2009 Nov;91(11):2556-61.

134.
Lee JK. Bilateral atypical femoral diaphyseal fractures in a patient treated with alendronate sodium. Int J Rheum Dis. 2009 Jul;12(2):149-54.

135.
Leung F, Lau TW, To M, Luk KD, Kung AW. Atypical femoral diaphyseal and subtrochanteric fractures and their association with bisphosphonates. BMJ Case Rep. 2009;2009. pii: bcr10.2008.1073. ePub 2009 Mar 5.

136.
Schneider JP. Bisphosphonates and low-impact femoral fractures: current evidence on alendronate-fracture risk. Geriatrics. 2009 Jan;64(1):18-23.

137.
Armamento-Villareal R, Napoli N, Diemer K, Watkins M, Civitelli R, Teitelbaum S, Novack D. Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. Calcif Tissue Int. 2009 Jul;85(1):37-44. Epub 2009 Jun 23.

138.
Cermak K, Shumelinsky F, Alexiou J, Gebhart MJ. Case reports: subtrochanteric femoral stress fractures after prolonged alendronate therapy. Clin Orthop Relat Res. 2010 Jul;468(7):1991-6. Epub 2009 Dec 18.

139.
Bunning RD, Rentfro RJ, Jelinek JS. Low-energy femoral fractures associated with long-term bisphosphonate use in a rehabilitation setting: a case series. PM R. 2010 Jan;2(1):76-80.

140.
Edwards MH, McCrae FC, Young-Min SA. Alendronate-related femoral diaphysis fracture--what should be done to predict and prevent subsequent fracture on the contralateral side? Osteoporos Int. 2010 Apr;21(4):701-3. Epub 2009 Jun 27.

141.
Isaacs JD, Shidiak L, Harris IA, Szomor ZL. Femoral insufficiency fractures associated with prolonged bisphosphonate therapy. Clin Orthop Relat Res. 2010 Dec;468(12):3384-92. Epub 2010 Aug 31.

142.
Girgis C, Sher D, Seibel MJ. Atypical femoral fractures are associated with bisphosphonate use. Presented at the Annual Meeting of the American Society for Bone and Mineral Research. 2010 Sep 16-20; Toronto, CA.

143.
Odvina CV, Levy S, Rao S, Zerwekh JE, Rao DS. Unusual mid-shaft fractures during long-term bisphosphonate therapy. Clin Endocrinol (Oxf). 2010 Feb;72(2):161-8. Epub 2009 Mar 19.

144.
Napoli N, Novack D, Armamento-Villareal R. Bisphosphonate-associated femoral fracture: implications for management in patients with malignancies. Osteoporos Int. 2010 Apr;21(4):705-8. Epub 2009 Aug 11.

145.
Wang JZ. Divergent trends between typical and atypical hip fractures and prevalence of bisphosphonate use in the US elderly, 1996-2007. Presented at the Annual Meeting of the American Society for Bone and Mineral Research; 2010 Sep 16-20; Toronto, CA.

146.
Girgis CM, Seibel MJ. Atypical femur fractures: a complication of prolonged bisphosphonate therapy? Med J Aust. 2010 Aug 16;193(4):196-8.

147.
Giusti A, Hamdy NA, Dekkers OM, Ramautar SR, Dijkstra S, Papapoulos SE. Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. Bone. 2011 May 1;48(5):966-71. Epub 2010 Dec 31.

148.
Puah KL, Tan MH. Bisphosphonate-associated atypical fracture of the femur: Spontaneous healing with drug holiday and re-appearance after resumed drug therapy with bilateral simultaneous displaced fractures—a case report. Acta Orthop. 2011 Jun;82(3):380-2. Epub 2011 May 11.

149.
Gunawardena I, Baxter M, Rasekh Y. Bisphosphonate-related subtrochanteric femoral fractures. Am J Geriatr Pharmacother. 2011 Jun;9(3):194-8.

150.
Gomberg SJ, Wustrack RL, Napoli N, Arnaud CD, Black DM. Teriparatide, vitamin D, and calcium healed bilateral subtrochanteric stress fractures in a postmenopausal woman with a 13-year history of continuous alendronate therapy. J Clin Endocrinol Metab. 2011 Jun;96(6):1627-32. Epub 2011 Mar 23.

151.
Koh JS, Goh SK, Png MA, Ng AC, Howe TS. Distribution of atypical fractures and cortical stress lesions in the femur: implications on pathophysiology. Singapore Med J. 2011 Feb;52(2):77-80.

152.
Falkenberg MP. Atypical femoral fractures: a complication of prolonged bisphosphonate therapy? Med J Aust. 2011 Jan 17;194(2):102-3; author reply 103.

153.
Curtin BM, Fehring TK. Bisphosphonate fractures as a cause of painful total hip arthroplasty. Orthopedics. 2011 Dec 6;34(12):e939-44. doi: 10.3928/01477447-20111021-36.

154.
Mulgund M, Beattie KA, Anaspure R, Matsos M, Patel A, Adachi JD. Atypical femoral fractures in patients taking longterm alendronate. J Rheumatol. 2011 Dec;38(12):2686-7.

155.
Ishizuna K, Ota D, Fukuuchi A, Teraoka M, Fujii A, Mori M, Nishi T. A case of femoral diaphyseal fracture after long-term treatment with zoledronic acid. Breast Cancer. 2011 Oct 19. [Epub ahead of print]

156.
Ahlman MA, Rissing MS, Gordon L. Evolution of bisphosphonate-related atypical fracture retrospectively observed with DXA scanning. J Bone Miner Res. 2012 Feb;27(2):496-8.

Appendix 1 Pharmacovigilance Analysis Tools

A principal objective of postmarketing surveillance with use of spontaneous, post-approval adverse drug event reports is to provide a "safety net" that will catch rare and unexpected adverse drug events that may have been missed during the clinical development program. The size and scope of spontaneous reporting systems are desirable properties from the perspective of sensitivity. The downside of such large databases is that they are uncontrolled and contain millions of drug-event combinations, that unassisted human screening of the database becomes problematic.

Adverse drug effects are manifold and heterogeneous. Many situations may hamper the detection of early warning signs (signal detection) of adverse events. Current pharmacovigilance is based predominantly on spontaneous reporting and is mainly helpful in detecting type-B effects (rare, often allergic or idiosyncratic reactions that are usually unrelated to dosage, serious, unexpected, and unpredictable) and unusual type-A effects (those effects that are related to the pharmacologic effects of the drug and are dosage-related).

Those performing pharmacovigilance sometimes perform quantitative analyses of data from spontaneous reporting systems as a supplement to qualitative examination of individual case reports. For example, for a given drug, one can calculate a disproportionality measure: the frequency of a specific event relative to the frequency of all events for that drug and divide this value by the corresponding value for other drugs. If the frequencies are expressed as proportions, then this ratio is the proportional reporting ratio (PRR) if they are expressed as odds, then this ratio is the reporting odds ratio (ROR). It is widely recognized that, because of inconsistencies in adverse event reporting, disproportionality analyses are modest surrogates for controlled epidemiologic studies.

Assessment of Data Mining Methods

Proportional Reporting Ratio (PRR)[19]

The PRR approach was first described by Finney and further developed recently by Evans, Waller, and Davis. To describe the method, suppose that we are interested in developing a measure for the strength of the association between drug i and COSTART j. Let "a" denote n_{ij}, the number of reports for a given drug-COSTART combination, "b" denote the number of times that any other COSTART (coding symbol for a thesaurus of adverse reaction terms) is reported for drug i, "c" denote the number of times that $COSTART_{ij}$ is reported for all other drugs, and "d" denote the number of reports for any other drug-COSTART combination.

These values may be depicted in a contingency table:

	COSTART j	All Other COSTARTs
Vaccine i	a	b
All other vaccines	c	d

In this contingency table notation, the PRR signal for vaccine i and COSTART J is

$$PRRij = \frac{a/(a+b)}{c/(c+d)}$$

This fraction is the proportion of COSTART j reports for drug i divided by the proportion of COSTART j reports for all other drugs. A large PRR for a specific drug-COSTART pair indicates that the COSTART has been disproportionately reported for that drug compared with all of the other drugs in the FAERS database.

Empirical Bayes Geometric Mean (EBGM)

The empirical Bayes model assumes that the counts n_{ij} in each cell are random variables from Poisson distributions with unknown means n_{ij} where the n_{ij} are themselves random variables with a common distribution. This common distribution is usually taken to be a mixture of two gamma distributions, one centered at the null value corresponding to a coincidental adverse event and the other more dispersed and centered at a value corresponding to a true causal relationship between the drug and the adverse event. There are many alternative models that lead to similar results; the preceding one is a simple mixture model with two gamma components, one of which is highly dispersed and the other of which is concentrated near a value of 1. Simple alternative models assume a mixture of different distributions and use the observed counts n_{ij} to estimate the parameters, but one could also consider nonparametric techniques that allow the data to determine the shapes of the mixture components. This kind of framework, called a hierarchical model, is widely used in Bayesian practice. It allows one to exploit a simple Bayesian computational structure for inference while avoiding the need to choose a subjective prior for the unknown distribution of m_{ij}. Formally, the measure corresponding to drug i and COSTAR j is given by $\log_2 EBGM_{ij} = E[\log_2(\mu_{ij}/Eij)l\ \eta_{ij}]$, where the right-hand side of the equation denotes the expectation operator and E_{ij} is given by $(a + b)(a + c)/(a + b + c + d)$.

In the notation in the PRR section, and for the drug-COSTART pair of interest, i and j correspond to cell E_{11}. This expression calculates the expected value of the base-2 logarithm of the ratio between the estimated reporting ratio and the ratio under the assumption of no causal relationship, given the observed count of the spontaneous reports for that drug and that COSTART. A large value suggests that drug i might provoke the adverse event described by COSTART j. The practical effect of this hierarchical model framework is that it "shrinks" the estimates of the reporting ratio parameters in the Poisson distributions toward each other, thereby reducing the effect of sampling variation in the data. The shrinkage is greatest when E_{ij} is small and/or n_{ij}/E_{ij} is small, which typically occurs when a or b is small. Another advantage is that the model preserves the interpretability of the parameters and their estimates. The main drawback of this approach is that it is computationally intensive, taking several minutes to run and requiring investment in well-tested, special-purpose code. The computational burden depends on the number of rows and columns in the matrix, not on the number of report, so from the standpoint of scaling concerns, this performance is adequate for all foreseeable FAERS applications[23].

Naranjo Scale (Table E-2)

The Naranjo scale provides a weighted score (reflecting the probability that an adverse drug reaction exists) for each of the components that must be considered in establishing a causal relationship between a drug and an adverse drug effect (temporal sequence). The Naranjo scale has high inter-rater reliability (83% to 92% agreement, κ = 0.69 to 0.89, r = 0.91 to 0.95, estimated r = 0.92) and high intra-rater reliability (80% to 97% agreement, κ = 0.64 to 0.95, r = 0.91 to 0.98). This adverse drug reaction probability scale has contextual, content, and concurrent validity[22]. This adverse drug reaction probability scale is used in pharmacovigilance studies. Possible scores range from −4 to 13, with ≤0 considered "doubtful," 1 to 4 considered "possible," 5 to 8 considered "probable," and 9 or greater considered "definite."