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PHARMACOVIGILANCE SIGNALS DETECTION: BENZODIAZEPINES AND SKIN AND SUBCUTANEOUS TISSUE DISORDERS

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ABSTRACT: Pharmacovigilance compiles and analyzes spontaneous adverse drug reactions (ADRs) notifications reports on pharmacovigilance databases. Benzodiazepines have been related to skin and subcutaneous tissue disorders ADRs (SSTD-ADRs); tetrazepam was withdrawn in 2013 because of these ADRs. We intended to locate possible associations between cutaneous ADRs and benzodiazepines marketed in USA; for that, we calculated Data mining algorithms (PRR, ROR, IC and EBGM) on benzodiazepines spontaneous notifications reported to the American pharmacovigilance database. ROR yielded signals for eight drugs; PRR and IC for four, and EBGM only one. Clobazam originated a signal for "Stevens-Johnson syndrome" and "Blister"; midazolam for "Toxic epidermal necrolysis", "DRESS syndrome" and "Erythema"; quazepam for "Erythema multiform" and "Drug eruption"; and tetrazepam "Dermatitis bullous", "Toxic skin eruption", "Rash maculopapular" and "Rash erythematous". Tetrazepam exhibited signals by all Data mining algorithms calculated. Quazepam, clobazam and midazolam, by 3 algorithms (PRR, ROR and IC). Our results provide new data that come to increase the limited comparative data published on the sensibility of algorithms. However, larger studies providing new clinical evaluation on these associations will be required.

INTRODUCTION: Benzodiazepines (BZD), approved in the 1960s by the Food & Drug Administration (FDA), exert anxiolytic, sedative-hypnotic effects useful for sleep induction. They are also effective as adjuncts to anesthesia relaxation and amnesia, seizure prevention and as muscle relaxants [1, 2].

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These effects are associated to their capacity of selectively activate gamma-aminobutyric A (GABA-A) receptors. Today the benzodiazepine family compiles more than twenty compounds, and because of their potential for abuse, addiction or recreation, they are catalogued by the drug enforcement agency as schedule IV controlled substances [3].

Multiple evidence supports the fact that safety issues associated with a drug are frequently lacking during the premarketing clinical trials [4]. For instance, BZD are associated to adverse drug reactions (ADRs), which can be classified as:

frequent (sedation, drowsiness and ataxia), rare (dizziness, sedation, headache, depression, disorientation, dysphasia, tremor, changes in libido, urinary disorders, diarrhea or constipation) and "very rare" (hepatitis, jaundice, dermatitis, urticaria, pruritus, bleeding disorders, impaired vision and hearing, and skin and subcutaneous tissue disorders).

Pharmacovigilance focuses on the identification, quantification, evaluation and prevention of risks of using drugs already on the market. To achieve this, reports of suspected ADRs in databases operated by spontaneous ADRs reporting are systematically collected and analyzed. For instance, the United States FDA collects ADRs reported by the FDA Adverse Events Reporting System (FAERS), which has a public database accessible through the online interface Drug cite® [5].

Pharmacovigilance uses disproportionality analysis of spontaneous reporting databases by means of algorithms to assess the significant association of ADRs with a drug. So, whether an ADRs is detected as a signal or not depends on the algorithm used for signal detection. Among these algorithms, we can find the non-Bayesian (proportional reporting ratio (PRR) [6] and reporting odds ratio (ROR) [7]) and the Bayesian (Information Component (IC) [8], and Empirical Bayesian Geometric Mean (EBGM) [9]). Interestingly, these pharmacovigilance database provide early warnings of hazards that were missed before marketing a drug mainly because of the limitations of clinical trials, such as sample size, duration and application to ordinary practice [4].

Regarding BZDs, in 2007 the FDA issued a warning on estazolam and flurazepam for the risk of severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving [10, 11]. And in 2012, the EMEA concluded that there was no support for contraindicating prazepam in glaucoma [12].

In the present study, skin and subcutaneous tissue disorders-ADRs (SSTD-ADRs) related to benzodiazepine treatment and reported to FAERS, were analyzed. Our statistical analysis revealed that clobazam, midazolam, quazepam and tetrazepam generated signals by more than two algorithmic methods. In addition, we report the higher frequency of SSTD-ADRs such as skin and subcutaneous tissue disorders ADRs as "Bullosus conditons" and "Dermatitis". Our data corroborate that tetrazepam holds the highest scores in signal detection algorithms. Additionally, we found that other benzodiazepines (clobazam, midazolam, quazepam) present also algorithmic signals.

MATERIALS AND METHODS: Input data for this study were taken from the publicly accessible online in the FAERS database interface, Drug cite® [5]. The data covered the period comprised from the first quarter of 2004 (2004Q1) through the third quarter of 2012 (2012Q3). Benzodiazepines available in the USA where extracted from Daily Med®, following the recommendation and permission of the Center for Drug Evaluation and Research (CDER) of the FDA. Fifteen drugs belonging to the benzodiazepine group were analyzed. All drug names (generic and brand names) were collected, and were searched in Drugcite® on June 7th, 2014. Terms subjected to search were (literally): "alprazolam", "Xanax", "chlordiazepoxide", "Librax", "Librium", "clobazam", "clobazam (clobazam)", "Onfi", "clonazepam", "Klonopin", "clorazepate", "Tranxene", "diazepam", "diazepam Tab", "Diastat", "Valium", "estazolam", "flurazepam", "lorazepam", "lorazepam intensol", "Ativan", "midazolam", "oxazepam", "Serax", "quazepam", "Doral", "temazepam", "Restoril", "tetrazepam", "tetrazepam (tetrazepam)", "Myolastan (tetrazepam)", "Myolastan", "triazolam" and "Halcion".

Duplicated reports were identified and eliminated. Because FAERS allows registering arbitrary drug names, and trade names and abbreviations as well, all drug names were unified into generic names by means of a text-mining approach. Terms excluded because of duplicated data were: "chlordiazepoxide HCl", "clorazepate dipotassium", "flurazepam hydrochloride", "flurazepam HCl", "Dalmane", "midazolam hydrochloride", and "midazolam HCl".

We grouped ADRs collected in this database into various SOC MedDRA levels [13], and we chose the

High-Level Group Terms (HLGT) reported in more than 1% of the total drug notifications. We analyzed and performed data mining algorithms for ADRs grouped in "Skin and subcutaneous tissue disorders" (SOC MedDRA level), which comprises various HLGT: "Angioedema and urticaria", "Cornification and dystrophic skin disorders", "Cutaneous neoplasms benign", "Epidermal and dermal conditions", "Pigmentation disorders", "Skin and subcutaneous tissue disorders", "Skin and subcutaneous tissue infections and infestations", "Skin appendage conditions", "Skin neoplasms malignant and unspecified" and "Skin vascular abnormalities".

Data mining algorithms have been developed to identify drug-associated adverse events reported more frequently than expected (signals) [4, 14-17]. Examples of widely used algorithms are: PRR [6], ROR [7], IC [8] and EBGM [9].

All statistical algorithms are calculated from various two-by-two contingency or frequency table of counts, which involve the presence or absence of a particular drug and a particular event occurring in case reports. Based on these 2x2 tables and comparing the data with the background frequency of associations of drugs and suspected ADRs in FAERS database, following precision algorithms have been calculated: PRR – 1.96 SE (standard error) with Chi square (with Yates correction) and P value (Poisson probability) associated, ROR – 1.96 SE, IC – 2SD (standard deviation) and EBGM – 2SD. Adverse events are classified as signals depending on the extent to which drugs are associated to ADRs as assessed by the various statistical tests.

A value of 1 for any of these assessments that there is no association between the consumption of a drug and an event in the database [18]. A value of 6, for example, means that there are six times as many reports of this drug-event combination in the database than would be expected if drugs and events were reported independently of each other. Bayesian approximations (IC and EBGM) results in more statistically stable values, and incorporate information both about observed counts and expected co-occurrences together with their variability.

A signal is considered detected when using the PRR, the count of co-occurrences is ≥ 3 and the PRR ≥ 2 with an associated Chi2value ≥ 4 [6]. In the case of ROR, a signal occurs if the lower bound of the 95% two-sided confidence interval exceeds 1 [7]. Using IC, a signal is detected when the lower bound of the 95% two-sided confidence interval of the IC exceeds 0 [8]; a positive association is defined as IC – 2SD > 0 and negative as IC – 2SD < 0. Finally, using EBGM, a signal is detected when a lower one-sided 95% confidence limit of EBGM is greater than or equal to the threshold value 2 [9].

All these indices have been calculated according to processes described in the literature [7, 9, 14, 19]. All calculations were obtained using Excel® 2011 14.4.1.

RESULTS AND DISCUSSION: A total of 129,783 ADRs reported for any of 15 benzodiazepines presently studied were included in the FAERS database from 2004 to 2012Q3. These represent a 3.14% of the 4,137,812 drug reports notified to FAERS for the same period of time. The four benzodiazepines with highest total ADRs notified were: alprazolam 37,685 (29.04%), diazepam 24,127 (18.59%), clonazepam 21,383 (16.48%) and lorazepam 18,755 (14.45%) **Fig. 1**.

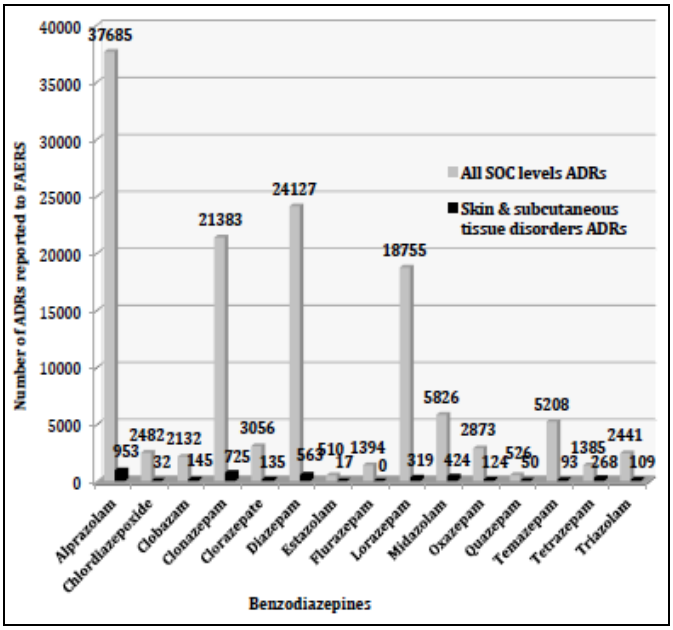

FIG. 1: SPONTANEOUS ADRs NOTIFIED TO FAERS (2004-2012Q3) FOR BENZODIAZEPINES AVAILABLE IN THE USA, AND CO-OCCURRENCES BETWEEN THEM AND "SKIN AND SUBCUTANEOUS TISSUE DISORDERS" SOC MedDRA LEVEL

Of these, 3,957 ADRs were "Skin and subcutaneous tissue disorders" ADRs (SSTD-ADRs). They represent 3.05% of the ADRs reported for the 15 benzodiazepines subjected to study. Co-occurrences (pair made up by a drug and an adverse event) took place with the following BZDs: alprazolam, 953 co-occurrences (24.08%), clonazepam 725 co-occurrences (18.32%), diazepam 563 co-occurrences (14.23%), midazolam 424 co-occurrences (10.72%), lorazepam 319 co-occurrences (8.06%) and with tetrazepam 268 co-occurrences (6.77%). We detected no SSTD-ADRs reports due to flurazepam **Table 1.**

TABLE 1: SIGNAL DETECTION FOR BENZODIAZEPINES-ASSOCIATED SSTD-ADRs REPORTED TO FAERS (2004Q1-2012Q3)

Drug	N (%)	PRR (95% CI)	Chi^2 test	p	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Alprazolam	953 (24.08)	0.78 (0.72, 0.83)	48.44	< 0.0001	0.77 (0.71, 0.83)	-0.27 (-0.49, -0.05)	0.83 (0.72)
Chlordiazepoxide	32 (0.81)	0.42 (0.30, 0.59)	25.90	< 0.0001	0.41 (0.30, 0.58)	-1.24 (-2.41, -0.07)	0.42 (0.19)
Clobazam	145 (3.66)	2.28 (1.94, 2.67)*	103.24*	< 0.0001	2.37 (2.00, 2.82)*	1.16 (0.57, 1.74)*	2.23 (1.49)
Clonazepam	725 (18.32)	1.14 (1.05, 1.23)	9.97	0.0016	1.14 (1.05, 1.24)*	0.15 (-0.10, 0.41)	1.11 (0.93)
Clorazepate	135 (3.41)	1.46 (1.24, 1.73)	19.36	< 0.0001	1.47 (1.25, 1.77)*	0.54 (-0.06, 1.13)	1.45 (0.96)
Diazepam	563 (14.23)	0.73 (0.67, 0.80)	51.02	< 0.0001	0.72 (0.66, 0.79)	-0.39 (-0.67, -0.10)	0.77 (0.63)
Estazolam	17 (0.43)	1.09 (0.69, 1.75)	0.14	0.7082	1.10 (0.68, 1.78)	0.13 (-1.49, 1.75)	1.09 (0.36)
Flurazepam	0 (0)	-	44.32	< 0.0001	-	-	-
Lorazepam	319 (8.06)	0.52 (0.46, 0.58)	134.25	< 0.0001	0.51 (0.46, 0.57)	-0.84 (-1.22, -0.47)	0.56 (0.43)
Midazolam	424 (10.72)	2.55 (2.32, 2.82)*	367.52*	< 0.0001	2.68 (2.41, 2.97)*	1.26 (0.91, 1.60)*	2.39 (1.88)
Oxazepam	124 (3.13)	1.43 (1.20, 1.70)	15.52	< 0.0001	1.45 (1.21, 1.74)*	-0.50 (-0.12, 1.12)	1.42 (0.92)
Quazepam	50 (1.26)	3.15 (2.41, 4.10)*	74.49*	< 0.0001	3.37 (2.51, 4.52)*	1.64 (0.63, 2.66)*	3.12 (1.55)
Temazepam	93 (2.35)	0.58 (0.47, 0.71)	28.85	< 0.0001	0.57 (0.46, 0.70)	-0.77 (-1.47, -0.08)	0.59 (0.36)
Tetrazepam	268 (6.77)	6.74 (6.02, 7.54)*	1258.49 *	< 0.0001	8.11 (7.07, 9.30)*	2.67 (2.19, 3.14)*	6.35 (4.56)*
Triazolam	109 (2.76)	1.48 (1.23, 1.78)	16.89	< 0.0001	1.50 (1.23, 1.82)*	0.55 (-0.11, 1.21)	1.47 (0.93)
Total	3957 (100)						

N. Number of co-occurrences. PRR: Proportional Reporting Ratio, ROR: Reporting Odds Ratio, IC: information component, EBGM: Empirical Bayesian Geometric Mean.CI: confidence interval (two-sided for ROR and IC, one-sided for EBGM). Chi^2: Chi square test with Yate´s correction, and one degree of freedom. P value (two tailed).*Signal detected, see "methods" for the criteria of detection

By using a PRR algorithm and Chi^2 test (with Yate´s correction and P value associated), a potential signal in pharmacovigilance is detected for four drugs: clobazam, midazolam, quazepam and tetrazepam (**Table 1**). On application of a ROR algorithm (with CI95% two-sided), a potential signal was found for eight drugs (clobazam, clonazepam, clorazepate, midazolam, oxazepam, quazepam, tetrazepam and triazolam). The application of an IC bayesian method (CI95% two-sided) detects a signal for clobazam, midazolam, quazepam and tetrazepam. The EBGM method (CI95% one-sided), only detected a signal for tetrazepam, because its lower bound of 95% CI is ≥ 2 (**Table 1**).

In order to gain insight on the signals above, we then analyzed only benzodiazepines with more than 2 potential signals these were: clobazam, midazolam, quazepam and tetrazepam.

In this case we found 887 SSTD-ADRs due to these BZD (**Table 1**). **Table 2** summarizes cutaneous ADRs found for these four benzodiazepines, grouped into High-Level Terms (HLT) MedDRA levels. HTL due to these 4 BZD, notified in a percentage higher than 10%, are displayed in **Tables 3-6**. Specifically these were: "Bullous conditions" HLT cases (239, 26.94%): Stevens-Johnson syndrome (92), Toxic epidermicnecrolysis (68), Blister (36), Erythema multiforme (25), Dermatitis bullous (12), Pemphigoid (3), Pemphigus (2) and Acquired epidermolysis bullosa (1). For "Dermatitis ascribed to specific agents" HLT (172 cases, 19.39%): DRESS syndrome (100), Drug eruption (24), Toxic skin eruption (48). For "Rashes, eruptions and exanthems" HLT (141, 15.90%): Rash (49), Rash maculo-papular (49), Rash generalized (20), Rash morbilliform (7), Rash macular (6), Systemic lupus erythematosus rash (6), Rash scarlatiniform (2), Mucocutaneous rash (1) and Rash vesicular (1). And finally, for "Erythemas" HLT MedDRA level (114, 12.85%): Erythema (72), Rash erythematous (23) and Generalised erythema (19).

TABLE 2: SSTD-ADRs IN BZD WHICH PRODUCE A PHARMACOVIGILANCE SIGNAL BY MORE THAN 2 ALGORITHM METHODS. (ADRs ARE GROUPED IN HIGH-LEVEL TERMS, HLT MEDDRA LEVELS)

	Clobazam	Midazolam	Quazepam	Tetrazepam	Total n (%)
Bullous conditions	79	95	19	46	239 (26.94%)
Dermatitis ascribed to specific agent	12	92	13	55	172 (19.39%)
Rashes, eruptions and exanthems	17	66	6	52	141 (15.90%)
Erythemas	13	79	1	21	114 (12.85%)
Pruritus	4	24	3	19	50 (5.64%)
Dermal and epidermal conditions	4	33	1	3	41 (4.62%)
Exfoliative conditions	2	7	0	19	28 (3.16%)
Dermatitis and eczema	0	2	4	19	25 (2.82%)
Papulosquamous conditions	0	5	3	9	17 (1.92%)
Pustularconditions	0	8	0	4	12 (1.35%)
Angioedemas	7	5	0	0	12 (1.35%)
Purpura and related conditions	0	0	0	9	9 (1.01%)
Connective tissue disorders	0	2	0	5	7 (0.79%)
Apocrine and eccrine gland disorders	6	0	0	0	6 (0.68%)
Photosensitivity and photodermatosis conditions	0	3	0	1	4 (0.45%)
Skin injuries and mechanical dermatoses	1	3	0	0	4 (0.45%)
Psoriatic conditions	0	0	0	4	4 (0.45%)
Urticarias	0	0	0	1	1 (0.11%)
Skin vasculitides	0	0	0	1	1 (0.11%)
Total	145	424	50	268	887

Tables 3-6 show the results obtained with pharmacovigilance algorithmic calculations for the most prevalent ADRs (more than 5%) notified in the most frequent HTL MedDRA levels (4 groups disaggregated above), for the four BZD which originated more than 2 signals by pharmacovigilance algorithms. **Table 3** displays data on "Bullous conditions" for the "Stevens-Johnson Syndrome" cases notified. A potential signal was detected only for clobazam with PRR and ROR. For "Toxic epidermal necrolysis", only midazolam generated a potential signal by means of ROR calculation. Clobazam generated a signal with PRR, ROR and IC, for "Blister". Quazepam generated a pharmacovigilance signal with PRR, ROR and IC, for "Erythema multiforme". And only tetrazepam originated a signal for "Dermatitis bullous", using PRR and ROR algorithms.

TABLE 3: SIGNAL DETECTION FOR BENZODIAZEPINES-ASSOCIATED BULLOUS CONDITIONS (239/887, 26.94%) ADRs IN SSTD-ADRs

Drug	n/N	PRR (95% CI)	Chi^2 test	P value	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Stevens-Johnson Syndrome (92/239, 38.49%)							
Clobazam	35/92	3.14 (2.12, 4.66)*	33.59*	< 0.0001	3.82 (2.40, 6.10)*	1.22 (-0.09, 2.52)	2.33 (0.94)
Midazolam	38/92	0.77 (0.51, 1.16)	1.46	0.2272	0.75 (0.48, 1.16)	-0.21 (-1.32, 0.90)	0.86 (0.40)

Quazepam	6/92	1.17 (0.53, 2.56)	0.02	0.8808	1.19 (0.49, 2.88)	0.21 (-2.59, 3.01)	1.16 (0.17)
Tetrazepam	13/92	0.38 (0.21, 0.68)	11.76	0.0006	0.35 (0.19, 0.64)	-1.10 (-2.93, 0.74)	0.47 (0.13)
Toxic Epidermal Necrolysis (68/239, 28.45%)							
Clobazam	14/68	1.33 (0.75, 2.34)	0.66	0.4159	1.36 (0.74, 2.52)	0.33 (-1.52, 2.18)	1.26 (0.35)
Midazolam	43/68	1.88 (1.15, 3.07)	6.38	0.0116	1.98 (1.19, 3.30)*	0.40 (-0.65, 1.45)	1.32 (0.64)
Quazepam	0/68	-	3.33	0.0682	-	-	-
Tetrazepam	11/68	0.45 (0.24, 0.85)	6.18	0.0129	0.42 (0.22, 0.82)	-0.90 (-2.87, 1.07)	0.54 (0.14)
Blister (36/239, 15.06%)							
Clobazam	29/36	21.2 (9.41, 47.77)*	113.50*	< 0.0001	26.25 (21.24, 61.31)*	2.30 (0.90, 3.70)*	4.93 (1.87)
Midazolam	5/36	0.18 (0.07, 0.45)	15.91	< 0.0001	0.17 (0.06, 0.43)	-1.78 (-4.51, 0.95)	0.29 (0.04)
Quazepam	2/36	0.99 (0.24, 3.99)	0	0.9827	0.98 (0.23, 4.22)	-0.02 (-4.06, 4.02)	0.99 (0.06)
Tetrazepam	0/36	-	14.79	0.0001	-	-	-
Erythema multiforme (25/239, 10.46%)							
Clobazam	1/25	0.21 (0.03, 1.57)	2.014	0.1558	0.21 (0.03, 1.55)	-2.03 (-6.78, 2.72)	0.24 (0.01)
Midazolam	7/25	0.43 (0.18, 1.02)	3.267	0.0707	0.42 (0.17, 1.00)	-0.77 (-3.14, 1.60)	0.59 (0.11)
Quazepam	11/25	13.15 (6.26, 27.64)*	63.948*	< 0.0001	16.58 (7.07, 38.89)*	2.96 (0.66, 5.27)*	7.81 (1.58)
Tetrazepam	6/25	0.73 (0.29, 1.82)	0.217	0.6416	0.72 (0.29, 1.83)	-0.33 (-2.89, 2.22)	0.79 (0.14)
Dermatitis bullous (12/239, 5.02%)							
Clobazam	0/12	-	1.320	0.2506	-	-	-
Midazolam	1/12	0.10 (0.01, 0.77)	6.076	0.0137	0.10 (0.01, 0.76)	-2.52 (-7.23, 2.19)	0.17 (0.01)
Quazepam	0/12	-	0.049	0.824	-	-	-
Tetrazepam	11/12	25.41 (3.29, 196.41)*	18.933*	< 0.0001	26.45 (3.40, 205.95)*	1.60 (-0.38, 3.58)	3.03 (0.77)

Table 4 displays data on "Dermatitis ascribed to specific agent". In this case, midazolam was the only BZD which originated a signal for "DRESS syndrome", by means of PRR and ROR algorithms. For "Toxic skin eruption", only tetrazepam caused a signal, using PRR and ROR. And quazepam generated a signal for "Drug eruption", by applying PRR and ROR.

TABLE 4: SIGNAL DETECTION FOR BENZODIAZEPINES-ASSOCIATED DERMATITIS ASCRIBED TO SPECIFIC AGENT (172/887, 19.39%) ADRs IN SSTD-ADRs

Drug	n/N	PRR (95% CI)	Chi^2 test	P value	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Drug rash with eosinophylia and systemic symptoms (DRESS) (100/172, 58.14%)							
Clobazam	4/100	0.21 (0.08, 0.57)	11.57	0.0007	0.19 (0.07, 0.53)	-2.03 (-5.08, 1.02)	0.25 (0.03)
Midazolam	69/100	2.43 (1.59, 3.71)*	19.35*	0.0001	2.71 (1.73, 4.23)*	0.53 (-0.32, 1.38)	1.44 (0.80)
Quazepam	6/100	1.07 (0.49, 2.33)	0.028	0.8673	1.08 (0.45, 2.60)	0.09 (-2.71, 2.89)	1.06 (0.15)
Tetrazepam	21/100	0.61 (0.38, 0.99)	4.059	0.0439	0.58 (0.35, 0.96)	-0.53 (-2.01, 0.96)	0.70 (0.25)
Toxic skin eruption (48/172, 27.91%)							
Clobazam	1/48	0.11 (0.02, 0.79)	6.488	0.0109	0.10 (0.01, 0.75)	-2.97 (-7.72, 1.78)	0.13 (0.01)
Midazolam	15/48	0.50	4.892	0.027	0.48	-0.61	0.65

		(0.27, 0.91)			(0.26, 0.89)	(-2.30, 1.08)	(0.20)
Quazepam	0/48	-	2.015	0.1558	-	-	-
Tetrazepam	32/48	4.62 (2.55, 8.36)*	30.178*	< 0.0001	5.11 (2.75, 9.49)*	1.14 (-0.11, 2.39)	2.21 (0.93)
Drug eruption (24/172, 13.95%)							
Clobazam	7/24	2.11 (0.89, 5.02)	2.079	0.1493	2.16 (0.88, 5.31)	0.84 (-1.62, 3.29)	1.78 (0.33)
Midazolam	8/24	0.55 (0.23, 1.28)	1.516	0.2182	0.54 (0.23, 1.27)	-0.52 (-2.76, 1.72)	0.70 (0.15)
Quazepam	7/24	6.89 (2.98, 15.94)*	21.33*	< 0.0001	7.85 (3.09, 19.94)*	2.37 (-0.30, 5.04)	5.17 (0.81)
Tetrazepam	2/24	0.21 (0.05, 0.89)	4.585	0.0322	0.20 (0.05, 0.87)	-1.86 (-5.72, 2.01)	0.28 (0.02)

Table 5 shows data on "Rashes, eruptions and exanthems". All four BZD generated a potential signal for "Rash" and "Rash generalized". For "Rash maculo-papular" a signal was detected for tetrazepam by using PRR and ROR algorithms.

TABLE 5: SIGNAL DETECTION FOR BENZODIAZEPINES-ASSOCIATED RASH, ERUPTIONS AND EXANTHEMAS (141/887, 15.90%) SSTD-ADRs

Drug	n/N	PRR (95% CI)	Chi^2 test	P value	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Rash (49/141, 34.75%)							
Clobazam	6/49	0.71 (0.31, 1.66)	0.360	0.5484	0.70 (0.29, 1.68)	-0.42 (-3.02, 2.19)	0.75 (0.12)
Midazolam	27/49	1.34 (0.76, 2.35)	0.820	0.3652	1.36 (0.76, 2.43)	0.21 (-1.09, 1.50)	1.15 (0.47)
Quazepam	5/49	1.90 (0.79, 4.61)	1.227	0.2681	2.00 (0.76, 5.30)	0.86 (-2.13, 3.85)	1.81 (0.23)
Tetrazepam	11/49	0.67 (0.34, 1.30)	1.119	0.2901	0.65 (0.33, 1.30)	-0.43 (-2.40, 1.55)	0.74 (0.19)
Rash maculo-papular (49/141, 34.75%)							
Clobazam	8/49	1.00 (0.48, 2.10)	0.000	0.9968	1.00 (0.46, 2.18)	-0.00 (-2.32, 2.32)	1.00 (0.20)
Midazolam	16/49	0.53 (0.29, 0.96)	4.149	0.0417	0.51 (0.28, 0.94)	-0.55 (-2.19, 1.09)	0.68 (0.22)
Quazepam	0/49	-	2.078	0.1494	-	-	-
Tetrazepam	25/49	2.41 (1.38, 4.18)*	9.630*	0.0019	2.55 (1.43, 4.55)*	0.76 (-0.63, 2.14)	1.69 (0.65)
Rash generalised (20/141, 14.18%)							
Clobazam	2/20	0.57 (0.13, 2.43)	0.221	0.6379	0.56 (0.13, 2.45)	-0.71 (-4.61, 3.19)	0.61 (0.04)
Midazolam	13/20	2.03 (0.81, 5.08)	1.772	0.1832	2.06 (0.81, 5.21)	0.44 (-1.36, 2.25)	1.36 (0.39)
Quazepam	0/20	-	0.379	0.5384	-	-	-
Tetrazepam	5/20	0.77 (0.28, 2.11)	0.071	0.7892	0.77 (0.28, 2.13)	-0.27 (-3.03, 2.48)	0.83 (0.12)

Table 6 exhibits data on "Erythemas". Only midazolam generated a signal for "Erythema", by PRR and ROR. For "Rash erythematous", only tetrazepam generated a potential signal, by PRR and ROR. Every BZD analyzed detected a signal for "Generalized erythema".

TABLE 6: SIGNAL DETECTION FOR BENZODIAZEPINES-ASSOCIATED ERYTHEMAS (114/887, 12.85%) ADRs IN SSTD-ADRs

Drug	n/N	PRR (95% CI)	Chi^2 test	P value	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Erythema (72/114, 63.16%)							
Clobazam	7/72	0.55 (0.26, 1.19)	2.015	0.1557	0.53 (0.24, 1.18)	-0.75 (-3.20, 1.70)	0.59 (0.11)
Midazolam	54/72	3.28	22.061*	< 0.0001	3.61	0.65	1.57

		(1.92, 5.58)*			(2.08, 6.26)*	(-0.30, 1.60)	(0.81)
Quazepam	1/72	0.24	1.86	0.1726	0.22	-2.02	0.25 (0.01)
		(0.03, 1.67)			(0.03, 1.62)	(-6.88, 2.84)	
Tetrazepam	10/72	0.37	9.080	0.0026	0.35	-1.12	0.46 (0.11)
		(0.19, 0.72)			(0.18, 0.69)	(-3.18, 0.93)	
Rash erythematous (23/114, 20.18%)							
Clobazam	0/23	-	3.469	0.0625	-	-	-
Midazolam	11/23	1.00	0.000	0.9981	1.00	0.00	1.00
		(0.44, 2.27)			(0.44, 2.29)	(-1.94, 1.95)	(0.26)
Quazepam	0/23	-	0.532	0.4656	-	-	-
Tetrazepam	12/23	2.52	4.384*	0.0363	2.59	0.79	1.73
		(1.12, 5.68)*			(1.13, 5.95)*	(-1.12, 2.69)	(0.46)
Generalised erythema (19/114, 16.67%)							
Clobazam	6/19	2.36	2.254	0.1333	2.42	0.95	1.93
		(0.91, 6.15)			(0.90, 6.48)	(-1.66, 3.56)	(0.32)
Midazolam	13/19	2.37	2.518	0.1126	2.41	0.52	1.43
		(0.90, 6.22)			(0.91, 6.40)	(-1.29, 2.32)	(0.41)
Quazepam	0/19	-	22.061	< 0.0001	-	-	-
Tetrazepam	0/19	-	7.006	0.0081	-	-	-

In this study, we investigated the association between 15 benzodiazepines and adverse drug reactions which were related to "Skin and subcutaneous tissue disorders" ADRs. To achieve this goal, we have used every available case-report included in the FAERS public database that is accessible on the online interface Drugcite®, and performed data mining algorithms for signal detection.

We noted a total of 129,783 ADRs reported cases for BZD in the period of time analyzed (2004 to 2012Q3). Of them, 3,957 were SSTD-ADRs, which represents 3.05% of the total BZD-reported ADRs. We have shown that the four BZD with more ADRs notified are, alprazolam> diazepam >clonazepam >lorazepam. This sequence cannot be explained by the half-life of each drug since these were short, intermedium, long and short, respectively. Even more, there seems to exist no relationship with the chemical structure as they belong to four different types (triazolo, 2-keto, 7-nitro and 3-hydroxi respectively). Interestingly, when ordering the BZDs by the number of SSTD-ADRs associated, we realized that the top three BZD remained unchanged but midazolam irrupted in the fourth place [319 (8.06%)]. Noteworthy, midazolam presents a very low total number of ADRs notified to FAERS.

Furthermore, we have been able to identify tetrazepam as the BZD exhibiting signals detected by all the mining algorithms calculated (PRR, ROR, IC and EBGM). Behind this BZD, quazepam, clobazam and midazolam present positive signals for 3 algorithms (PRR, ROR and IC). Finally, clorazepate and oxazepam, only for one (ROR). Our results provide new data that come to increase the limited comparative data published on the sensibility of algorithms. The data we present are in accordance with a previous work by Chen *et al*., that compared the timing of early signal detection with the PRR, ROR, IC and EBGM [20]. They concluded that ROR has the best performance, which is in line with our work. We show that the algorithm able to detect the highest number of positive signals is indeed ROR (8 signals) and the lowest is EBGM (1 signal).

Our study revealed that, for the 4 BZD with potential signals in more than 2 algorithms, the SSTD-ADRs (defined as High-Level Terms (HLT) MedDRA levels) with a percentage higher than 10% were: bullous conditions (26.94%), dermatitis ascribed to specific agent (19.39%), rashes, eruptions and exanthemas (15%) and erythema (12.85%).

Among BZDs, tetrazepam rendered signals with at least one algorithm. This for the following Preferred Terms (PT) of the MedDRA classification: dermatitis bullous, toxic skin eruption, maculo-papular rash and erythematous rash. In addition, our data supports the July 2013 determination of suspending tetrazepam-containing medicines due to the occurrence of life-threatening skin reactions [21].

This decision was taken by EMA after the analysis of the cases reported to the French database BNPV [22]. Our present algorithm data add relevant information to our previous work on tetrazepam withdrawal [23, 24], in which we systematically revised this drug within the medical literature. We detected a lack of randomized controlled clinical trials evaluating tetrazepam's efficiency and safety. Indeed, we failed to find a turning point in the amount of ADRs reported following tetrazepam withdrawal aimed to underpin the validity of the withdrawal [23, 24].

We found a signal for Midazolam in either HTL: dermatitis ascribed to specific agents (for the PT: DRESS Syndrome) and erythemas (for the PT: erythema). According to this, midazolam has been described as causing exanthema and pruritus, and a case of a 36 year-old man of urticarial reaction after injection administration [25]. Quazepam generates signals in the HLT Bullous conditions (for the PT: erythema multiform) and in dermatitis ascribe to specific agents (for the PT: drug eruption). Clobazam produces signals only in one HLT: bullous conditions (for the PT: Stevens-Johnson Syndrome and blister). It is noteworthy to say that our data support the fact that the FDA issued a warning to the public because of clobazam causing Stevens-Johnson Syndrome at any time during treatment [26]. However, we failed to support the report by Redondo *et al*. showing clobazam as a cause of a fatal toxic epidermal necrolysis [27]. In our study, although clobazam was associated to 14 ADRs associated to this SOC MedDRA level, the applications of algorithms failed to raise it as a pharmacovigilance signal.

As any other pharmacovigilance database, Drugcite® has limitations. One of these is the reporting rate, which can vary within the particular ADRs [28]. Another limitation is the fact that ADRs are usually underreported [29-33]. There is even spontaneous reporting. Still, despite these limitations, many important safety "signals" have been identified using these systems [34]. Calculating disproportionality parameters for an entire database has been carried out by some experts [8]. Other authors prefer to analyze safety signals by traditional individual-case literature report methods instead of using quantitative methods base on disproportionality analysis (DPA) of spontaneous reporting databases [35]. Data mining of FAERS database might disclose previously unknown, but clinically important associations, and provide practitioners with useful guidelines to make better clinical decisions.

Finally, it is worth commenting that knowledge on these drug-effect associations is relevant for experts in pharmacovigilance. Indeed, there is little, if any, information published on the present topic. For instance, an electronic PubMed search for quazepam and any of the signals for both HLT, recently performed by us we failed to find any publication describing these skin ADRs. Traditional and quantitative pharmacovigilance methods provide different and complementary types of pharmacovigilance alerts. Literature and individual case reports highlight an adverse event that has occurred once or a few times, and DPA identifies medical events that are being reported on aggregates, with greater relative frequency for a drug and events. Ideally, using both approaches would lead to an efficient and effective pharmacovigilance strategy.

CONCLUSION: Our results provide new data that come to increase the limited comparative data published on the sensibility of algorithms. However, larger studies providing new clinical evaluation on these associations will be required.

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REFERENCES:

1. Huh J, Goebert D, Takeshita J, Lu BY, Kang M. Treatment of generalized anxiety disorder: a comprehensive review of the literature for psychopharmacologic alternatives to newer antidepressants and benzodiazepines. Prim Care Companion CNS Disord. 2011; 13(2):
2. Shader RI, Greenblatt DJ. Use of benzodiazepines in anxiety disorders. N Engl J Med. 1993; 13; 328(19): 1398-405.
3. DEA. http://www.dea.gov/druginfo/dsshtml. Last accessed 20 June 2015.
4. Almenoff JS, Pattishall EN, Gibbs TG, Du Mouchel W, Evans SJ, Yuen N. Novel statistical tools for monitoring the safety of marketed drugs. Clin Pharmacol Ther. 2007; 82(2):157-66.
5. Drugcite. http://www.drugcite.com. Last accessed 03 March 2015.
6. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from

spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001; 10(6): 483-6.
7. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002; 11(1): 3-10.
8. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, *et al*. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998; 54(4): 315-21.
9. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf. 2002; 25(6): 381-92.
10. FDA.http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152112.htm. Last accessed 20 May 2015.
11. FDA.(http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152700.htm). Last accessed 20 May 2015.
12. EMEA.http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/07/WC500130391.pdf. Last accesed 20 May 2015.
13. Meddra. http://www.medalerts.org/vaersdb/meddra/. Last accesed 15 February 2015.
14. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009; 18(6):427-36.
15. Hauben M, Reich L. Drug-induced pancreatitis: lessons in data mining. Br J Clin Pharmacol. 2004; 58(5): 560-2.
16. Almenoff J, Tonning JM, Gould AL, Szarfman A, Hauben M, Ouellet-Hellstrom R, *et al*. Perspectives on the use of data mining in pharmaco-vigilance. Drug Saf. 2005; 28(11): 981-1007.
17. Hauben M, Bate A. Decision support methods for the detection of adverse events in post-marketing data. Drug Discov Today. 2009; 14(7-8): 343-57.
18. Leaman R, Wojtulewicz L, Sullivan R, Skariah A, Yang J, Gonzalez G. Towards internet-age pharmacovigilance: extracting adverse drug reactions from user posts in health-related social networks. Proceedings of the 2010 Workshop on Biomedical Natural Language Processing. 2010; 117–25.
19. Gould AL. Practical pharmacovigilance analysis strategies. Pharmacoepidemiol Drug Saf. 2003; 12(7): 559-74.
20. Chen Y, Guo JJ, Steinbuch M. Comparison of sensitivity and timing of early signal detection of four frequently used signal detection methods: An empirical study based on the US FDA Adverse Event Reporting System database. Pharm Med. 2008; 22:359-65.
21. EMA.http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Tetrazepam_containing_medicinal_products/Procedure_started/WC500137136.pdf. Tetrazepam. Last accesed 20 June 2015.
22. BNPV.http://ansmsantefr/var/ansm_site/storage/original/application/e5063c53b7ce823b02cd0c2dc546b5bcpdf. Last accesed 20 June 2015.
23. Proy-Vega B, Aguirre C, de Groot P, Solis-Garcia del Pozo J, Jordan J. On the clinical evidence leading to tetrazepam withdrawal. Expert Opin Drug Saf. 2014; 13(6): 705-12.
24. Proy-Vega B, Cano-Cuenca N, Aguirre C, Solis-Garcia del Pozo J, Jordan J. Requiem for tetrazepam. Rev Neurol. 2013; 1; 57(1): 1-2.
25. Moran CG, Graham GP. Drug points: Adverse skin reaction to midazolam. Br Med J (Clin Res Ed) 1986; 293(6550).
26. FDA.http://wwwfdagov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm377340htm). Last accesed 20 June 2015.
27. Redondo P, Vicente J, Espana A, Subira ML, De Felipe I, Quintanilla E. Photo-induced toxic epidermal necrolysis caused by clobazam. Br J Dermatol. 1996; 135(6): 999-1002.
28. Rodriguez EM, Staffa JA, Graham DJ. The role of databases in drug postmarketing surveillance. Pharmacoepidemiol Drug Saf. 2001; 10(5): 407-10.
29. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006; 29(5):385-96.
30. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009; 32(1): 19-31.
31. Figueiras A, Herdeiro MT, Polonia J, Gestal-Otero JJ. An educational intervention to improve physician reporting of adverse drug reactions: a cluster-randomized controlled trial. JAMA. 2006; 296(9): 1086-93.
32. Herdeiro MT, Polonia J, Gestal-Otero JJ, Figueiras A. Improving the reporting of adverse drug reactions: a cluster-randomized trial among pharmacists in Portugal. Drug Saf. 2008; 31(4): 335-44.
33. Golomb BA, McGraw JJ, Evans MA, Dimsdale JE. Physician response to patient reports of adverse drug effects: implications for patient-targeted adverse effect surveillance. Drug Saf. 2007; 30(8): 669-75.
34. Davis S, King B, Raine JM. Spontaneous reporting-UK. 2nd ed: John Wiley & Sons Ltd; 2007.
35. Hauben M, Reich L. Potential utility of data-mining algorithms for early detection of potentially fatal/disabling adverse drug reactions: a retrospective evaluation. J Clin Pharmacol. 2005; 45(4): 378-84.

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