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Look-alike and sound-alike drugs: A potential cause of cutaneous adverse reactions to drugs

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Running head: Cutaneous adverse reaction due to look-alike and sound-alike drugs

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Dear editor,

Cutaneous adverse drug reactions (CADRs) are the most frequent adverse reactions to drugs, with incidence ranging from 1% to 3%. Severe cutaneous adverse reactions (SCARs) to drugs are associated with mortality and drug-development challenges.[1] A contributor to dispensing errors are look-alike and sound-alike (LASA) drug names. Approximately a quarter of medication errors are the result of orthographic (look-alike) and phonetic (sound-alike) similarity between drug names.[2] We investigated CADRs due to erroneous substitution of LASA medicines. We also present a systematic

comparison of homologies for Stevens Johnson syndrome and Toxic Epidermal Necrolysis (SJS-and-TEN)-inducing drugs in the French medicine pharmacopeia.

For collection of cases, we first conducted a nationwide retrospective survey of CADRs induced by drug-dispensing error through the French Investigators for Skin Adverse Reactions to Drugs (FISARD) group of the French Society of Dermatology. Second, we performed a search in the pharmacovigilance database and in the medication error database of the French National Agency for Medicines and Health Products Safety [Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)] between 1985 and 2016 by using a search string, created ad hoc and combining appropriate key words within the standardized Medical Dictionary for Regulatory Activities (MedDRA) queries "severe cutaneous adverse reaction" ("drug error", "overdosage" and "accidental overdosage") with Boolean operators "AND" and "OR".

From the ANSM database, we obtained 113 events, most involving overdosage or administration mistake. We found nine cases of CADRs (including five SCARs) due to dispensing error, all reported within the past ten years. The five SCARs were three SJS-and-TEN and two drug reactions with eosinophilia and systemic symptoms (DRESS), all due to erroneous substitution of LAMISIL® (terbinafine) with LAMICTAL® (lamotrigine). The four non-severe CADRs were maculopapular exanthemas; two of them were due to erroneous substitution of LAMISIL® (terbinafine) with LAMICTAL® (lamotrigine); the other two were due to erroneous substitution of METEOXANE® with Methotrexate and DAKIN® with DAKTARIN®. The first three SCARs had been previously reported in the literature.[3,4] None of the patients had history of CADR.

For the systematic comparison of homologies, we obtained from the ANSM website 4,133 drugs names available in France on January 1, 2015. From Mockenhaupt *et al*.[5], we identified 124 drugs at high risk of inducing SJS-and-TEN (43 international-nonproprietary names associated with 81 brand-names). We then measured the orthographic similarity of the 124 SJS-and-TEN-inducible drugs to each of the 4,133 drug names, using a string-matching algorithm called superposition matching.[6] This algorithm has been shown to provide a good account of perceptual confusions involving words.[6–8] It calculates a match score between 0 and 1 for any pair of letter strings, 0 indicating complete dissimilarity and 1 a perfect match between the two strings. We hypothesized that pairs of drugs with higher match scores would have greater likelihood of resulting in dispensing errors. With a matching score cutoff of 0.5 (considered at risk of error), 446 homologies were at risk of error; 310 (69%) were errors due to the LASA brand name. With a cutoff of 0.7 (considered at high-risk of error), 35 homologies were at high risk of error (Supplementary Table 1); 33 (94%) were errors due to the LASA brand name. The median match score was 0.74 [IQR 0.71-0.76].

Considering the high under-reporting rate of drug-adverse reactions and that all our cases were reported within the past 10 years, we found an annual potential incidence of 18 avoidable CADRs due to drug dispensing error in France (67 million inhabitants) and 138 in the European Union (512 million inhabitants).

We report the first systematic comparison of CADRs resulting from confusion due to LASA drug names. The SCARs induced by delivery of LAMICTAL® instead of LAMISIL® can be explained by the greater risk of adverse events when LAMICTAL® is introduced at high posology. We report only nine cases of CADRs, but this may reflect the absence of systematic and compulsory reporting of medical adverse events leading to a high under-reporting rate of drug adverse reactions. It is noteworthy that we observed CADRs involving brand name confusion even though prescription in INN is mandatory.

We urge the authorities (e.g., European Medicines Agency, UK Medicines and Healthcare products Regulatory Agency, US Food and Drug Administration) to consider the risks associated with similar drug names. Prevention is important because drug confusions are life-threatening and can lead to possible long-term complications or sequela and there is no golden standard treatment.[1] Our study emphasizes the need for a public policy including the limitation of drug homologies to reduce the risk of avoidable SCARs.

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REFERENCES

1 Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet* 2017; **390**:1996–2011.

2 Emmerton LM, Rizk MFS. Look-alike and sound-alike medicines: risks and 'solutions'. *Int J Clin Pharm* 2012; **34**:4–8.

3 Le Loarer F, Carré-Gislard D, Baricault S, Bravard P. [Severe drug eruption caused by a medication error] Toxidermie sévère due à une erreur de délivrance médicamenteuse. *Ann Dermatol Venereol* 2009; **136**:364–365 (in French).

4 Duparc A, Lasek A, Gros C, *et al.* [Toxic epidermal necrolysis caused by erroneous substitution of lamotrigine for terbinafine] Nécrolyse épidermique toxique la lamotrigine par erreur de délivrance. *Ann Dermatol Venereol* 2010; **137**:736–738 (In French).

5 Mockenhaupt M, Viboud C, Dunant A, *et al.* Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: Assessment of Medication Risks with Emphasis on Recently Marketed Drugs. The EuroSCAR-Study. *J Invest Dermatol* 2008; **128**:35–44.

6 Davis CJ. The spatial coding model of visual word identification. *Psychol Rev* 2010; **117**:713–58.

7 Davis CJ, Bowers JS. Contrasting five different theories of letter position coding: Evidence from orthographic similarity effects. *J Exp Psychol Hum Percept Perform* 2006; **32**:535–57.

8 Lambert BL, Lin SJ, Chang KY, Gandhi SK. Similarity as a risk factor in drug-name confusion errors: the look-alike (orthographic) and sound-alike (phonetic) model. *Med Care* 1999; **37**:1214–25.

9 Sassolas B, Haddad C, Mockenhaupt M, *et al.* ALDEN, an algorithm for assessment of drug causality in stevens-johnson syndrome and toxic epidermal necrolysis: Comparison with case-control analysis. *Clin Pharmacol Ther* 2010; **88**:60–8.

Table 1. Homologies at high risk of inducing SJS-and-TEN

Potentialy confusing drug	Notoriety of drug §	Match score ¶	Sjs-ten inducing drug	Notoriety of drug §
ACIDRINE ® (Myrtécaïne laurylsulfate)	0	0.72	ADIAZINE ® (sulfadiazine)	3
ADENYL ® (adenosine phosphate)	0	0.71	GARDENAL ® (phenobarbital)	3
ADEPAL ® (lévonorgestrel+éthinylestradiol)	-1	0.79	ALEPSAL ® (caffeine+ phenobarbital)	3
ADEPAL ® (lévonorgestrel+éthinylestradiol)	-1	0.71	GARDENAL ® (phenobarbital)	3
ARESTAL ® (loperamide)	0	0.74	ALEPSAL ® (caffeine+phenobarbital)	3
ARTHROCINE ® (sulindac)	2	0.75	AZITHROMYCINE	2
ARTHROCINE ® (sulindac)	2	0.77	CLARITHROMYCINE	2
ARTHROCINE ® (sulindac)	2	0.82	ERYTHROCINE ® (erythromycine)	2
AZATHIOPRINE	0	0.72	AZITHROMYCINE	2
CANOL ® (artichoke+aphloïa)	0	0.82	CYCLADOL ® (piroxicam)	3
CARDIOXANE ® (dexrazoxane)	0	0.71	CEFTRIAXONE	2
CEFALINE ® (caffeine acetaminophen)	1	0.81	CEFALEXINE	2
CEFALINE ® (cafein+acetaminophen)	1	0.7	CEFIXIME	2
CLARADOL ® (acetaminophen)	1	0.72	CYCLADOL ® (piroxicam)	3
DOXYLAMINE	-1	0.72	DOXYCYCLINE	2
ERYTHROCINE ® (erythromycin)	2	0.75	ARTHROCINE ® (sulindac)	2
IMNOVID ® (pomalidomide)	0	0.74	INDOCID ® (indometacine)	2
LAMISIL ® (terbinafine)	**0**	**0.75**	**LAMICTAL ® (lamotrigine)**	**3**
LAROXYL ® (amitriptyline)	-1	0.78	CLAMOXYL ® (amoxicilline)	2
LECTIL ® (betahistine)	0	0.71	TILCOTIL ® (tenoxicam)	3

LIDENE ® (doxylamine)	-1	0.76	LODINE ® (etodolac)	2
MELODIA ® (ethinylestradiol+gestodene)	-1	0.75	MELOXICAM	3
MINOCYCLINE	2	0.71	MIDECAMYCINE	2
MOCLAMINE ® (moclobemide)	0	0.72	MINOCYCLINE	2
NEORAL ® (ciclosporine)	0	0.71	KEFORAL ® (cefalexine)	2
NIVAQUINE ® (chloroquine)	0	0.74	NEVIRAPINE	3
PEFLACINE ® (pefloxacine)	2	0.71	PYOSTACINE ® (pristinamycine)	2
PHYSIOMYCINE ® (metacycline)	2	0.71	PRISTINAMYCINE	2
RITALINE ® (methylphenidate)	0	0.78	SERTRALINE	3
ROVALCYTE ® (valganciclovir)	0	0.76	ROVAMYCINE ® (spiramycine)	2
ROVAMYCINE ® (spiramycine)	2	0.72	VIBRAMYCINE ® (doxycycline)	2
SPIRAMYCINE	2	0.78	PRISTINAMYCINE	2
SPIRAMYCINE	2	0.75	VIBRAMYCINE ® (doxycycline)	2
TEMODAL ® (temozolomide)	0	0.78	TEXODIL ® (cefotiam)	2
VIBRAMYCINE ® (doxycycline)	2	0.75	SPIRAMYCINE	2

¶Color is graduated depending on the match score: green for the lower score and red for the highest score; a score > 0.7 indicates high risk. § Notoriety of drug has been attributed according to algorithm of drug causality for epidermal necrolysis (ALDEN)[9] score depending on the estimated relative risk (RR) evaluated by Mockenhaupt et al. [5]; 3: strongly associated drug, 2: associated drug, 1: suspected drug, 0: unknown, -1: not suspected drug.