ON THE CLINICAL EVIDENCE LEADING TO TETRAZEPAM WITHDRAWAL

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BACKGROUND
In July 2013, the European Medicines Agency suspended the marketing authorization of tetrazepam across the European Union, due to serious cutaneous adverse drug reactions (ADR). Herein, we examine information described in PubMed and reported to the main Pharmacovigilance Databases (PhDB), related to ADR associated to tetrazepam.

PURPOSE
We tried to ascertain described evidence on cutaneous ADR due to tetrazepam, which could have led to the end of commercialization of this drug that had been over 40 years in the market.

MATERIAL & METHODS
First, we conducted a search in MEDLINE and Cochrane (January 2015) about ADR due to tetrazepam, in peer-reviewed journals. Inclusion criteria were: studies performed on humans or tetrazepam-induced ADR case reports. Secondly, we collected data of spontaneous reporting of suspected ADR due to tetrazepam, from 1989 until December 2014, from the main PhDB: Spanish (FEDRA), French (BNPV) and American (FAERS).

RESULTS
30 manuscripts were included in our systematic review, which encompass data from 72 subjects, all of them suffering from any kind of cutaneous ADR related to tetrazepam (100%). No other ADR were found. The most frequent ADR described were: airborne-contact dermatitis (26 cases), maculopapular exanthema (17 cases), toxical epidermal necrolysis (5 cases, 1 patient died) and erythema multiforme (5 cases). Additionally, we identified 3481 tetrazepam-associated ADR in PhDB (924 from FEDRA, 1616 from BNPV and 941 from FAERS). Of them, cutaneous ADR were the most reported ADR (32.0% in FEDRA, 49.8% in BNPV, and 12.7% in FAERS). PhDB included other tetrazepam-associated ADR: neurological (12.5%), gastrointestinal (7.7%), psychiatric (5.7%), among others. Regarding cutaneous ADR in all PhDB, the most frequent severe events described were: erythema multiforme (59 cases, 1 with fatal ending), Stevens-Johnson syndrome (33 cases, 1 with lethal evolution), Lyell syndrome (33 cases notified, 9 fatal outcome) and DRESS syndrome (15 cases).

CONCLUSION
Our study reveals discrepancies in the information provided by these two different sources, both in the number of reported cases as well as in the kind of ADR reported. We stress the importance of a better knowledge communication between scientific literature and pharmacovigilance agencies, to prevent the use of marketed drugs with well-established side effects during long periods.