1. Instruments for Assessment of Case Reports

1.1 Horn 2007 [1]

The Drug Interaction Probability Scale (DIPS) is a 10-item instrument that assesses causality for drug-drug interaction (DDI) case reports and takes into consideration previous credible reports, consistency with known interactive properties, time course of the interaction, results of de-challenge and re-challenge, and alternative explanations. Each of the 10 items is equally weighted with a value of either zero or 1 and summary score is obtained by simple addition of points across the 10 items. The higher the total score, the more probable the adverse reaction was caused by the DDI (i.e., >8 = Highly Probable; 5-8 = Probable; 2-4 = Possible; <2 = Doubtful). The developers of the DIPS note that lower scores are possible when there are fewer collaborating reports in the literature. A formal validation of the DIPS instrument has not been published and its reliability has not been established to date.

1.2 Naranjo 1981 [2]

The Naranjo adverse drug reaction probability scale is a 10-item instrument that uses previous evidence and patient-level data (i.e., case report) to assess the likelihood that an adverse event is drug related. Like the DIPS scale, each question is given a value of zero or 1 and the items are summed to an overall total score. The intra-rater reliability of the Naranjo scale varied from correlations of 0.17 to 0.98 among 6 physicians or pharmacists and 3 different phases. The percent agreement between raters was high (r = 0.84 to 0.93). It has been widely accepted and frequently used when assessing adverse reactions due to drug therapy. Despite its many relevant questions related to DDIs, this instrument fails to specifically address more than one agent given concurrently, a necessary condition for DDIs. Validity of the instrument was evaluated using multiple methods. One approach used consensus agreement by three experts and presence of collaborating publications. Another approach compared one expert to ratings by non “experts.” Content validity was assessed comparing results from the 63 cases studies to 28 prospectively collected cases. The last validity assessment approach evaluated concurrent validity by comparing the 63 cases to another published algorithm. Across the various validity assessment approaches, Kappa statistic values and correlations were good to excellent (0.64 to 0.96).

2 Instruments for Overall Assessment of Evidence for a Drug-Drug Interaction

2.1 Böttiger 2009 [3]

Böttiger et al. described a system used in Sweden and Finland to categorize DDIs based on clinical relevance and level of documentation for development of a database for clinical decision support. The level of documentation categories range from 0 to 4: 0, data derived from extrapolation on the basis of studies with similar drugs; 1, data derived from incomplete case reports and/or in vitro studies; 2, Data derived from well-documented case reports; 3, data derived from studies among healthy volunteers and/or pilot studies among patients; and 4, data derived from controlled studies in relevant patient populations. Two classifications were created, one for level of seriousness and a second for the quality of data. Seriousness levels were assigned an alpha character of A to D with A being a minor interaction and D being an interaction that is clinically relevant and should be avoided. Evidence was rated from 0 to 4. A value of 0 indicated that data was extrapolated from studies of similar medications. Zeros are assigned when there is a potentially dangerous DDI that has not, and probably never will be, documented in clinical studies. The system also specifies inclusion and exclusion criteria. A value of 4 was assigned when data were derived from controlled studies in the relevant population. The reliability and validity of the instrument was not reported.
2.2 Valuck 2000 [4]

Valuck et al. developed a 5-step process for evidence-based assessment of published DDI information and presentation of that information in a standardized format: i) search the medical literature for published DDI information; ii) assess the relevance of the articles; iii) assess the quality of the articles; iv) assess DDI causality; and v) abstract the findings and present the evidence. The authors described the process to evaluate the DDI literature, but did not create or validate a unique tool. They recommended the Naranjo scale for assessing causality.

2.3 van Roon 2005 [5]

Similar to Böttiger et al., van Roon et al. described a system to categorize DDIs based on clinical relevance and level of documentation for clinical decision support in the Netherlands. This system uses four core parameters: i) evidence on the interaction; ii) clinical relevance of the potential adverse reaction resulting from the DDI; iii) risk factors; and iv) incidence of the adverse reaction in patients given the combination. The quality of evidence rating ranged from 0 to 4 with a value of 0 being assigned to evidence based on pharmacodynamics studies in animals, in vitro studies with limited predictive data for humans, or data on file. Controlled studies in patients or health volunteers with clinically relevant endpoints were assigned values of 4. The authors did not provide information on the reliability or validity of the process or rating of study quality scale.

References