OncoRx-IQ: a tool for quality assessment of online anticancer drug interactions

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Abstract

Objective. The quality of online anticancer drug interaction information varies among online drug databases. We describe the creation of OncoRx-IQ, a tool which assesses the information quality of online drug databases for anticancer drug interactions, and a pilot study done with the tool.

Design. OncoRx-IQ was designed in the form of a questionnaire containing 25 questions in three quality domains, separated into two sections (Section A: content accuracy and Section B: ease-of-use and reliability). Each question was scored based on the number of options assigned.

Setting. A pilot study utilizing this tool was done on four drug databases (Drugs.com, Drug Digest, Medscape and Micromedex). Statistical analyses of the composite and domain scores were done using descriptive statistics, Spearman’s correlation coefficient and Friedman and Wilcoxon signed-rank tests.

Participants. Six pre-registration pharmacists participated in the pilot study.

Main Outcome Measures. The drug databases were evaluated based on the accuracy of their drug interaction content, usability and reliability, as well as their overall quality.

Results. Micromedex (66.9%) and Drug Digest (35.8%) were the highest and lowest scoring databases, respectively. Micromedex scored the highest in all quality domains (content accuracy 56.3%, ease-of-use 75.0% and reliability 73.6%), whereas Drug Digest scored the lowest in content accuracy (8.0%) and reliability (48.2%).

Conclusions. We have created and pilot-tested OncoRx-IQ, a quality assessment tool, which helps clinicians systematically evaluate the quality and information accuracy of drug databases for anticancer drug interaction information. We hope this tool can lay the groundwork for future long-term evaluation of online drug interaction information.

Keywords: anticancer/chemotherapy drug interactions, content accuracy, drug databases, quality assessment, reliability, usability

Introduction

Cancer patients undergoing chemotherapy are particularly susceptible to drug interactions [1]. The clinical consequences of these interactions are significant because anticancer drugs possess narrow therapeutic ranges and are inherently toxic [1]. It is thus important for healthcare professionals to keep themselves informed with the most current drug interaction information, particularly involving newer anticancer drugs. However, their ability to keep abreast with the latest anticancer drug-related information is likely to be hindered by inherent delays in traditional literature publication processes [2]. Therefore, the use of clinical decision support tools, such as online drug databases, can be useful to obtain up-to-date interaction information in a timely, efficient and accessible manner [3]. Physicians tend to utilize the internet to access the latest information on specific health-related topics [4]. Although drug databases can provide relevant and current drug interaction information in a convenient manner, there is much concern regarding the wide variation in the quality of such online health-related information [4, 5].

Several tools have been developed to evaluate the quality of online health information and guide healthcare professionals and patients to the best sources [6]. Some manifest as codes of conduct for voluntary compliance, whereas others provide guidance to users in the form of a questionnaire or checklist. Five currently available
Table 1 Summary and comparison of the characteristics and evaluation criteria of five currently available quality assessment tools

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HONcode</th>
<th>DISCERN</th>
<th>Netscoring</th>
<th>eEUROPE</th>
<th>DARTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aims</td>
<td>To standardize the reliability of medical and health information available on the World Wide Web</td>
<td>To provide users with a valid and reliable way of assessing the quality of information on treatment choices</td>
<td>To provide a set of criteria that can be used to assess the quality of health information on the internet</td>
<td>To help users distinguish valid and reliable information from those that are inaccurate or misleading</td>
<td>To allow users to identify good quality information</td>
</tr>
<tr>
<td>Specific to a clinical speciality</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Quantitative assessment (score/weight)</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Content accuracy evaluation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Evaluation criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authorship</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Disclaimer</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Editorial review</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Financial disclosure</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Presence of bias</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>User privacy</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Purpose of database</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Referencing</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Target audience</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Navigation tools</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Links to other databases</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>User support features</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Loading speed</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
</tbody>
</table>

✓, the assessment tool contains the characteristic or criteria. X, the assessment tool does not contain the characteristic or criteria.
assessments of their evaluation criteria. Although these tools are useful in appraising online drug databases, they also possess limitations in terms of utility. Tools such as Netscoring [7], HONcode [11], and DARTS assessment tools [9], are time-consuming to use. On the other hand, quality assessment tools with fewer questions provide a faster and user-friendly way to evaluate health information websites. These tools also differ in terms of their quality assessment criteria. For example, DISCERN [10] and eEurope [8] do not include the presence of disclaimers and biasness as part of their evaluation criteria (Table 1). In contrast, the Health on the Net code (HONcode) [11] and DARTS [9] do not consider editorial review and target audiences of the websites as part of their quality assessment. Some tools like HONcode, eEurope and DARTS also do not provide a scoring system, which makes objective comparisons among databases difficult.

More importantly, a common limitation among these tools is the absence of assessment criteria for evaluating the accuracy of health-related content. Furthermore, these tools do not cater toward any specific clinical specialty and can only be used to evaluate general health information websites. Despite the potential of drug interactions occurring in cancer patients [1, 12], from our knowledge, there is currently no quality rating instrument that evaluates drug databases for information on anticancer drug interactions. We have therefore created OncoRx-IQ, an assessment tool which evaluates the overall quality of drug information databases and the content accuracy of online anticancer drug interaction information. The utility of this tool was then tested in a pilot feasibility study which systematically analyzed four drug databases for anticancer drug interactions.

Methods

Definition of quality

Akin to the operationalized quality definition for health-related websites put forth by Provost et al. [5], the quality of online drug databases in this study is defined as the level of excellence which characterizes an online drug database in terms of its ability to satisfy drug interaction information needs.

Creation of the OncoRx-IQ tool

The development of OncoRx-IQ was based on our review of the rating instruments described previously. Its criteria for assessing the overall quality of a drug database are similar to the criteria detailed in the second half of Table 1, with additional criteria for assessing drug interaction content. The evaluation criteria of each section of OncoRx-IQ, together with explanations on what users should look out for in each criterion, are shown in Table 2.

OncoRx-IQ is created in the form of a questionnaire which consists of 25 questions separated into two sections. Section A assesses the accuracy and comprehensiveness of the interaction content of a drug database (27 points), and section B evaluates its overall quality (40 points). Questions in section B are further subdivided into two domains—ease-of-use (12 points) and reliability (28 points).

The questions in section A (Q1–12) specifically assess the interaction parameters between a combination chemotherapy regimen EP (consisting of the anticancer drugs etoposide and cisplatin) and vorinostat (an anticancer drug) with valproic acid (an antiepileptic drug). Summaries of the studies and reference citations are provided for verification of the interaction evidences. These include in vitro and animal studies, case reports and human studies, as well as product information of the interacting drugs. The rationale of selecting the regimen EP was to assess whether the databases could identify the pharmacokinetic interactions based on chemotherapy regimen acronyms. Vorinostat, a relatively new anticancer drug, was also selected because it manifests a pharmacodynamic interaction with valproic acid. Furthermore, this interaction could be used to assess how updated the drug databases are. An antiepileptic drug was chosen because of its indication in patients with brain tumors and brain metastases who often manifest seizures [12]. These interactions would be clinically relevant to the large majority of healthcare professionals (e.g. neurosurgeons, neurologists, medical and radiation oncologists) who prescribe antiepileptic drugs as prophylaxis to patients with cancer [13].

On the other hand, questions in section B (Q13–25) are based on the 15 criteria shown in the second part of Table 2. Database usability is assessed according to whether it has certain tools and features which allows easy navigation, such as a help function, site map or menu system, and the loading speed of the database. Conversely, database reliability is determined through quality aspects such as its credibility (e.g. authorship, presence of bias), the types of drug-related information and resources it provides, its target audiences, user privacy policy and how its drug-related content should be interpreted by users (e.g. disclaimers). The reader is referred to the Appendix for further details of the OncoRx-IQ tool.

Database selection and pilot testing

OncoRx-IQ was reviewed by four male undergraduate students (21–23 years old) from the Department of Pharmacy, National University of Singapore, to ensure its user-friendliness. Alterations were made according to their feedback, and their responses were not considered for evaluation. The tool was then distributed to a panel of six pre-registration pharmacists (four females and two males, 24–26 years old) after modification as a pilot study to evaluate the drug databases. A search was conducted in Google in February 2009 with the following keywords: drug interactions, drug interaction checkers, drug interaction databases, chemotherapy interaction databases, chemotherapy regimen interactions, oncology interaction databases, oncology drug interaction databases, anticancer drug interaction databases and...
antineoplastic drug interaction databases. From each search, the top five hits that provided direct links to freely accessible drug databases were considered for evaluation. Links to journal articles and other drug databases targeted for patient use were excluded. Some databases appeared within the top five hits on more than one occasion. The top three databases which appeared most frequently in our searches were selected for evaluation. These were Drugs.com, Medscape and Drug Digest. Micromedex Healthcare Series was also included for evaluation as it was a commonly used database by healthcare professionals [14]. Table 3 provides the publisher details and hyperlinks of the evaluated databases.

Table 2 Evaluation criteria in the OncoRx-IQ tool with explanations on what each criterion entails

<table>
<thead>
<tr>
<th>Section</th>
<th>Evaluation criteria</th>
<th>Explanation of criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content accuracy</td>
<td>Effects of interaction</td>
<td>Provision of the drug interaction effects and/or clinical manifestations</td>
</tr>
<tr>
<td></td>
<td>Mechanism of interaction</td>
<td>Provision of the mechanism of drug interaction</td>
</tr>
<tr>
<td></td>
<td>Evidence of interaction</td>
<td>Provision of evidences which substantiate the drug interaction (e.g. case reports, in vitro/animal/human studies, package inserts)</td>
</tr>
<tr>
<td></td>
<td>Management strategies</td>
<td>Provision of appropriate recommendations to manage a drug interaction</td>
</tr>
<tr>
<td>Overall quality</td>
<td>Authorship</td>
<td>Presence of the names and credentials of authors</td>
</tr>
<tr>
<td></td>
<td>Disclaimer</td>
<td>Presence of a statement indicating that information should not replace a healthcare professional’s advice</td>
</tr>
<tr>
<td></td>
<td>Editorial review</td>
<td>Explanation of the database’s content verification procedure</td>
</tr>
<tr>
<td></td>
<td>Financial disclosure</td>
<td>Indication of the database’s sources of funding</td>
</tr>
<tr>
<td></td>
<td>Presence of bias</td>
<td>Presence of advertisements and/or affiliations</td>
</tr>
<tr>
<td></td>
<td>User privacy</td>
<td>Presence of a privacy policy statement pertaining to users</td>
</tr>
<tr>
<td></td>
<td>Purpose of database</td>
<td>Indication of the database’s objectives</td>
</tr>
<tr>
<td></td>
<td>Referring</td>
<td>Presence of citations for the editorial content</td>
</tr>
<tr>
<td></td>
<td>Target audience</td>
<td>Indication of who the database is intended for</td>
</tr>
<tr>
<td></td>
<td>Navigation tools</td>
<td>Presence of a site map, index or menu system</td>
</tr>
<tr>
<td></td>
<td>Links to other databases</td>
<td>Presence of hyperlinks to other drug databases for verification of drug information</td>
</tr>
<tr>
<td></td>
<td>User support features</td>
<td>Presence of a help feature or frequently asked questions (FAQ) section</td>
</tr>
<tr>
<td></td>
<td>Loading speed</td>
<td>Acceptability of the time taken for the database to load</td>
</tr>
<tr>
<td></td>
<td>Drug interaction risk information</td>
<td>Indication of the likelihood of a drug interaction occurring</td>
</tr>
<tr>
<td></td>
<td>Drug interaction severity information</td>
<td>Indication of the severity of a drug interaction</td>
</tr>
</tbody>
</table>

Table 3 Publisher details and uniform resource locators (URLs) of drug databases evaluated with the OncoRx-IQ tool

<table>
<thead>
<tr>
<th>Number</th>
<th>Drug database</th>
<th>Publisher</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drugs.com</td>
<td>Cerner Multum™, Micromedex™ and Wolters</td>
<td><a href="http://www.drugs.com">http://www.drugs.com</a></td>
</tr>
<tr>
<td>2</td>
<td>Medscape®</td>
<td>WebMD</td>
<td><a href="http://www.medscape.com">http://www.medscape.com</a></td>
</tr>
<tr>
<td>4</td>
<td>Micromedex® Healthcare Series</td>
<td>Thomson Reuters</td>
<td><a href="http://www.micromedex.com">http://www.micromedex.com</a></td>
</tr>
</tbody>
</table>
Discussion

The quality of drug databases, especially in the context of oncology chemotherapy regimens, is critical for ensuring patient safety and effective treatment. Various online drug databases, such as Micromedex, Drug Digest, Medscape, and Drugs.com, are used to assess drug interactions on a routine basis. Drug Digest was rated the best database for usability, with Micromedex being the best for content accuracy. However, none of these databases were rated above 50% for reliability. Micromedex scored highest for usability (75.0%), but lowest for content accuracy (8.0%). In contrast, Medscape had the highest composite score (66.9%), followed by Drug.com (58.9%). Among all the databases, Micromedex was rated as the best in terms of overall quality with the highest composite score of 60.5%, followed by Medscape (62.3%). Drug Digest followed with 56.3%, and Drugs.com obtained the second highest score (66.9%). A few databases, like ProDrug, had the lowest inter-rater score (4.1), which led to a statistical variance in their composite quality (P = 0.046). OncoRx-IQ was an assessment tool for evaluating the quality of drug databases from the pilot study.

Results

The quality of drug databases was high among the evaluators for each domain, as well as the composite scores. Spearman’s domain correlation coefficient was used to correlate the domain scores to the composite scores. The results showed that all tests were carried out to check for variance in scores for each quality domain, and the Friedman and Wilcoxon signed-rank tests were used to correlate the domain scores to the composite scores. All tests were two-tailed, and P-values below 0.05 were considered statistically significant.

Table 4

<table>
<thead>
<tr>
<th>Quality domain</th>
<th>Evaluated databases</th>
<th>statistical significance</th>
<th>Level of agreement among evaluators&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drugs.com</td>
<td>Medscape</td>
<td>Drug Digest</td>
</tr>
<tr>
<td></td>
<td>Scores Mean ± SD (% score)</td>
<td>Scores Mean ± SD (% score)</td>
<td>Scores Mean ± SD (% score)</td>
</tr>
<tr>
<td>Content accuracy</td>
<td>9.2 ± 3.8 (34.0)</td>
<td>4.8 ± 3.4 (17.9)</td>
<td>2.2 ± 1.2 (8.0)</td>
</tr>
<tr>
<td>Ease-of-use</td>
<td>8.2 ± 1.9 (68.1)</td>
<td>8.0 ± 1.5 (66.7)</td>
<td>8.3 ± 2.1 (69.4)</td>
</tr>
<tr>
<td>Reliability</td>
<td>16.5 ± 4.2 (58.9)</td>
<td>15.5 ± 5.1 (55.4)</td>
<td>13.5 ± 2.7 (48.2)</td>
</tr>
<tr>
<td>Composite scores</td>
<td>33.8 ± 7.1 (50.5)</td>
<td>28.3 ± 7.8 (42.3)</td>
<td>24.0 ± 4.1 (35.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Level of agreement among evaluators was evaluated using Kendall’s coefficient of concordance. *P < 0.05.
anticancer drug interaction information from online databases still remains a subjective decision influenced by the clinicians’ familiarity and experience with the databases [14]. Evaluation studies have suggested that assessment tools can be useful as long as they possess customized criteria for evaluating domain-specific information [15, 16]. Thus, this tool was created to evaluate the quality of these databases for oncology drug interactions in relation to three domains: content accuracy, usability and reliability.

From our pilot study results, the composite scores were largely affected by scores in both the content accuracy and reliability domains. Content accuracy in OncoRx-IQ was evaluated based on the interactions between the chemotherapy regimen EP and valproic acid causing increased risks of anticancer drug and hematological toxicities and loss of seizure control [17–19], as well as between vorinostat and valproic acid leading to increased risks of severe thrombocytopenia and gastrointestinal bleeding [20–23]. Although these two parameters were allocated almost equivalent weights, for the databases in which content accuracy played a major role in correlating to their overall quality, such as Drugs.com ($r^2 = 0.89$), its reliability played a secondary role. As for the other databases which did not score as well in content accuracy, such as Medscape and Drug Digest, the reliability scores had a higher impact in their overall quality assessments ($r^2 = 0.89$ for Medscape, $r^2 = 0.82$ for Drug Digest). Consequently, these two databases also had lower composite scores due to their lower ratings in both of these domains. In contrast, usability of the databases was not a determining factor in their overall quality.

Interestingly, all the evaluated databases fared poorly in terms of content accuracy, with Micromedex as the only database which scored higher than 50%. Although both Micromedex and Drugs.com managed to identify two interacting pairs (valproic acid with cisplatin and vorinostat), the information in Micromedex was more detailed and specific, and thus could possibly explain its higher scores in this domain. However, closer inspection of the drug interaction content in the databases showed that there were deficiencies in the drug interaction information provided for users. For example, Micromedex, Drugs.com and Drug Digest only managed to identify one of the interaction effects stated in the interaction profile in the Appendix between cisplatin (one of the anticancer drugs in the regimen EP) and valproic acid. The interaction between cisplatin and valproic acid could lead to decreased plasma valproic acid concentrations resulting in loss of seizure control, as well as an increased risk of hematological toxicity due to inhibition of cytochrome P450 2C9-mediated metabolism of cisplatin [17–19]. The databases previously described did not manage to identify the latter interaction which necessitates monitoring of signs and symptoms of bleeding as a management plan [17, 24, 25]. Furthermore, despite providing suggestions to monitor for seizure control, none of the databases indicated alternative non-interacting antiepileptic drugs such as gabapentin or levetiracetam as part of managing the drug interaction [25].

Remarkably, the interaction between etoposide and valproic acid due to inhibition of cytochrome P450 3A4-mediated etoposide metabolism [17, 24] was not identified in any of the online databases assessed. However, an evaluator who used the CD-ROM version of Micromedex indicated that he managed to identify this interaction pair. Medscape (17.9%) and Drug Digest (8.0%) were the lowest scorers for content accuracy, obtaining less than one-third the score of Micromedex (56.3%). These low scores could be explained by the fact that Medscape only managed to identify one out of the three drug interaction pairs (vorinostat and valproic acid), whereas Drug Digest did not manage to identify any of the interactions. Moreover, a quick search also showed that vorinostat was not in the list of drugs in Drug Digest.

Not surprisingly, our results showed that all evaluators agreed that content accuracy was an important component of determining quality of a drug interaction database. In fact, the inter-rater agreement for this domain was the highest ($W' = 0.79$), which was much more than that for reliability ($W' = 0.54$). Although Micromedex seemed to fare the best among all the databases in terms of content accuracy, there is still room for improvement in the comprehensiveness of drug interaction information provided for users. Nevertheless, an average of 56.3% for the content accuracy of a professional subscription database has to be considered nothing more than modest, given its popularity and extensive use among healthcare professionals.

Database reliability was differentiated from content accuracy in that this domain ascertained the level of trustworthiness of the drug databases through criteria such as authorship information, editorial review processes and the possible presence of bias. Interestingly, even though Micromedex was deemed to be the most reliable database based on their domain scores (73.6%), there were, in fact, two evaluators who rated Drugs.com as being more reliable than Micromedex. Their ratings could have been attributed to the presence of the HONcode approval seal in combination with a sentence which stated that the Drugs.com website ‘compl(ied) with the HONcode standard for trustworthy health information’. The reliability score of Drug Digest, however, was not as high as that of Drugs.com, even though it was also HONcode certified. This could probably be due to Drugs.com displaying an additional ‘TRUSTe certified privacy’ logo on its homepage in addition to its HONcode certification. TRUSTe is an independent organization that ensures online privacy and protection of confidential user information on certified websites so as to instill the trust and confidence in visitors and users of these websites, such as Drugs.com [26]. These auxiliary features could have served to demonstrate Drugs.com’s commitment to user privacy, which was also an indicator in OncoRx-IQ of the reliability of a drug database, and thus could have played a role in influencing the responses of the evaluators.

As part of assessing reliability, a question was also posed in OncoRx-IQ on whether the databases contained a disclaimer which specified that the drug information provided was not meant to replace the advice of a healthcare professional (Appendix, Q25). Although all but one of the evaluators agreed that Drugs.com clearly displayed such a disclaimer, only half of them agreed that this disclaimer was clearly displayed in Medscape to users. This discrepancy could be
attributed to the manner in which the databases displayed this piece of vital information to their users. Users of Drugs.com were required to read and agree to a set of terms and conditions, which includes a disclaimer, before being allowed to access the drug interaction checker. However, this disclaimer would only be shown to users if they had clicked the link on ‘Terms of Use’ in Medscape. Granted that the presence of such a disclaimer may not be as important in institutional subscription databases (e.g. Micromedex) which are predominantly used by health professionals, its presence in freely accessible online databases assumes a far greater significance. Unlike the former type of databases which are mainly accessed by healthcare professionals who complement their interpretation of the drug interaction content with their professional judgment, the latter online databases which offer free access can also be used by patients, who may alter their dosing regimens themselves based on the information which they find in these databases.

Usability of the databases was assessed with questions on various aspects of user-friendliness such as a help feature or frequently asked questions section, website navigation tools, as well as questions indicative of the evaluators’ expectations on loading times and overall expediencies of the drug databases. This domain was allocated the lowest weightage in OncoRx-IQ because its scores could be affected by users’ prior experiences and familiarity with the databases. One of the questions (Appendix, Q15) asked whether the databases could detect interactions with combination chemotherapy regimens based on their acronyms, since such combination regimens are frequently administered in patients with cancer. Certain chemotherapy regimens may consist of as many as 7–8 drugs, and it is not only time-consuming to search for drug interactions of each individual drug within the regimen, but also inconvenient for clinicians who, in oncology practice, may have time constraints in clinic visits. If they are in a rush for time, searching for multiple drug-pair interactions in a combination regimen may prone them to accidental omissions of a drug interaction search with a particular anticancer drug within the regimen, which may lead to a possibility of drug-related problems and adverse outcomes in patients. Examples of such regimens include BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) [27] and the double-delayed intensification regimen for pediatrics (vincristine, dexamethasone, doxorubicin, 1-asparaginase, cyclophosphamide, cytarabine, thioguanine and methotrexate) [28]. The ability of a database to detect interactions based on the acronyms of the combination regimens would thereby eliminate the need to enter each individual drug in the regimen as a drug interaction search strategy. However, none of the databases that were evaluated in this study had such a feature, suggesting that this feature could potentially be useful for drug databases which cater toward clinical oncology practice. Nevertheless, the scores for ease-of-use were similar among the databases, with Micromedex achieving the highest score of 75.0% (Table 4). The high score obtained with Micromedex could have been attributed to the familiarity of the evaluators with this database given its prevalent use as a drug information resource in local hospitals, even though statistical variance was not observed ($P = 0.631$). Medscape, on the other hand, obtained the lowest score (66.7%), possibly because the evaluators were required to register for a free account and log into Medscape as an additional step before being able to access the drug interaction checker. This step, however, was not a prerequisite to use the interaction checkers from Drugs.com and Drug Digest; hence, the hassle of spending time to register for an account was avoided.

The level of agreement among the evaluators were the lowest for usability of the databases ($W = 0.12$), suggesting an element of subjectivity in determination of this quality component. The scores in this domain could have been affected by the familiarity and prior experiences of the evaluators with these databases, and thus they could have placed a lower emphasis for ease-of-use of the databases which they were already familiar with during their assessments. Nonetheless, we felt that the evaluation of this domain was still necessary as part of overall quality of a drug database, since users who are unfamiliar with the drug database and using it for the first time would probably place a higher emphasis in navigating the website and how to carry out searches for particular drug interactions.

**Limitations and future work**

The major limitation of this study was the length of time required for each evaluator to assess the 4 drug databases. Evaluation of the databases was a laborious task, and feedback from the evaluators indicated that each person took an approximate 45 min to an hour to fully complete the evaluations. This long duration could have caused them to be more fatigued and less meticulous in their evaluations, thus explaining the subtle differences in our results. It was for this same reason that our tool was not distributed to clinicians, since evaluating these databases would require them to devote almost an hour of their time and concentration on top of their busy schedules. Pre-registration pharmacists were recruited into the study since they were already practicing in the clinical setting and would somewhat be also familiar with the area of drug interactions. Nevertheless, our overall results were not adversely affected by these slight inaccuracies as shown from the high level of agreement observed in the composite scores ($W = 0.81$). Still, clinicians’ views are important as their clinical interpretations of any drug interactions are of utmost value. Hence, future OncoRx-IQ studies should be targeted at this population group with fewer numbers of databases being assigned for evaluation.

Another limitation was the presence of Likert-scaled questions in the OncoRx-IQ tool, which inevitably imparted subjectivity in the quality assessment of the databases. However, evaluating the databases without these questions would result in a less comprehensive assessment of quality. We believe that certain aspects of quality, such as the convenience of using a database and loading within an acceptable time frame, are more efficiently and perhaps more exhaustively, determined by subjective assessments of each individual user, especially if the database is unfamiliar to the user. In order to cater for
practical quality assessments using the OncoRx-IQ tool, a compromise of three databases was decided based on the feedback of our preliminary review with the undergraduate students. The top three databases that appeared the most frequently in our search in Google were chosen, with the assumption that these databases would be the most frequently encountered and utilized by users. Nonetheless, there is a wide variety of online drug interaction databases that can be considered in larger scale studies involving the OncoRx-IQ tool.

Conclusion

OncoRx-IQ is an assessment tool developed to systematically assess the quality and content accuracy of drug databases for anticancer drug interaction information. Besides assessing the overall quality features of a drug database, such as its reliability and usability, our tool additionally evaluates the databases for accuracy of their drug interaction information. Although a direct correlation between good quality online drug information and positive treatment outcomes has yet to be established in large scale studies, we believe that accurate and good quality drug interaction information has a pivotal role to play in aiding healthcare professionals make sound clinical decisions by facilitating safe and efficacious use of anticancer agents. Thus, this tool has been developed in an effort to increase the awareness of healthcare professionals and patients alike regarding the quality of online anticancer drug interaction information and also lays the groundwork for the long-term evaluation of such drug interaction information. Needless to say, the evaluation of interaction information should be time-dependent, and the drug interaction profiles should also be individualized to include the most current information based on published literature. Nevertheless, we hope that OncoRx-IQ will not only be a useful quality assessment tool for oncology clinicians to evaluate online anticancer drug interaction information, but also an educational tool for students in the oncology, medical and allied-health fields on the wide-ranging quality of online drug interaction information available.

Acknowledgements

The authors would like to thank the pharmacy undergraduate students for their contribution toward the final version of the OncoRx-IQ tool, and the quality evaluators for their time and effort in assessing the drug databases.

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### Appendix. OncoRx-IQ: Quality Assessment of Anticancer Drug Interaction Information

#### Section A: Content Accuracy (27 points)

(a) Please refer to the following profile for the interaction between the chemotherapy regimen EP (etoposide, cisplatin) and valproic acid.

<table>
<thead>
<tr>
<th>Specific Combination</th>
<th>Interaction Effect(s)/Clinical Consequences</th>
<th>Mechanism(s) of Interaction</th>
<th>Evidence(s) of Interaction</th>
<th>Summarized Details of Case Reports/Studies</th>
<th>Recommendation(s) for Management</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide–valproic acid</td>
<td>Increased risk of etoposide toxicity</td>
<td>Inhibition of CYP3A4-mediated etoposide metabolism by valproic acid</td>
<td>One human study</td>
<td>In a cohort study of 70 patients, the risk of hematological toxicity was shown to be three times higher when etoposide-containing chemotherapy was co-administered with valproic acid</td>
<td>Consider the use of alternative antiepileptic drugs</td>
<td>1. Bourg et al. [17] (PMID: 11300327) 2. Vecht et al. [24] (PMID: 12849118)</td>
</tr>
<tr>
<td>Cisplatin–valproic acid</td>
<td>(A) Decreased plasma concentrations of valproic acid resulting in a loss of seizure control</td>
<td>(A) Probable chemotherapy-induced intestinal malabsorption of valproic acid</td>
<td>Two case reports</td>
<td>A young woman with epilepsy experienced tonic-clonic seizures during antineoplastic therapy with Adriamycin (doxorubicin) and cisplatin. Her plasma valproic acid concentrations were found to have decreased from 40.9 to 10 mg/l. A 34 year old male epileptic patient concurrently receiving valproic acid and cisplatin-based chemotherapy for the treatment of a testicular tumour showed an approximate 50% decrease in plasma valproic acid concentrations.</td>
<td>(A) Monitor for seizure control. Consider adding gabapentin or levetiracetam only if seizure control with valproic acid is insufficient</td>
<td>1. Neef and de Voogd-van der Straaten [18] (PMID: 3128415) 2. Ikeda et al. [19] (PMID: 15842559) 3. Bourg et al. [17] (PMID: 11300327) 4. Vecht et al. [24] (PMID: 12849118)</td>
</tr>
<tr>
<td></td>
<td>(B) Increased risk of hematological toxicity</td>
<td>(B) Inhibition of CYP2C9 by valproic acid, resulting in decreased cisplatin metabolism</td>
<td>One cohort study</td>
<td>In a cohort study of 70 patients, the risk of hematological toxicity was shown to be three times higher when cisplatin-containing chemotherapy was co-administered with valproic acid</td>
<td>(B) Monitor for signs and symptoms of chemotherapy-induced hematological toxicity</td>
<td>5. Vecht et al. [25] (PMID: 14765386)</td>
</tr>
</tbody>
</table>
**Interacting drug pair: etoposide and valproic acid**

1. Is / are the correct interaction effect(s) provided for the above drug pair?
   - (0) No / incorrect effect(s) provided
   - (1) General effect(s) provided
   - (2) Detailed effect(s) provided

2. Is / are the correct mechanism(s) of interaction provided for the above drug pair?
   - (0) No / incorrect mechanism(s) provided
   - (1) General mechanism(s) provided
   - (2) Specific mechanism(s) provided

3. Is / are the correct evidence(s) (e.g. case reports, animal, human or in vitro studies) provided for the interaction concerning the above drug pair?
   - (0) No / incorrect evidence(s) provided
   - (1) Only reference(s) provided
   - (2) Summarized evidence(s) w/o details provided
   - (3) Detailed evidence(s) provided

4. Is / are the appropriate recommendation(s) provided to manage the interaction for the above drug pair?
   - (0) No / incorrect recommendation(s) provided
   - (1) General recommendation(s) provided
   - (2) Specific recommendation(s) provided

**Interacting drug pair: cisplatin and valproic acid**

5. Is / are the correct interaction effect(s) provided for the above drug pair?
   - (0) No / incorrect effect(s) provided
   - (1) General effect(s) provided
   - (2) Detailed effect(s) provided

6. Is / are the correct mechanism(s) of interaction provided for the above drug pair?
   - (0) No / incorrect mechanism(s) provided
   - (1) General mechanism(s) provided
   - (2) Specific mechanism(s) provided

7. Is / are the correct evidence(s) (e.g. case reports, animal, human or in vitro studies) provided for the interaction concerning the above drug pair?
   - (0) No / incorrect evidence(s) provided
   - (1) Only reference(s) provided
   - (2) Summarized evidence(s) w/o details provided
   - (3) Detailed evidence(s) provided

8. Is / are the appropriate recommendation(s) provided to manage the interaction for the above drug pair?
   - (0) No / incorrect recommendation(s) provided
   - (1) General recommendation(s) provided
   - (2) Specific recommendation(s) provided
(b) Please refer to the following profile for the interaction between the anticancer drug vorinostat and valproic acid

<table>
<thead>
<tr>
<th>Interaction Details between Vorinostat and Valproic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specific ACD-AED Combination</strong></td>
</tr>
</tbody>
</table>
| Vorinostat–Valproic acid | Severe thrombocytopenia and gastrointestinal bleeding | Additive inhibition of histone deacetylase (HDAC) by valproic acid and vorinostat (both HDAC inhibitors) | One animal study | In vitro and animal studies have shown the HDAC inhibitory activity of valproic acid and vorinostat | The manufacturer recommends close monitoring of the patient’s platelet count every 2 weeks | 1. Göttlicher et al. [20] (PMID: 11742974)  
2. Eyal et al. [21] (PMID: 15230695)  
3. Phiel et al. [22] (PMID: 11473107)  
4. Merck & Co. Inc. [23] |

Interacting drug pair: vorinostat and valproic acid

9. Is / are the correct interaction effect(s) provided for the above drug pair?
   (0) No / incorrect effect(s) provided
   (1) General effect(s) provided
   (2) Detailed effect(s) provided

10. Is / are the correct mechanism(s) of interaction provided for the above drug pair?
    (0) No / incorrect mechanism(s) provided
    (1) General mechanism(s) provided
    (2) Specific mechanism(s) provided

11. Is / are the correct evidence(s) (e.g. case reports, animal, human or in vitro studies) provided for the interaction concerning the above drug pair?
    (0) No / incorrect evidence(s) provided
    (1) Only reference(s) provided
    (2) Summarized evidence(s) (w/o details) provided
    (3) Detailed evidence(s) provided

12. Is / are the appropriate recommendation(s) provided to manage the interaction for the above drug pair?
    (0) No / incorrect recommendation(s) provided
    (1) General recommendation(s) provided
    (2) Specific recommendation(s) provided
Section B: Overall Quality (40 points)

(a) Ease of use (12 points)
13. Does the database contain a help feature?
   (0) No
   (1) Yes

14. Does the database contain a site map, index or menu system that facilitates navigation?
   (0) No
   (1) Yes

15. Can the database search for drug interactions using chemotherapy regimen acronyms (e.g. BEACOPP, ESHAP, R-CHOP)?
   (0) No
   (1) Yes

16. Can the database search for more than one drug interaction simultaneously (e.g. drug interactions between valproic acid and the following anti-cancer drugs: cisplatin, etoposide, vorinostat)?
   (0) No
   (1) Yes

b) Reliability (28 points)
18. Does the database state its source(s) of funding?
   (0) No
   (1) Yes

19. Does the database contain any evidence of bias (e.g. advertisements)?
   (0) Yes
   (1) No

20. Does the database state the name(s) and credential(s) of its author(s)?
   (0) No information provided
   (1) Only name(s) provided
   (2) Name(s) and credential(s) provided
   (3) Name(s) and credential(s) (with explanations) provided
21. Does the database state how it is reviewed for information accuracy?

(0) No information
(1) Reviewed internally
(2) Reviewed externally

22. Is the probability AND the severity of the interactions stated?

(0) None stated / unclear
(1) Only probability OR severity stated
(2) Both stated

23. How does the database cite the source(s) used to compile the drug interaction information?

(0) No sources cited
(1) Information extracted from external drug database
(2) Exact source(s) (e.g. journal articles, books, product inserts) cited

24. Are there links to other sources (e.g. Pubmed abstracts and/or original articles, online drug databases) to verify the drug interaction information in the database?

(0) No
(1) Yes

25. How far would you agree with the following statements with regards to the drug database?

Strongly Disagree
Disagree
Neutral
Agree
Strongly Agree

i) Clearly states the types of drug-related information it provides
ii) Clearly states the types of personal information it collects and how the information is used
iii) Clearly states who the target audiences are
iv) Specifies that the information is NOT meant to replace the advice of a healthcare professional

References


