Additional file 3. RpDoc® medical database

Screening for and assessment of drug interactions

Goal setting

The medical-scientific editorial team of RpDoc® Solutions GmbH identifies drug interactions by continuously monitoring medical-scientific publications and the notifications of national and international regulatory authorities. A structured process is then employed to systematically analyze and assess them. To help doctors and pharmacists analyze and evaluate drug therapies, the updated knowledge of management options concerning clinically relevant interactions is then summarized and the interactions and management options, along with references, entered into the RpDoc® medical database.

In addition, the RpDoc® medical database contains recommendations made to avoid specific drug combinations that may result from the parallel application of guidelines for individual diseases in patients with multimorbidity. These recommendations have been unanimously agreed upon by medical and pharmaceutical societies and are published as S2K Guidelines by the AWMF Working Group of Scientific Medical Societies.

The basic principles of screening for and evaluating interactions for the RpDoc® medical databases are presented below.

Screening for interactions

The medical-scientific editorial team of RpDoc® Solutions GmbH monitors more than 8,000 peer-reviewed scientific journals listed in the EMBASE or the PUBMED database every week. Risk warnings issued by American and European regulatory authorities for medicinal products, the FDA and EMA, as well as by the German Federal authorities responsible for pharmaceuticals, the Federal Institute for Drugs and Medical Devices (BfArM), and the Paul-Ehrlich Institute, are also monitored weekly. Risk warnings issued by the Drug Commission of the German Medical Association (AkdÄ) and the Drug Commission of German Pharmacists (AMK) are also taken into account.

Assessment of causality

The WHO UMC algorithm is used to evaluate the causality of adverse drug reactions and the information entered into the RpDoc® medical database.

The various methodological approaches available to categorize the causality of adverse drug reactions were compared in a review published in 2018[1]. The WHO algorithm (WHO-UMC) proved to be the most suitable for assessing the causality of adverse drug reactions resulting from drug interactions. It was developed for the International Drug Monitoring Program by the WHO, in collaboration with national pharmacovigilance centers, and is also suitable for the assessment of warning signals stemming from case reports [2]. In contrast to the Naranjo algorithm, WHO-UMC is also suitable for assessing organ toxicity, side effects of overdoses, and drug interactions [3, 4].

DIPS (Drug Interaction Probability Scale) criteria were used to evaluate case descriptions of drug interactions [5].

Assessment of quality of evidence

The evaluation of quality of evidence is based on the GRADE system (Grading of recommendations Assessment, Development and Evaluation) [6]. In evidence evaluations, prospective randomized studies and meta-analyzes are generally assumed to provide high quality evidence. However, indications of adverse drug interactions are often found in case reports and non-randomized studies. Such warnings as those found in Dear Doctor letters from pharmaceutical manufacturers and drug safety mails from the Drug Commission of the German Medical Association can nevertheless be plausible and justify strong recommendations on how to avoid a specific risk.

In the absence of randomized studies, GRADE can still be used. The instrument of “Good Practice Statements" is suitable for situations in which no prospective randomized studies exist, but convincing indirect evidence is available [7]. Good practice statements can justify strong recommendations even if no randomized studies exist, as long as indirect evidence unequivocally supports the recommendation, and other criteria are met [7]. In this case, different sources of evidence can be informally linked (linked evidence) to one another in order to provide information on net benefit [7].

An example of an evaluation of clinical relevance

For liability reasons, pharmaceutical manufacturers provide information on every conceivable risk associated with the use of their drugs, both individually and in combination with other medications, regardless of clinical relevance. When analyzing a drug therapy, consideration of these risk warnings will result in consideration of a high proportion of irrelevant warnings ("alert overkill") [8]. In order to achieve practical relevance, it is necessary to limit warnings to those that are clinically relevant, i.e. to warnings that should be considered when making therapy decisions [9, 10]. The resulting difference is illustrated in the following example:

Product information (Section 4.5) on siponimod (Mayzent) notes that siponimod should not be administered in combination with medicines that “prolong the QT interval". It is only logical that this contraindication is consistently found in databases that contain product information, e.g. in the IBM Micormedex database (classified as "major" = red).

Studies have been submitted by the pharmaceutical company for approval and are available in the European Product Assessment Report of the EMA. These clearly show that siponimod does not increase the QT interval: “A thorough QT study was conducted (study A2118). No effect of siponimod on the QTc interval was detected. ... metabolites are not expected to have significant effects on the QTc interval. "(EMA / CHMP / 652767/2019).

However, the studies also show that siponimod lowers the heart rate. A reduction in heart rate extends the intervals measured by ECGs, including the QT interval, but not the frequency-corrected QT interval that determines the risk of sudden cardiac death. The RpDoc® medical database therefore includes no warning against administering siponimod at the same time as QT interval prolonging drugs, but rather against drugs that may result in additive heart rate reduction.

Design of the recommendations

The design of recommendations has a significant influence on their applicability and effectiveness in practice. In order to facilitate the implementation of recommendations, management options aimed at minimizing risks should be provided in addition to descriptions of avoidable risks [11]. When a warning has high specificity, e.g. because it names particularly affected patient groups or dosages, its effectiveness is increased [10].

When formulating recommendations for action, the recommendations developed by a group of experts on the content of interaction warnings are taken into account [12]. In addition to information on the unwanted effects of a specific drug combination, information on predisposing and risk-minimizing factors, the incidence of adverse effects, and the level of evidence concerning the risk of interaction, are also provided. Pharmacological plausibility and the mechanism of interaction are presented in addition to management options. In particular, references are made to equivalent therapeutic alternatives, as well as recommended surveillance measures in case the drug combination is maintained.

Recommendations for action on drug therapies in multimorbidity

There are guidelines for the evidence-based treatment of numerous diseases, but the parallel application of guidelines for each individual disease can, in multimorbidity, lead to unfavorable and risky drug combinations [13].

To resolve these therapeutic conflicts, medical and pharmaceutical scientific societies develop recommendations for action that the AWMF, with the support of the AdAM and TOP innovation fund projects, publishes in S2K Guidelines. RpDoc® Solutions GmbH is involved in both these innovation fund projects as a technology partner, and recommendations developed for drug therapies in multimorbidity are continuously updated in the RpDoc® medical database.

For an overview of the AdAM and TOP projects, please see the brief summary provided by the joint federal committee (https://innovationsfonds.g-ba.de/).

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