Mini Review

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Impact of interactions between drugs and laboratory test results on diagnostic test interpretation – a systematic review

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Abstract: Intake of drugs may influence the interpretation of laboratory test results. Knowledge and correct interpretation of possible drug-laboratory test interactions (DLTIs) is important for physicians, pharmacists and laboratory specialists. Laboratory results may be affected by analytical or physiological effects of medication. Failure to take into account the possible unintended influence of drug use on a laboratory test result may lead to incorrect diagnosis, incorrect treatment and unnecessary follow-up. The aim of this review is to give an overview of the literature investigating the clinical impact and use of DLTI decision support systems on laboratory test interpretation. Particular interactions were reported in a large number of articles, but they were fragmentarily described and some papers even reported contradictory findings. To provide an overview of information that clinicians and laboratory staff need to interpret test results, DLTI databases have been made by several groups. In a literature search, only four relevant studies have been found on DLTI decision support applications for laboratory test interpretation in clinical practice. These studies show a potential benefit of automated DLTI messages to physicians for the correct interpretation of laboratory test results. Physicians reported 30–100% usefulness of DLTI messages. In one study 74% of physicians sometimes even refrained from further additional examination. The benefit of decision support increases when a refined set of clinical rules is determined in cooperation with health care professionals. The prevalence of DLTIs is high in a broad range of combinations of laboratory tests and drugs and these frequently remain unrecognized.

Keywords: clinical laboratory test; (computerized) clinical decision support; diagnostic error; drug laboratory test interaction; patient safety.

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Introduction

Diagnostic tests, such as laboratory analysis of body fluids, represent an important part of today's healthcare. The use of diagnostics is expanding and tests are becoming increasingly complex. Therefore, diagnostic test interpretation is becoming more complicated and diagnostic errors more common [1, 2]. There is a shifting role for laboratory specialists towards support and consultation of physicians for the interpretation of laboratory test results [3–5]. One of their roles will be to eliminate harm from diagnostic errors and thereby improve the safety and quality of diagnostics. The Society to Improve Diagnosis in Medicine (SIDM) was established in 2015 to catalyze the changes necessary to reach this goal (Society to improve diagnosis in medicine. Availble at: https://www.improvediagnosis. org/ [accessed July 1, 2018]). It is important for all stakeholders to acknowledge the need for diagnostic expertise, to counterbalance policy makers that tend to focus on volume, efficiency and cost reduction in laboratory medicine, rather than quality and clinical effectiveness [6].

A common source of diagnostic error is the lack of knowledge of drug-laboratory test interactions (DLTIs). Misinterpretation of test results may lead to a delayed or erroneous diagnosis, unnecessary extra diagnostic tests or therapy which may harm patients.

Drugs frequently influence physiological *in vivo* processes and thereby affect the patients' laboratory test results. A drug may have an intended or unintended effect on a laboratory test result [7]. Intended effects of drugs on laboratory test results are not the focus of this review, because it will normally not lead to diagnostic confusion. Moreover, the reason to request laboratory tests often is to monitor drug therapy, i.e. an elevation in free thyroxin levels due to levothyroxine treatment.

An elevated level of chromogranin A can be indicative of activity of a neuroendocrine tumor. However, as an example of an unintended effect of a drug, this may also result from the administration of frequently prescribed proton pump inhibitors (PPIs). PPIs stimulate enterochromaffin cells which results in elevated levels of chromogranin A. Case reports describe expensive imaging with no abnormalities and a normalized chromogranin A level after discontinuation of the PPI [8]. This example illustrates that unnecessary discomfort and expenditure could have been avoided if this unintended physiological interaction had been recognized promptly. Another example is an elevated creatinine level in patients using trimethoprim. By inhibiting creatinine secretion, trimethoprim can lead to an elevation in serum creatinine independently of any changes in the glomerular filtration rate (GFR) [9]. This factitious creatinine elevation impacts on GFR estimation and may, in certain cases, erroneously lead to the conclusion of an impaired kidney function.

In some cases the interactions between drugs and laboratory tests disturb the analytical process *in vitro*, which may have an important negative clinical impact, as affected laboratory test results may not reflect the clinical situation of the patient. These analytical interactions should be avoided by using an alternative assay or erroneous test interpretation should be eliminated by warning systems. An extreme example of the danger of an analytical drug-test interaction is an erroneously high glucose level that can occur in continuous ambulatory peritoneal dialysis (CAPD) patients, because some glucose test strips cannot distinguish glucose from other sugars (e.g. icodextrin, maltose) that can be present in CAPD fluid [10]. The improper administration of insulin has resulted in fatal consequences in a number of these cases.

Yao et al. investigated the presence of DLTIs in all labels of single ingredient Food and Drug Administration (FDA) approved drugs [7]. Only analytical interactions were included in the search. A total of 134 out of 1368 labels (9.8%) were positive for an interaction with at least one laboratory test. Thirty-one labels indicated that the drug does not interfere with laboratory tests. All the other labels did not contain information about DLTIs, indicating that studies about DLTIs have been lacking for most drugs. The number of DLTIs described in the literature is substantial with a number of about 50,000 [11]. Therefore, the application of a knowledge-based electronic expert system with concise and evidence-based DLTI information seems necessary. A knowledge-based expert system may send automatic messages about interactions based on the combination of data from pharmacy and laboratory data systems. Pharmacists already make extensive use of computerized clinical decision support with and without using laboratory test results. These expert systems contain clinical rules to monitor drug therapy, to alert on possible interactions or side effects of drugs. Laboratory results are also routinely used to adjust dosage of medication, for instance, in patients with impaired kidney function [12]. These pharmacological decision support systems have proven to be beneficial and are still improving [13]. *Vice versa*, expert systems could also be used for laboratory test interpretation based on pharmacological data in the department of clinical chemistry, but such systems are not yet available in today's clinical practice.

Decision support applications are based on algorithms. To build DLTI algorithms, relevant information about interactions is conditional. Information about DLTI can be found in literature but is very fragmentarily described

and sometimes even contradictory effects are reported, i.e. the effect of a drug on a laboratory test may result in both an increase or decrease of measured values [14, 15]. Therefore, several DLTI databases have been introduced to provide an overview of interactions and the corresponding available literature [7, 16]. Databases were published by the US Library of Medicine (Dailymed database. https://dailymed.nlm.nih.gov/dailymed/. [Accessed: July 1, 2018]), the American Association of Clinical Chemistry (AACC) (AACC database: effects on clinical laboratory tests. http://clinfx.wiley.com/aaccweb/aacc/. [Accessed: July 1, 2018]) which was based on the work of Young [11], the Swedish Society for Clinical Chemistry in collaboration with the National Corporation of Pharmacies (Database Drug effects in clinical chemistry. http://www.tryding.se/. [Accessed: July 1, 2018]), which was based on the work of Tryding et al. [17], Multirec [Multirec drug laboratory effects database. http://www.multirec.fi/products/mr-dle/. (Accessed: July 1, 2018)] and the First DataBank MedKnowledge (First DataBank MedKnowledge. http://www.fdbhealth.com/fdbmedknowledge/. [Accessed: July 1, 2018]) .

The aim of this review is to give an overview of the literature investigating the clinical impact and use of DLTI decision support applications on laboratory test interpretation and discuss future developments.

Methods

A systematic literature search was conducted to collect studies investigating the impact and use of DLTI decision support applications on interpretation of laboratory test results. Studies were extracted from PubMed and the Cochrane Library using the key words 'drug test interaction', 'drug interference', 'DLTI', 'drug laboratory test effect', 'DLE', 'laboratory test interaction' and 'decision support' or 'laboratory computer'. The search was limited to studies in humans and in the English language. Both ambulant and hospitalized patients were included in the reviewed study population. No specific study characteristics were excluded with the exception of case reports. Related articles and quoted articles from relevant articles were also reviewed. The search period ended July 2018. We also summarized available DLTI databases, which were found in the references of the conducted systematic literature search.

Results

With the search strategy and the keywords described above, 139 articles were found. Thirty-five articles were about decision support applications for drug prescribing. Nine articles described decision support applications in other medical departments. Eleven articles described drug-drug interactions and three articles a specific drug-laboratory test interaction. Sixty articles did not deal with drugs, laboratory tests or interactions at all. Three articles were about our topic of interest: DLTI decision support in laboratory test interpretation [18–20]. One other relevant article [21] was selected, which was found in the references of a related article [7]. These four qualifying studies are summarized in Table 1.

Friedman et al. introduced an automatic reporting system of possible drug-test interactions in a university hospital in 1978 [21]. The system was able to recognize more than 20,000 possible interactions adopted from the drug-test interaction file from the National Institute of Health. This DLTI database contained a complete overview of the literature per interaction, but these interaction reports did not always contain a clear conclusion about the drug effect on a laboratory test result [22]. For a period of 16 months, the system searched the digital health records from patients for abnormal laboratory test results and drugs that were administered to the patient. It then searched the DLTI database and printed reports for each patient indicating all possible DLTIs. Four different departments participated: internal medicine, surgery, gynecology and the intensive care unit. Most DLTIs were found in the intensive care unit. The drugs most frequently causing interaction messages were furosemide, hydrochlorothiazide, acetaminophen and penicillin. The laboratory tests most frequently reported in interaction messages were the white blood cell count, hemoglobin, potassium and glucose. Physicians reported that the system had both educational and clinical value. Of the interaction messages, 30% were found to be useful and in 4% of all reports this resulted in changes in patient's management. In addition to interviewing physicians, 186 patient records were selected randomly by the research staff to review the interactions. Almost half of the messages concerned a possible idiosyncratic toxic effect (e.g. aplastic anemia or hepatitis) or a toxic dose dependent effect. However, no evidence of toxicity was found in the patient record. In approximately one third of cases an alternative explanation was found for the deviated laboratory test result. Approximately 20% of the interaction messages were categorized as clinically relevant: the interaction was the most probable explanation of the deviated test result. From the review by the expert panel of patient reports, it was concluded that in 0.1% of cases physicians altered their therapeutic strategy because of the interaction message.

Table 1: Characteristics and results of reviewed studies.

Study	Country	Study period	Included departments, n	Included DLTIs, n	Way of reporting to physicians	Evaluation of messages	Effect of DLTI message on medical management
Friedman et al. [21]	USA	16 months	4	>20,000	Printed reports, no manual filter	Questionnaires to 40 physicians, review by expert panel of effect of interaction messages in 186 patient reports	4% changes in medical management (questionnaire results) 0.1% changes in management (according to documented evidence review)
Groves and Gajewski [18]	USA	NR	NR	>20,000	Printed and digital reports alongside laboratory test results	NR	NR
McNeely [19]	Canada	3 months	NR	NR	NR	Polls to general practitioners and specialists	Specialists report to 'enjoy' being provided with drug interference data
Kailajärvi et al. [20]	Finland	10 months	26	48[a]	Printed and digital reports alongside laboratory test results, automatic and manual filter by laboratory physician	Questionnaires to 23 physicians	74% of physicians consider changes in medical management

NR, not reported. [a]Only endocrinological tests.

Groves and Gajewski [18] described a comparable DLTI system as used by Friedman et al. [21]. The technical aspects of the system were described extensively, but the clinical usefulness of the DLTI messages was not reported.

In 1983, McNeely described an approach to implement automatic interpretative comments on specialized laboratory test results [19]. Comments about potential drug interference were also included, but specifications of these comments were not described. The clinical usefulness of DLTI information was only briefly mentioned: clinicians reported to 'enjoy' the provided drug interference data.

More recently, Grönroos et al. proposed a computerized DLTI decision support application and described the basic terms of the concept [23–25]. This application was examined by Kailajärvi et al. on practical usefulness and appreciation by physicians during 10 months in 26 wards of a university hospital [20]. Thirty-four drugs and 18 hormone tests were included, resulting in a total of 48 possible DLTIs. These interactions were all classified as clinically relevant and were well documented in the literature. They all reflected an undesired effect of a drug. The system would only send a DLTI message when the onset and duration of the interaction were in concordance with the administration date of the drug and test result.

In the study period, 3845 hormone test results were produced. Of all hormone test results, 11% were accompanied by a DLTI message. More than 90% of the DLTI messages concerned effects on thyroid stimulating hormone, parathyroid hormone and free thyroxin. Twenty-three internal medicine physicians were surveyed and considered the messages useful. In addition, these alerts had caused 74% of the physicians to sometimes refrain from additional further examinations.

Apart from these four studies, no further research was found about DLTI decision support applications in clinical practice.

Discussion

In this review, we searched for literature about the impact and use of DLTI decision support applications on laboratory test interpretation by health care professionals.

A total of four reports were found. Two of the studies have shown a high prevalence of DLTIs in hospitalized patients (up to 43% of all patients, depending on which ward [21] and up to 11% of endocrinological test results [20]). The potential beneficial effects of automated DLTI warning messages for health care professionals who interpret laboratory test results is significant [20, 21].

The clinical benefit was determined from a limited retrospective evaluation of patient records in one study [21], and surveys with physicians in three studies [19–21]. One study only briefly mentioned positive feedback from

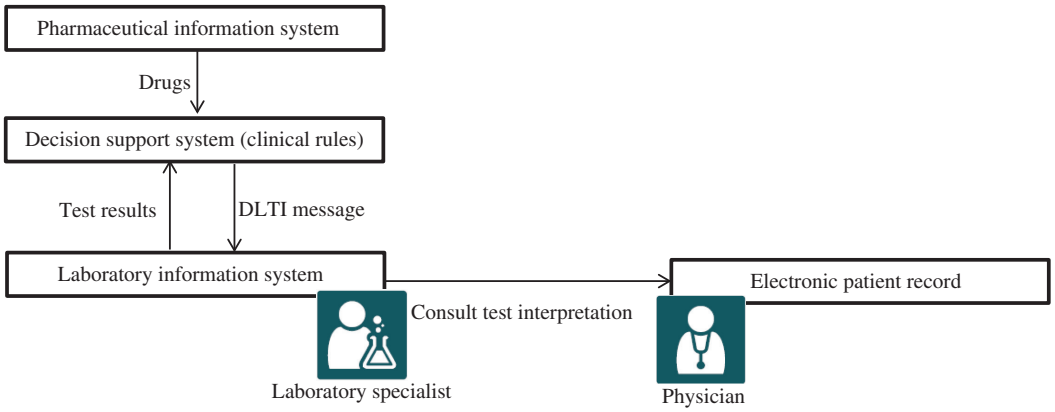

Figure 1: Conditions needed for automated DLTI decision support.

specialists about DLTI information [19]. In the other two studies, physicians reported 30–100% of DLTI messages to be useful [20, 21]. These differences in reported usefulness could be explained by differences in study design. Kailajärvi et al. included 48 interactions with common laboratory tests and drugs [20] whereas Friedman et al. studied more than 20,000 interactions, including interactions with less frequently requested laboratory tests and drugs [21]. Furthermore, in the study of Kailajärvi et al. the messages were automatically selected based on predefined usefulness criteria and thereafter, judgement by the laboratory specialist before sending the DLTI messages to the responsible physician, while the other study did not apply any selection.

There are several DLTI databases, which are useful for healthcare professionals when they suspect a possible DLTI, but a disadvantage of such databases is that physicians have to actively suspect an interaction before they consult a database. This disadvantage is eliminated when decision support applications are introduced. The available DLTI databases can be used for automated decision support, but there are some important limitations. In some databases the clinical relevance of interactions is lacking, or literature is listed but not summarized. Also, some databases do not contain information on the degree, duration and incidence of the effect or of risk factors (such as age or gender) and often cited literature is not up to date. Databases should ideally contain a summary and a conclusion of the available literature and should be updated continuously [26].

Research showed the added value of decision support applications to alert health care professionals on possible DLTIs and the effectiveness of such a system increases when a refined set of clinical rules is determined in cooperation with health care professionals who use the system [20, 21]. These refined clinical rules are needed to prevent excessive numbers of DLTI messages and consequently so-called 'alert fatigue' of physicians [27]. Although the benefit of DLTI decision support was already shown in the past [21], it is not widely implemented today. To implement a DLTI decision support tool, an accessible DLTI database is crucial. Moreover, in a DLTI decision support system, current drugs and laboratory tests have to be uniformly registered and coded in a digital patient record and data exchange between the systems must be realized. An example of the structure of the conditional data exchange is shown in Figure 1. Finally, a proper connection between the patient records of different healthcare professionals (i.e. physicians and pharmacists) is a requirement for a complete overview of possible interactions.

Awareness of DLTIs is essential for correct interpretation of laboratory test results and consequently correct diagnosis and treatment of patients. The existing literature shows a high prevalence of DLTI in a variable range of laboratory tests and drugs. It is likely that in daily practice the prevalence of DLTI is even higher, as interactions are not systematically examined or reported. Promising new methods of interaction detection have recently been published, such as data analytics examining temporal correlations between drug administration and laboratory value changes [28].

A Dutch consortium of the Society of Clinical Chemistry and Laboratory Medicine (NVKC) is currently performing a multicenter pilot study to investigate the prevalence of DLTIs and the value of an automated DLTI decision support system in clinical practice. The purpose of the study is to get a proof of concept of the system, which is expected to support laboratory specialists and physicians in the correct interpretation of laboratory test results. The final goal is to reduce diagnostic errors and thereby contribute to improve healthcare.

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